UNIVERSITY OF BIRMINGHAM

Use of Oral Anticoagulants in Eastern Saudi Arabia: Assessment of Patients' Adherence and Exploring Views of Health Care Professionals

By

ABDELRAHMAN BASHIR ELHAG MEDANI

A thesis submitted to the University of Birmingham for the degree of **DOCTOR OF PHARMACY**

School of Pharmacy

Institute of Clinical Science

College of Medical and Dental Sciences

University of Birmingham

August 2023

Abstract

Oral anticoagulants (OACs) are one of the mainstays of the treatment and prevention of cardiovascular diseases. Yet, in contrast with other regions of the world, the Middle East region has reported low levels of adherence to OACs. In this DPharm study, patient's adherence to OACs was assessed in Eastern Saudi Arabia. As a first step, a systematic literature review was conducted to investigate adherence to OACs in the Middle East. Then, a cross-sectional study was conducted at the cardiac centre (PSCC) in Alhassa area, Eastern Saudi Arabia, using surveys and the self-reported Hill-Bone scale to evaluate OACs adherence. Finally, interviews were conducted to investigate Health Care Professionals' perceptions and experiences on OAC prescriptions and adherence in Eastern Saudi Arabia. According to the systematic review, adherence to OACs in this region varied between 5% and 54%. Besides, the majority of the literature was on warfarin, a commonly prescribed OAC in this region. Three hundred and twelve participants were recruited in the study. Based on the statistical analysis result, 29.8% of the participating patients adhere to their OACs medications. Moreover, warfarin (34%) was adhered to more frequently than Direct Oral Anti Coagulants (DOACs) (22%). A binary logistic regression analysis found adherence to OACs to be significantly influenced by age, gender, medication duration, OACs knowledge, and missed doses. Fifteen HCPs were interviewed in the study. Based on interviews with HCPs, it became clear that effective communication strategies could improve communication between practitioners at different levels of care, and between HCPs and OAC users. Training pharmacists to offer pharmaceutical services to individuals on OACs, such as conducting medication use reviews and assessing new medications, will have a beneficial effect on enhancing medication adherence.

Acknowledgements

I would like to express my deep gratitude to the following individuals and institutions who played a key role in the completion of this thesis:

First and foremost, I extend my heartfelt appreciation to my dedicated and insightful supervisors, Dr. Zahraa Jalal and Professor Anthony Richard Co. Their guidance, expertise, and unwavering support throughout this research journey have been invaluable.

I am indebted to the entire staff at the Prince Sultan Cardiac Centre (PSCC) in Hofuf, eastern Saudi Arabia, for their cooperation, assistance, and access to resources, which made this study possible. Their commitment to advancing medical research is truly commendable.

To my children and family, I offer my profound thanks for their enduring patience, encouragement, and understanding. Their unwavering support and belief in my abilities have sustained me through the challenges of this academic pursuit.

In addition, I would like to express my gratitude to all the friends and colleagues who provided moral support and offered their insights during this academic effort.

This thesis is the culmination of the efforts and contributions of many, and I am deeply grateful to everyone who has been a part of this journey.

Table of Contents

Abstract ---------- *i*

Acknowledgements ---------- *iii*

Table of Contents ---------- *iv*

List of Tables ---------- *xiv*

List of figures ---------- *xvi*

Abbreviations ---------- *xvii*

Structure of this thesis ---------- *xx*

CHAPTER ONE: INTRODUCTION ---------- *1*

1. 1. Background ---------- *2*

1.2. Atrial fibrillation ---------- *3*

1.3. Guidelines for using OACs in AF patients ---------- *5*

1.4. Venous Thromboembolism ---------- *11*

1.4.1. Deep vein thrombosis ---------- **12**

1.4.2. Pulmonary embolism ---------- **13**

1.5. Oral anticoagulants ---------- *14*

1.5.1. Vitamin K Antagonists (VKA) ---------- **14**

1.5.2. Direct Oral Anticoagulants (DOACs) ---------- **14**

1.5.2.1. Dabigatran ---------- **14**

1.5.2.2. Rivaroxaban ---------- **15**

1.5.2.3. Apixaban ---------- **16**

1.5.2.4. Edoxaban ---------- **17**

1.6. Impact of introducing of DOACs in clinical practice ---------- *18*

1.7. Patients' compliance to medication regimens ---------- *21*

1.8. Patients' persistence with using medications ---------- *21*

1.9. Patients' adherence to medication ---------- *22*

1.10. The influential factors that affect adherence to medications ---------- *22*

1.10.1. Patients related factors ---------- **22**

1.10.2. Physicians related factors ---------- **23**

1.10.3. Health Systems related factors ---------- **23**

1.11. Patients' non-adherence to medication ---------- *24*

1.11.1. Strategies to reduce patients' non-adherence to medications ---------- **24**

1.12. Assessment of patients' adherence to medications ---------- *26*

1.13. Subjective methods for measuring adherence to medications ---------- *26*

1.14. Objective methods for measuring adherence to medications ---------- *26*

1.15. Direct methods for measuring adherence to medications ---------- *26*

1.16. Indirect methods for measuring adherence to medications ---------- *27*

1.16.1. Pill count ---------- **27**

1.16.2. Clinician assessments and self-reporting ---------- **28**

1.16.3. Patient kept diaries ---------- **28**

1.16.4. Patients interviews by clinicians ---------- **28**

1.16.5. Motivational interviews ---------- **29**

1.16.6. Questionnaires and scales ---------- **29**

1.16.6.1. Brief Medication Questionnaire (BMQ) ---------- **30**

1.16.6.2. Hill-Bone Compliance Scale (Hill-Bone) ---------- **30**

1.16.6.3. Eight-item Morisky Medication Adherence Scale (MMAS-8) ---------- **31**

1.16.6.4. Medication adherence questionnaire (MAQ) ---------- **31**

1.16.6.5. Self-efficacy for appropriate medication uses scale (SEAMS) ---------- **32**

1.16.6.6. Medication adherence report scale (MARS) ---------- **32**

1.17. Adherence to medications in the Middle East ---------- *34*

1.18. Health system in Saudi Arabia ---------- *35*

1.19. Adherence to medications in Saudi Arabia ---------- *36*

1.19.1. Adherence to antidiabetic medications in Saudi Arabia ---------- 36

1.19.2. Adherence to antihypertensive medications in Saudi Arabia ---------- 36

1.20. Adherence to OACs in Saudi Arabia ---------- 37

1.21. Conclusion ---------- 39

1.22. Purpose of conducting this study ---------- 39

1.23. Research aims and objectives ---------- 40

1.23.1. Aims ---------- 40

1.23.2. Objectives ---------- 40

CHAPTER TWO ---------- 41

RESEARCH METHODOLOGY ---------- 41

2.1. Theoretical framework ---------- 42

2.2. Theoretical paradigms ---------- 42

2.3. The theoretical framework for this research ---------- 43

2.4. Mixed methods research ---------- 44

2.4.1. Sequential explanatory design in this study ---------- 45

2.5. Quantitative research ---------- 46

2.5.1. Cross-sectional study design ---------- 47

2.5.2. Collection of data for cross-sectional study in this thesis ---------- 48

2.6. Qualitative research ---------- 48

Thematic analysis ---------- 49

Collection of data for thematic analysis in this thesis ---------- 50

2.7. Methodological Framework in this Thesis ---------- 51

2.8. Reliability of the study ---------- 53

2.9. Validity of the study ---------- 54

2.10. Research ethical considerations ---------- 54

CHAPTER THREE ---------- 55

A SYSTEMATIC REVIEW OF ADHERENCE TO ORAL ANTICOAGULANTS AMONG ATRIAL FIBRILLATION PATIENTS IN THE MIDDLE EAST ---------- *55*

3.1. Introduction ---------- *56*

3.1.1. Prevalence and incidence Atrial Fibrillation ---------- **56**

3.1.2. Prevalence of AF in the Middle East ---------- **57**

3.1.3. Use of OACs for management of AF and for prevention of ischaemic stroke ---------- **57**

3.1.4. Burden of AF and stroke on health systems ---------- **61**

3.1.5. Adherence to medications ---------- **62**

3.1.6. Rationale for importance of adherence to OACs in AF patients ---------- **62**

3.1. 7. Measuring adherence to medications ---------- **66**

3.2. Materials and Methods ---------- *68*

3.2.1. Search protocol ---------- **69**

3.2.2. Eligibilty criteria ---------- **69**

3.2.3. Evaluation of the studies ---------- **71**

3.3.Results ---------- *71*

3.3.1. Evaluation of the selected studies ---------- **72**

3.3.2. Study design ---------- **72**

3.3.3. Settings of the selected studies ---------- **73**

3.3.4. Duration of the selected study ---------- **73**

3.3.5. Tools to measure adherence to OACs ---------- **74**

3.3.6. Tools to measure patients' satisfaction with OACs ---------- **75**

3.3.7. Measuring effectiveness and usage of OACs ---------- **75**

3.3.8. Overview of the objectives of selected studies ---------- **75**

3.3.9. Outcomes of the objectives of the selected studies ---------- **76**

3.3.10. Limitations to studies ---------- **83**

3.3.11. Key findings ---------- **83**

3.4. Discussion ---------- *84*

3.5. Recommendation for the practice and policy makers ---------- *89*

3.6. Conclusion ---------- *89*

CHAPTER FOUR ---------- *91*

ASSESSMENT OF ADHERENCE TO ORAL ANTICOAGULANTS IN EASTERN SAUDI ARABIA -- *91*

4.1. Background ---------- *92*

4.2. Aim of the study ---------- *93*

4.3. Method of the study ---------- *94*

4.3.1. Design of the study ---------- **94**

4.3.2. Location of the study ---------- **94**

4.3.3. Population of the study ---------- **95**

4.3.4. Inclusion/exclusion criteria ---------- **95**

4.3.5. Informed consent ---------- **95**

4.3.6. Ethical approval by Institutional Review Board ---------- **95**

4.4. Collection of data ---------- *96*

4.4.1. Sample size calculation ---------- **96**

4.4.2. Measuring adherence to OACs ---------- **96**

4.4.3. Assessment of patients' experience with taking OACs ---------- **96**

4.4.4. Statistical analysis ---------- **97**

4.5. Results ---------- *97*

4.5.1. Characteristics of the participants ---------- **97**

4.5.1.1. Demographics of participants in the study ---------- **97**

4.5.1.2. Comorbidities among participating patients ---------- **98**

4.5.1.3. Indications for prescribing OACs for the participants ---------- **99**

4.5.1.4. Prescribed OACs for the participants ---------- **100**

4.5.1.5. Duration of taking OACs by the participants ---------- **101**

4.5.2. Measuring adherence of the participants to OACs ---------- **104**

4.5.2.1. Examination of reliability of the Arabic translated Hill-Bone scale ---------- **104**

4.5.2.2. Calculation of adherence of the participants to OACs ---------- 106
4.5.2.3. Adherence to OACs among warfarin users ---------- 108
4.5.2.4. Adherence to OACs among DOACs users ---------- 108
4.5.2.5. Overall adherence among OACs users ---------- 109
4.5.3. Assessment of relationships between patients' characteristics and adherence to OACs 110
4.5.3.1. Age of patients ---------- 110
4.5.3.2. Sex of the patients ---------- 110
4.5.3.3. Level of education ---------- 111
4.5.3.4. Indications for prescribing OACs ---------- 111
4.5.3.5. Types of prescribed OAC ---------- 112
4.5.3.6. Duration on OACs ---------- 112
4.5.3.7. Total number of co-morbidities ---------- 113
4.5.4. Patients' experiences with taking OACs ---------- 114
4.5.4.1. Awareness about indications for OACs ---------- 114
4.5.4.2. Awareness about INR target for warfarin users ---------- 115
4.5.4.3. Compliance with advice of prescribers about taking OACs ---------- 115
4.5.4.4. Experience of patients with missing doses of OACs ---------- 116
4.5.4.5. Reported reasons for non-adherence to OACs ---------- 116
4.5.4.6. Perception of patients about therapeutic benefits of OACs ---------- 117
4.5.4.7. Influence of patients' perception on adherence to OACs ---------- 117
4.5.5. Assessment of relationships between patients' experiences with taking OACs and adherence to OACs ---------- 118
4.5.5.1. Patients' awareness about indication of taking OACs ---------- 118
4.5.5.2. Awareness about INR target among warfarin users ---------- 119
4.5.5.3. Adherence to the advice of prescribers about taking OACs ---------- 120
4.5.5.4. Missing doses of OACs by patients ---------- 120
4.5.5.5. Reasons for non-adherence of patients to OACs ---------- 121
4.5.5.6. Patients' perception on therapeutic benefits of OACs ---------- 121
4.5.5.7. Influence of patients' perception on adherence to OACs ---------- 122

4.5.6. Prediction of adherence to OACs among participants ---------- *123*

4.6. Discussion ---------- *124*

4.6.1. Key findings ---------- **125**

4.6.2. Relating our findings to previous literature ---------- **127**

4.6.3. Strengths and limitations ---------- **129**

4.7. Conclusion ---------- *130*

CHAPTER FIVE: A QUALITATIVE STUDY OF PATIENTS' ADHERENCE TO ORAL ANTICOAGULANTS: INVESTIGATING THE PERSPECTIVE OF HEALTHCARE PROFESSIONALS AND EXAMINING THE ROLE OF PHARMACISTS IN PROMOTING PATIENTS' ADHERENCE TO OACS ---------- *132*

5.1. Introduction ---------- *133*

5.2. Aim of the study ---------- *134*

5.3. Design of the study and collection of the data ---------- *134*

5.4. Conduction of the interviews ---------- *135*

5.5. Ethical clearance ---------- *136*

5.6. Location of the interviews ---------- *136*

5.7. Data management and analysis ---------- *136*

5.8. Findings of qualitative interviews with HCPs ---------- *137*

5.8.1. Characteristics of the HCPs ---------- **137**

5.8.2. Extracted themes from the interviews with HCPs using thematic analysis ---------- **138**

5.9. Outcomes of the extracted themes ---------- *139*

5.9.1. Theme 1: Viewpoints of HCPs on factors influence prescribing of OACs ---------- **139**

5.9.1.1. HCPs perspectives on patients' illness perception when prescribing OACs ---------- **139**

5.9.1.2. Relationship between adherence to OACs and illness perception ---------- **140**

5.9.1.3. Effect of patient safety consideration when prescribing OACs ---------- **140**

5.9.1.4. Influence of clinical factors on selection of OACs ---------- **141**

5.9.1.5. Non-clinical factors that affect selection of OAC ---------- **144**

5.9.1.6. Concordance about OACs---------- 145

5.9.1.7. Effect of cost as a factor on prescribing OACs---------- 145

5.9.2. Theme 2: Assessment of adherence to OACs among OACs users ----------146

5.9.2.1. Utilisation of scales to measure adherence in routine practice---------- 146

5.9.2.2. Assessment of adherence among warfarin users ---------- 147

5.9.2.3. Assessment of adherence among DOACs users ---------- 147

5.9.3. Theme 3: Perspectives of HCPs on patients' adherence to OACs ----------148

5.9.3.1. Perspective of interviewees on overall adherence to OACs ---------- 148

5.9.3.2. Variations in adherence to OACs between hospitalised and discharged patients ---------- 149

5.9.4. Theme 4: Impediments for adherence among OACs users----------149

5.9.4.1. Viewpoints of HCPs on identification of non-adherent patients---------- 149

5.9.4.2. Perception of HCPs on reasons for non-adherence among OACs' users---------- 151

5.9.5. Theme 5: Viewpoints of interviewed HCPs on supporting adherence of patients who are taking OACs ----------152

5.9.5.1. Counselling of OACs' users ---------- 152

5.9.5.2. Counselling for patients who are taking warfarin ---------- 153

5.9.5.3. Counselling for DOACs patients---------- 154

5.9.5.4. Availability of adherence aids for OACs users ---------- 155

5.9.5.5. Social care input in facilitating adherence to OACs---------- 156

5.9.6. Theme 6: Insight of pharmacists and pharmacy technicians in issues related to adherence to OACs ----------156

5.9.6.1. Accreditation of pharmacists and pharmacy technicians for conducting advanced pharmaceutical services ---------- 157

5.9.6.2. Perceptions of pharmacists and pharmacy technicians in monitoring warfarin users ---------- 157

5.9.6.3. Input of pharmacists and pharmacy technicians in supporting polypharmacy patients ------- 158

5.9.6.4. Use of validated scales in routine pharmacy practice ---------- 159

5.9.6.5. Barriers to patients' education by pharmacists and pharmacy technicians ---------- 159

5.9.6.6. Availability of pharmaceutical services for OACs users in community pharmacies---------- 160

5.9.6.7. Sales of OTC medicines to OACs users in community pharmacies ---------- 161

5.10. Similarities and disparities among interviewed HCPs ---------- *162*

5.11. Incorporation of outcomes of HCPs interviews and findings of cross-sectional study ---------- *165*

5.11.1. Overall Adherence ---------- **165**

5.11.2. Patient Profiles ---------- **165**

5.11.3. Effect of age and education on adherence to OACs ---------- **166**

5.11.4. Duration of OAC Use ---------- **166**

5.11.5. Correlation between sex, comorbidities, and adherence to OACs ---------- **166**

5.11.6. Awareness about reasons for prescribing OACs ---------- **166**

5.11.7. Reasons for Missing Doses ---------- **166**

5.12. Discussion ---------- *167*

CHAPTER SIX ---------- *170*

OVERALL DISCUSSION ---------- *170*

6.1. Systematic review of data on adherence to OACs in the Middle East ---------- *172*

6.1.1. Systematic review of data on patients' related factors affecting adherence to OACs' in the Middle East ---------- **173**

6.2. Assessment of adherence to OACs in Eastern Saudi Arabia ---------- *174*

6.3. Study of patients' related factors and their impact on adherence to OACs in Eastern Saudi Arabia ---------- *175*

6.3.1. Impact of age on adherence to OACs in Eastern Saudi Arabia ---------- **175**

6.3.2. Adherence to OACs, general literacy, and health literacy in Eastern Saudi Arabia ---------- **176**

6.4. Adherence to OACs and indications for prescribing these medications ---------- *176*

6.5. Reasons for non-adherence to OACs in Eastern Saudi Arabia ---------- *177*

6.6. Increasing adherence to DOACs in Eastern Saudi Arabia is a necessity ---------- *178*

6.7. Outcomes of interviews with HCPs in Eastern Saudi Arabia ---------- *179*

6.7.1. Strengthening the role of hospital pharmacists in Eastern Saudi Arabia ---------- **180**

6.7.2. Communications between physicians, patients, and other HCPs in Eastern Saudi Arabia 182

6.7.3. Social care and needs of adherence to OACs in Eastern Saudi Arabia ---------- 184

6.7.4. Integration of the results from quantitative and qualitative data ---------- 185

6.8. Research strengths and limitations ---------- 186

6.8.1. Strengths ---------- 186

6.8.2. Limitations ---------- 187

6.9. Recommendations for practice ---------- 188

6.10. Future research ---------- 189

6.11. Conclusion ---------- 191

References ---------- 193

Appendix I ---------- 215

Ethical Approvals of University of Birmingham, and ---------- 215

Ethics Committee in the site of the study (Prince Sultan Cardiac Centre PSCC), Saudi Arabia ---------- 215

Appendix II ---------- 218

Prospero Registration, JBI Critical Appraisal Checklists for Cross-Sectional and Cohort Studies, and Table of Data Extraction ---------- 218

JBI Critical Appraisal Checklist for cohort studies ---------- 221

Appendix III ---------- 231

Patient Information, Participants' consent, Hills-Bone Scale, and patients Experience with Oral Anticoagulants questionnaire ---------- 231

Appendix IV ---------- 239

Interview Schedule of Health Care Professionals ---------- 239

List of Tables

TABLE.1.1. COMPARISON OF THE NICE, ESC, AND AHA GUIDELINES FOR TREATMENT OF AF. 10

TABLE 1.2. SUMMARY OF THE METHODS FOR MEASURING ADHERENCE (ANGHEL ET AL., 2019)....33

TABLE 2.1. METHODOLOGY OVERVIEW....53

TABLE 3.0. PRESCRIBING OF DOACS FOR PATIENTS WITH IMPAIRMENT OF RENAL FUNCTION....59

TABLE 3.1. SUMMARY OF METHODS FOR MEASURING ADHERENCE (OSTERBERG,2005) 67

TABLE 3.2. ADHERENCE MEASURES AND AUTHORS OF THE PUBLICATIONS 74

TABLE 3.3. SATISFACTION WITH ORAL ANTICOAGULANTS MEASURES AND AUTHORS OF PUBLICATIONS....75

TABLE 3.4. OVERVIEW OF THE OBJECTIVES OF THE STUDIES 76

TABLE 3.5. OUTCOMES OF THE OBJECTIVES OF THE SELECTED STUDIES....77

TABLE 3.6. OUTCOMES OF THE ASSESSMENT OF PATIENTS' RELATED FACTORS AND ADHERENCE TO OACS IN THE SELECTED STUDIES.79

TABLE 4.1. DEMOGRAPHIC CHARACTERISTICS OF THE PARTICIPANTS 98

TABLE 4.2. DISTRIBUTION OF COMORBIDITIES AMONG PARTICIPATING PATIENTS....99

TABLE 4.3. INDICATIONS FOR PRESCRIBING OACS AMONG THE PARTICIPATING PATIENTS 100

TABLE 4.4. PRESCRIBING PATTERNS OF OACS AMONG MALE AND FEMALE PATIENTS....100

TABLE 4.5. DURATION ON OACS AMONG MALE AND FEMALE PATIENTS 101

TABLE 4.5A. DURATION ON OACS ACCORDING TO OAC TYPE 102

TABLE 4.5.B SUMMARISES THE BIO-DEMOGRAPHIC DATA FOR THE PARTICIPANTS IN THE STUDY. 102

TABLE 4.6. LIKERT SCALE FOR INTERPRETATION OF CRONBACH'S ALPHA 105

TABLE 4.7. OBTAINED RESPONSES FOR THE ARABIC TRANSLATED VERSION OF THE HILL-BONE QUESTIONNAIRE 105

TABLE 4.8. RESPONSES TO EACH QUESTION OF THE ARABIC TRANSLATED HILL-BONE SCALE....106

TABLE 4.9. TOTAL POINTS SCORED BY RESPONDENTS TO ARABIC TRANSLATED HILL-BONE SCALE 107

TABLE 4.10. CLASSIFICATION OF RESPONSES TO THE ARABIC TRANSLATED HILL-BONE SCALE BY WARFARIN USERS 108

TABLE 4.10[A.] CLASSIFICATION OF RESPONSES TO THE ARABIC TRANSLATED HILL-BONE SCALE BY DOACS USERS....108

TABLE 4.10[B]. OVERALL CLASSIFICATION OF RESPONSES TO THE ARABIC TRANSLATED HILL-BONE SCALE BY OACS USERS....109

TABLE 4.10[C]. CLASSIFICATION OF RESPONSES TO THE ARABIC TRANSLATED HILL-BONE SCALE BY DOACS USERS....109

TABLE.4.11. AGE GROUPS AND STATUS OF ADHERENCE TO OACS AMONG PARTICIPANTS 110

TABLE.4.12. ADHERENCE TO OACS AMONG MALE AND FEMALE PARTICIPANTS....111

TABLE.4.13. LEVEL OF EDUCATION AND ADHERENCE TO OACS AMONG PARTICIPANTS 111

TABLE 4.14. INDICATIONS FOR PRESCRIBING OACS AND STATUS OF ADHERENCE TO OACS 112

TABLE 4.15. TYPES OF PRESCRIBED OACS AND ADHERENCE TO OACS 112

TABLE 4.16. DURATION OF TIME SINCE PATIENTS HAVE STARTED TAKING OACS AND ADHERENCE TO OACS 113

TABLE 4.17. PRESENCE OF CO-MORBIDITIES AND STATUS OF ADHERENCE TO OACS 113

TABLE 4.18. OUTCOME OF CHI SQUARE RESULTS FOR RELATIONSHIPS BETWEEN ADHERENCE TO OACS AND PATIENTS' CHARACTERISTICS. 114

TABLE 4.19. AWARENESS OF PARTICIPANTS ABOUT INDICATIONS FOR TAKING OACS 114

TABLE 4.20. RESPONSES TO THE QUESTION: DO YOU KNOW YOUR INR TARGET? (FOR WARFARIN USERS ONLY) 115

TABLE 4.21. RESPONSES OF PARTICIPANTS TO THE QUESTION HOW YOU TAKE OACS? 115

TABLE 4.22. RESPONSES TO THE QUESTION: HOW OFTEN DO YOU MISS A DOSE OF YOUR OAC? 116

TABLE 4.23. RESPONSES TO THE QUESTION: DO YOU HAVE ANY REASON FOR NOT TAKING YOUR ORAL ANTICOAGULANT? 117

TABLE 4.24. RESPONSES OF PATIENTS TO THE QUESTION: DO YOU THINK YOU ARE GETTING THERAPEUTIC BENEFITS FROM ORAL ANTICOAGULANT? 117

TABLE 4.25. RESPONSES OF PATIENTS TO THE QUESTION: DO YOU THINK ANY OF THE REPORTED BARRIERS, IF ANY, AFFECT YOUR BELIEFS ABOUT YOUR ORAL ANTICOAGULANTS? 118

TABLE 4.26. AWARENESS OF PATIENTS ABOUT INDICATIONS FOR TAKING OACS 119

TABLE 4.27. AWARENESS ABOUT INR TARGET AMONG WARFARIN USERS 119

TABLE 4.28. PATIENTS FOLLOWING OF PRESCRIBERS' ADVICE ON HOW TO TAKE OACS 120

TABLE 4.29. HOW OFTEN PARTICIPANTS MISS DOSES OF OACS 121

TABLE 4.30. REPORTED REASONS FOR NON-ADHERENCE AS REPORTED BY PARTICIPANTS 121

TABLE 4.31. PATIENTS VIEWS ON THERAPEUTIC BENEFITS OF OACS 122

TABLE 4.32. PATIENTS' PERCEPTIONS ON THERAPEUTIC BENEFIT AND ADHERENCE TO OACS 122

TABLE 4.33. OUTCOME OF CHI-SQUARE ANALYSIS OF RELATIONSHIPS BETWEEN ADHERENCE TO OACS AND PATIENTS EXPERIENCE WITH OACS. 123

TABLE 4.34. OUTCOME OF BINARY LOGISTIC REGRESSION FOR PREDICTING FACTORS OF ADHERENCE TO OACS AMONG PARTICIPANTS 124

TABLE.5.1. CHARACTERISTICS OF HCPS WHO PARTICIPATED IN THE QUALITATIVE INTERVIEWS 137

TABLE 5.2. THEMES AND SUBTHEMES PRODUCED FROM ANALYSING THE HCPS INTERVIEWS USING THEMATIC ANALYSIS. 138

List of figures

Figure 1.1. Summary of NICE (NG196) for management of AF (Perry et al., 2021).....7

Figure 1.2. ESC guidelines for the diagnosis and management of atrial fibrillation (Hindricks et al., 2021) 8

Figure 1.3. ACC/AHA guidelines for management of AF (January et al., 2019).....9

Figure 1.4. Trends of use of OACs in England between 2009 and 2019 (Afzal et al., 2021).....19

Figure 1.5. Reported serious ADRs for prescribed OACs between 2009-2019 (Afzal et al., 2021) 20

Figure 1.6. Differences between compliance and persistence (Cramer et al., 2008).....21

Fig. 3.1. Consort diagram for selection of studies.....70

Figure 5.1. Identified factors which influence prescribing of OACs as perceived by HCPs 143

Abbreviations

8-MMAS	**8-item Morisky Medication Adherence Scale**
ABC	**AF Better Care**
ACC	**American College of Cardiology**
ACTS	**Anti-Clot Treatment Scale**
ADRs	**Adverse drug Reactions**
AF	**Atrial Fibrillation**
AHA	**American Heart Association,**
AXIS	**Appraisal Tool for Cross-Sectional Studies**
BMQ	**Brief Medication Questionnaire**
CAD	**Coronary Artery Disease**
DASS	**Duke Anticoagulation Satisfaction Scale**
DM	**Diabetes Mellitus**
DOACs	**Direct oral anticoagulants**
DVT	**Deep Vein Thrombosis**
ECG	**Electro Cardio Gram**
ESC	**European Society of Cardiology**
GBD	**Global Burden of Disease Study**
HCPs	**Health Care Professionals**

HDI	**Human Development Index**
IHD	**Ischaemic Heart Disease**
INR	**International Normalised Ratio**
ISPOR	**Pharmacoeconomics and Outcomes Research**
JBI	**Joanna Briggs Institute**
LVEF	**Left Ventricle Ejection Fraction**
MAQ	**Medication Adherence Questionnaire**
MARS	**Medication Adherence Report Scale**
MEMS	**Medication Events Monitoring System**
MHRA	**Medicines and Healthcare Products Regulatory Agency**
NHS BSA	**National Health services Business Services Authority**
NICE	**National Institute for Health and Care Excellence**
NVAF	**Non-valvular Atrial Fibrillation**
NYHA	**New York Heart Association**
OACs	**Oral Anti Coagulants**
PE	**Pulmonary Embolism**
PSCC	**Prince Sultan Cardiac Centre**
RCTs	**Randomised Controlled Trials**

SEAMS	**Self Efficacy for Appropriate Medication use Scale**
TIA	**Transient Ischaemic Attack**
TTR	**Time in Therapeutic Range**
UN	**United Nations organisation**
VKA	**Vitamin K Antagonists**
VKOR	**Vitamin K Epoxide Reductase**
VTE	**Venous Thrombo Embolism**
WHO	**World Health Organisation**

Structure of this thesis

The findings from this DPharm thesis are presented over a series of chapters, describing the research activities.

Chapter One serves as background information on adherence to medications with focus on medical conditions for which OACs are prescribed, importance of adherence to OACs, methods used to measure adherence to OACs. This chapter then describes primary prevention of AF and VTE using OACs. It also provides overall aims, objectives and the structure of this thesis.

Chapter Two describes the theoretical and methodological approaches used in the thesis. This chapter also gives the justification of research design and implemented research methods in this thesis. Finally, this chapter discusses the techniques used to increase reliability and validity, as well as the ethical considerations in this research.

Chapter Three presents a systematic review of adherence to OACs in the Middle East and effects of the patients' related factors on adherence to these medications.

Chapter Four presents a cross-sectional study in Eastern Saudi Arabia evaluating adherence to OACs and assessing the patients' perspective on taking OACs and their views on adherence to OACs.

Chapter Five presents the second study which used a qualitative approach and interviews with HCPs in Eastern Saudi Arabia to explore adherence to OACs from practitioners' point of view, explore the pharmacists' role in supporting patients particularly OACs' users, and the role of facilitators and barriers faced by healthcare practitioners when providing care for OACs' users.

Chapter Six concludes the thesis by discussing overall findings of the research. This chapter integrates the key findings from all studies and highlights implications for practice and policy in relation to improving patients' adherence to OACs in Eastern Saudi Arabia. The chapter also

reports overall key strengths and limitations of this work as well as suggests areas for further research.

Thesis structure	Title
Chapter I	Introduction and research aims and objectives
Chapter II	Methodology
Chapter III	Systematic review of assessment of adherence to oral anticoagulants and patients' related factors among AF patients in the Middle East
Chapter IV (Study one)	Assessment of adherence to OACs in Eastern Saudi Arabia: A cross-sectional study
Chapter V (Study two)	Exploring views of health care professionals on adherence to oral anticoagulants in Eastern Saudi Arabia: A semi-structured qualitative study
Chapter VI	Overall discussion

CHAPTER ONE: INTRODUCTION

1. 1. Background

The Global Burden of Disease Study 2021 (GBD, 2021) revealed that ischaemic heart disease (IHD) and stroke collectively caused one in four deaths worldwide. IHD impacts people of all backgrounds around the globe, irrespective of the healthcare quality in their respective countries. (Bull et al., 2020). However, individuals who live in developing countries are at higher risk of these conditions compared to the population of the developed countries. This is due to the lack of appropriate health services, which are necessary to reduce the impact of IHD and stroke conditions on patients' quality of life as it undermines their ability to be productive and limits their capabilities to support themselves and their families (Mathers et al., 2005). The Middle East area is considered as part of the developing world, which includes countries with high levels of illiteracy, elevated prevalence of communicable and non-communicable diseases, mixed socio-economic levels, and variable demographic backgrounds (GBD, 2021). Recently, some parts of this region suffered a deterioration in the provision of health services following civil wars in countries such as Iraq, Syria, and Yemen. Yet the Middle East area also includes countries which are classified as some of the richest countries due to the high-income revenues generated from the exportation of oil, metals, and gas (World Bank, 2014), placing these countries in the forefront in the challenge of improving the quality of the health services in the region. Some countries are implementing ambitious plans to enhance the excellence of the offered medical care. For example, Kingdom of Saudi Arabia is the biggest world reservoir of oil which represents the main source of income in the country (World Bank, 2014). In this country, IHD and stroke are responsible for 40.2% of the total deaths according to the GBD 2019. Such rate of death can be reduced as conditions such as IHD, and stroke are preventable if appropriate treatment approaches are implemented (GBD, 2019, Shankari et al., 2020).

1.2. Atrial fibrillation

Atrial fibrillation (AF) is a long-standing disorder that can seriously affect a patient's quality of life and costs healthcare systems annually (Markides and Schilling, 2003). In 2020 the cost of hospitalisation related to AF in the UK was estimated between 2269 and 4030 million pound (Burdett and Lip, 2022). The condition is a risk factor for developing stroke and other embolic phenomena, leading to life threatening and significant disability (Olesen et al., 2011; Lip et al., 2017). The aetiology of AF is frequently unclear, although it is believed to arise from difficulties with the electrical signals that manage the heart's rhythm. Ordinarily, the heart's electrical impulses commence in the sinoatrial (SA) node, a small bundle of cells situated in the right atrium. From there, the impulses course through a sequence of specialised cells designated as the atrioventricular (AV) node, subsequently progressing into the ventricles - the lower chambers of the heart - inducing them to contract and propel blood through the body (Lip et al., 2017). In the case of AF, the electrical impulses in the atria become disordered, causing the atria to quiver instead of contracting in a synchronised fashion. This can give rise to an erratic and frequently accelerated heartbeat, resulting in symptoms like palpitations, shortness of breath, tiredness, wooziness, and chest discomfort (Amin et al., 2016).

AF is usually associated with advanced age, elevated blood pressure, underlying cardiac and respiratory diseases, and congenital heart disease. The disease is classified, based on the duration of irregular heartbeats, as paroxysmal (< 7 days), persistent (> 7days), long standing persistent (> 12 month), and permanent AF (Peters and Woodward, 2019).

The main objective for treatment of AF is to restore haemodynamic stability to reduce the risk of clotting, and subsequently the risk of stroke (Chao et al., 2018; McManus et al., 2012). Cardioversion (restoring the normal rhythm) is the first option for treatment of AF. If this strategy is unsuccessful, then use of pharmacological agents is appropriate. OACs are the mainstay for reducing the risk of thrombosis because of AF (Amin et al., 2016). Moreover, beta blockers or calcium channel blockers can be used to control the heart rate when there is

evidence of rapid ventricular response (Gelder, et al., 2015). In addition, digoxin can be used as a second line, although this is less common due to its known adverse effects (Kotecha et al., 2020). Amiodarone is another available therapy for AF patients for rhythm control (Siddoway et al., 2003).

Risk of stroke should be stratified for AF patients using the CHADs-2-Vasc score before starting OACs. In this formula: heart failure scores 1 point, hypertension scores 1 point, age more than 75 scores 2 points, diabetes mellitus scores 1 point, history of stroke scores 1 point, transient ischemic attack scores 2 points, peripheral vascular disease scores 1 point, age 65-74 scores 1 point, and female sex scores 1 point. The CHADS2-Vasc score is widely used by clinicians to guide anticoagulant therapy decisions for patients with AF. Generally, patients with a score of 2 or higher are at moderate to high risk of stroke and should receive anticoagulant therapy, while those with a score of 0 or 1 are at low risk and may not require anticoagulant therapy. The score has been validated in numerous studies and is recommended by international guidelines for the management of AF (Lane et al., 2012; McManus et al., 2012). Recently, the ORBIT Score has been developed. It is being used to evaluates the likelihood of significant bleeding in individuals who are taking anticoagulants for AF. ORBIT score has superseded the HAS-BLED calculator in determining the risk because research has demonstrated that it has a superior accuracy in forecasting the absolute bleeding risk compared to other bleeding risk tools. ORBIT score applies equally to male and female patients without any preference for a specific gender in the scoring system. The components of the score consist of sex (1 point), haemoglobin levels below 12g/dl (2 points), age over 74 years (1 point), history of bleeding (2 points), Glomerular Filtration Rate (GFR) less than 60 mL/min/1.73 m2 (1 point), and treatment with antiplatelet agents (1 point). Patients who score 2 points or less are deemed to be low risk, those who score 3 points are considered moderate risk, while those who score 4 points or higher are classified as high risk for bleeding (O'Brien et al., 2015).

1.3. Guidelines for using OACs in AF patients

Guidelines for treatment of AF provide general recommendations for the management of the condition on evidence-based principles. Several guidelines are available for management of patients who suffer AF such as NICE guidelines (NG 196) for AF: diagnosis and management, the European Society of Cardiology (ESC) Guidelines for the diagnosis and management of AF, and the American Heart Association, American College of Cardiology (AHA/ACC) guideline for the management of patients with AF.

The NICE guidelines suggest that individuals diagnosed with AF who are at high risk of stroke should be offered anticoagulation using OACs, with DOACs being the preferred first option and vitamin K antagonists (VKA) as a secondary option. However, the guidelines also consider the risk of bleeding when making this recommendation. The NICE guidance also advise use of the CHA2DS2-VASc score, which is more comprehensive as it considers a wider range of risk factors, including gender and vascular disease, compared to the simpler CHADS2-Vasc scoring system to assess the risk of stroke. NICE guidelines also recommend use of ORBIT bleeding risk score for predicting the probability of bleeding for AF patients. If the treatment with OACs is not successful or it was not tolerated by patients, the NICE guidance suggests use of radio frequency point by point ablation. Figure 1 summarises the NICE NG196 guidance for management of patients with AF. In addition, the 2020 ESC guidelines for the diagnosis and management of atrial fibrillation provide recommendations on diagnosis and management of AF (Hindricks et al., 2021). In addition to this guidance, the ESC published quality indicators to improve quality of care for AF patients. For diagnosis of AF, the ESC guidelines emphasise use of 12-lead ECG tracing or rhythm strip showing a typical AF pattern for more than 30 seconds.

Regarding the treatment of AF, the ESC guidelines established the AF Better Care (ABC) pathway, which can be interpreted as follows: A: Avoid stroke with use of anticoagulants. B:

Better symptom management through patient-centred and symptom-directed decisions on rate or rhythm control. C: Comorbidity and cardiovascular risk factors management, including lifestyle improvements. Figure 2 summarises the 2020 ESC guidelines for the diagnosis and management of atrial fibrillation (Hindricks et al., 2021).

ACC guidelines for management of AF recommend use of OACs therapy for AF patients to minimise the risk of stroke. To calculate the risk of stroke among AF patients, the guidelines recommend use CHA2DS2-VASc score calculator. Scores of ≥2 in men or ≥3 in women warrant prescribing OACs for the AF patients. The guidance advises that patients at low risk should not prescribed OACs. In high-risk patients for thrombo-embolic events, the 2019 ACC guidelines recommend long-term anticoagulation therapy after cardioversion based on the CHA2DS2-VASc score. OACs therapy can be excluded in patients with low risk of thromboembolism and a definite AF duration ≤48 h. Figure 1.3 summarises the ACC/AHA guidelines for management of AF.

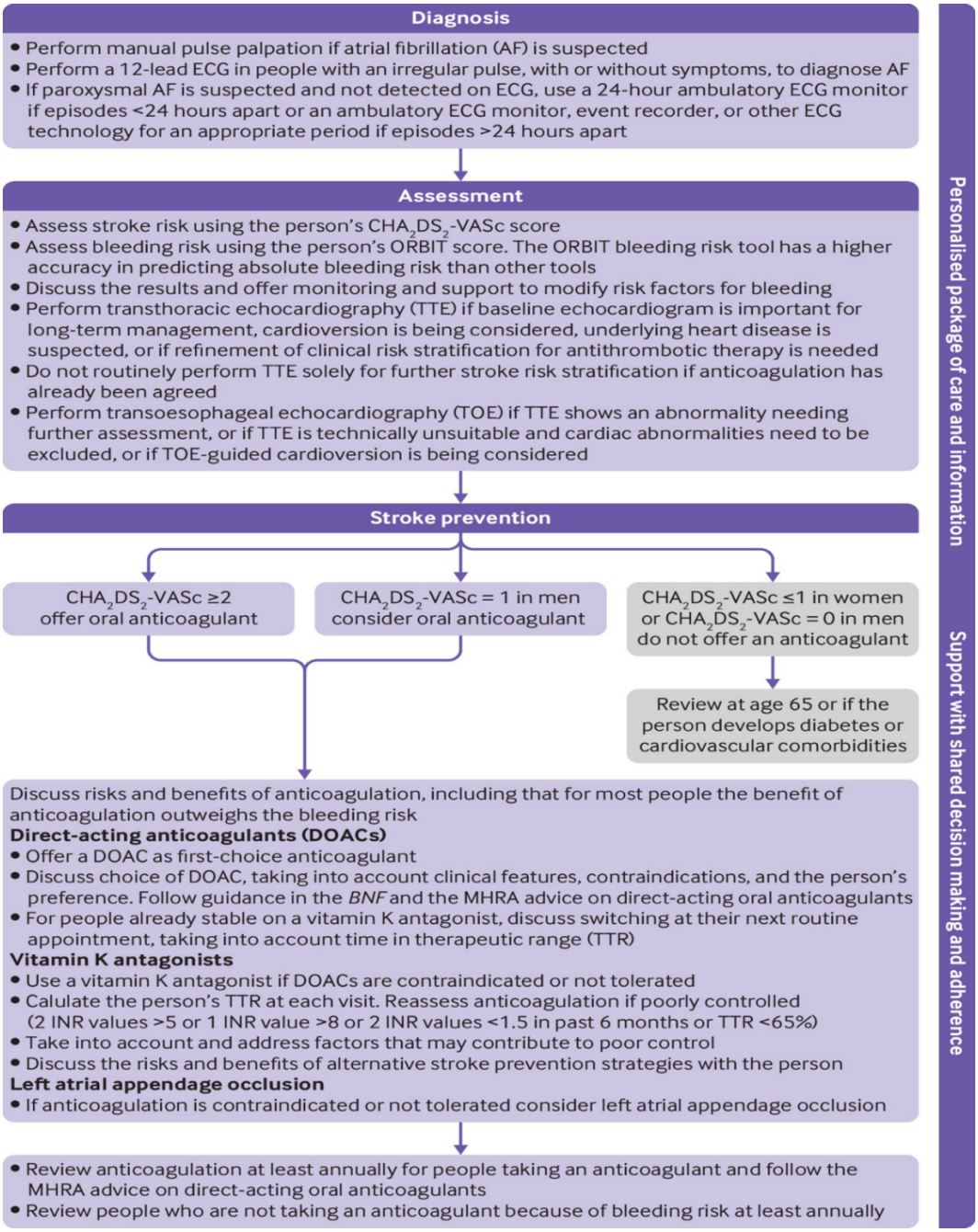

Figure 1.1. Summary of NICE (NG196) for management of AF (Perry et al., 2021).

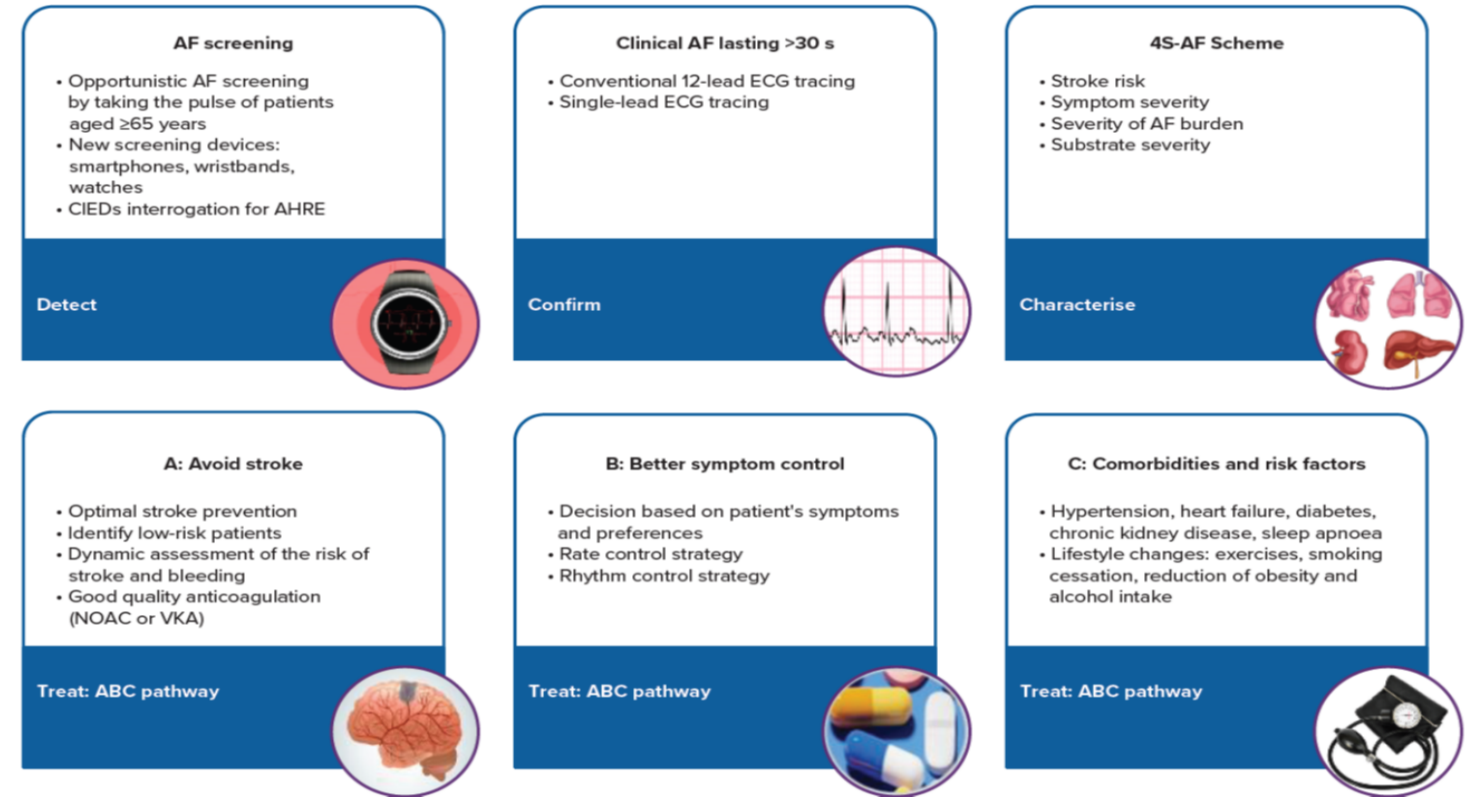

Figure 1.2. ESC guidelines for the diagnosis and management of atrial fibrillation (Hindricks et al., 2021)

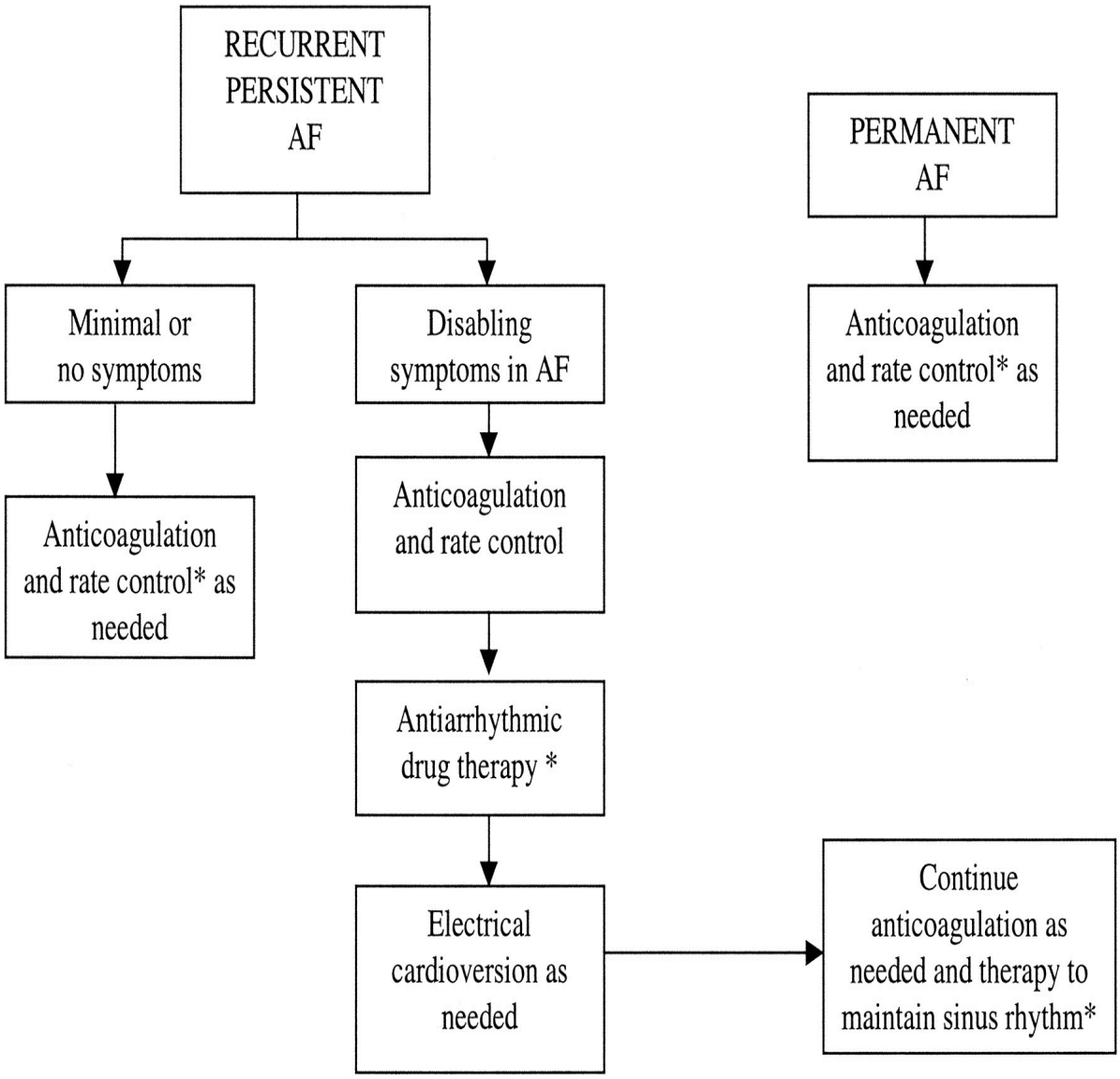

Figure 1.3. ACC/AHA guidelines for management of AF (January et al., 2019)

In 2014, the Saudi Centre for Evidence Based Health Care and McMaster University Clinical Practice Guidelines issued "clinical practice guideline on antithrombotic treatment of patients with non-valvular Atrial Fibrillation". This guidance represents the cornerstone for medical practice to manage AF in Saudi Arabia. The guidance recommends that anticoagulation should not be offered to patients who are at low risk of stroke. For patients with non-valvular atrial fibrillation at intermediate risk of stroke (e.g., CHADS2 score = 1), the guideline recommends oral anticoagulation rather than no antithrombotic therapy or aspirin. The guidance also advises that DOACs should be prescribed as first line therapy and VKA are the alternative in case of DOACs are contra indicated or not tolerated. The Saudi guidelines contains evidence that is shared by other guidelines such as NICE, ESC, and ACC. Table 1.1. compare the NICE, ESC, and AHA guidelines for treatment of AF.

Table.1.1. Comparison of the NICE, ESC, and AHA guidelines for treatment of AF.

	Nice Guidelines 196 for AF	***European Guidelines for AF***	***American Guidelines for AF***
Year	2021	2020	2019
Definition of AF	AF is a supraventricular arrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function.	AF is a supraventricular arrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function.	AF is a supraventricular arrhythmia characterized by uncoordinated atrial activation with consequent deterioration of atrial mechanical function.
Classification of AF	Classification based on symptom severity and duration, comorbidities, and risk of thromboembolism (CHA2DS2-VASc score).	Classification based on symptom severity and duration, comorbidities, and risk of thromboembolism (CHA2DS2-VASc score).	Classification based on symptom severity and duration, comorbidities, and risk of thromboembolism (CHA2DS2-VASc score).
Screening for AF	Opportunistic screening	Opportunistic screening	Not recommended for routine screening
Assessment of stroke risk	CHA2DS2-VASc score/ORBIT Score	CHA2DS2-VASc score	CHA2DS2-VASc score
Assessment of bleeding risk	HAS-BLED score/ORBIT score	HAS-BLED score/ORBIT score	Bleeding risk should be assessed
Antithrombotic therapy	Anticoagulation therapy with DOACs or warfarin	Anticoagulation therapy with DOACs or warfarin	Anticoagulation therapy with DOACs or warfarin

	is recommended for patients with a CHA2DS2-VASc score of 2 or greater.	is recommended for patients with a CHA2DS2-VASc score of 2 or greater.	is recommended for patients with a CHA2DS2-VASc score of 2 or greater.
Cardioversion	Electrical or pharmacological cardioversion is recommended in patients with recent onset of AF	Electrical or pharmacological cardioversion is recommended in patients with recent onset of AF	Electrical or pharmacological cardioversion is recommended in patients with recent onset of AF
Rate control strategy	Beta-blockers, calcium channel blockers, or digoxin are recommended for rate control.	Beta-blockers, calcium channel blockers, or digoxin are recommended for rate control.	Beta-blockers, calcium channel blockers, or digoxin are recommended for rate control.
Rhythm control strategy	Rhythm control with antiarrhythmic drugs or catheter ablation is recommended for selected patients.	Rhythm control with antiarrhythmic drugs or catheter ablation is recommended for selected patients.	Rhythm control with antiarrhythmic drugs or catheter ablation is recommended for selected patients.
Follow-up	Regular follow-up is recommended to assess symptom control, adverse effects of treatment, and stroke risk.	Regular follow-up is recommended to assess symptom control, adverse effects of treatment, and stroke risk.	Regular follow-up is recommended to assess symptom control, adverse effects of treatment, and stroke risk.

1.4. Venous Thromboembolism

The term venous thromboembolism (VTE) is used to describe blood clots that can travel through the blood stream to reach other blood vessels, usually veins, to cause blockage (Schmaier et al., 2018). It can be divided in two conditions namely deep vein thrombosis (DVT) and pulmonary embolism (PE) (Zhang et al., 2018). Worldwide, VTE is the third most common cause of death from cardiovascular disease after heart attacks and stroke (Seifi et al., 2018). Thrombosis UK reports that blood clots are a factor in one in four deaths, and that the majority of VTE cases (55-60%) occur either during or after hospitalisation. The organisation also notes that VTE is the primary cause of preventable deaths in hospital settings (Wendleboe and Raskob, 2016).

1.4.1. Deep vein thrombosis

A deep vein thrombosis (DVT) is a blood clot, which may occur within the deep veins, it usually happens, but not is restricted to, the proximal and distal veins of the legs (Naringrekar et al., 2019). DVT can also be detected in the veins of the arms as well as the mesenteric and cerebral veins. According to Nuffield trust report (2019) on rates of VTE risk assessment and deaths from VTE-related events after discharge from hospitals, in the UK the incidence of DVT in 2019 was 215 per 100,000 hospital discharges (Appleby et al., 2020). In other parts of Europe for example in Germany, the Nuffield trust report (2019) documented that the above rate was much higher, reaching 329 per 100,000 hospital discharges in 2019. Portugal reported the lowest DVT rate with only 16 cases per 100,000 hospital discharges in 2020.Published data from Western Saudi Arabia reported that hospital acquired DVT occurred in 10-40% surgical and medical patients (Essam et al., 2011).

DVT usually affects people who are more than 40 years old. The condition is not a sex specific and can happens in both males and females. DVT is more common in patients who suffer from malignant conditions, congestive heart failure, obstructive airway disease, and patients undergoing surgery (Zhang et al., 2018). The aim of treatment of DVT is to prevent further complications such as pulmonary embolism, reduce risk of morbidity, and prevent or minimise the risk of developing post thrombotic syndrome (Parker and Thachil, 2018). The 2020 NICE guidelines recommend use of anticoagulants as first line treatment in provoked and unprovoked DVT (NICE, 2020). Low molecular weight heparin, fondaparinux, and warfarin are among the medications that are used for treatment of DVT. The duration of treatment for DVT condition is usually between 3 and 6 months, however, this time is extended to up to 12 months when the patients are prone to recurrent episodes (Hirsh, 2001). Direct Oral Anti Coagulants (DOACs) are approved for prophylaxis of DVT (Kruger et al., 2019).

1.4.2. Pulmonary embolism

Pulmonary embolism (PE) describes disruption of blood flow in the pulmonary artery and arterioles as a result of a migrating thrombus. Arriving from other organs through the blood flow, the thrombus enters the pulmonary circulation and causes blockage (Goldhaber et al., 1997). PE and DVT are similar in origins, with PE in most cases is originated from DVTs in the lower extremities. Therefore, the risk factors for both conditions can be either genetic or acquired factors. The genetic factors mainly include thrombophilia, prothrombin gene mutation, protein C deficiency, protein S deficiency, and hyper homocysteine Mia (Gohil et al., 2009). The acquired factors include prolonged immobilisation (bed rest > 3 days, travel > 4 hours), recent orthopaedic surgery, malignancy, indwelling venous catheter, obesity, pregnancy, smoking, and use of oral contraceptive pills (Raskob et al., 2014). PE can be divided into two types: the first one is haemodynamically unstable PE in which the patient's systolic blood pressure drops > 40 mmhg from the baseline, consequently patients die from obstructive shock (severe right ventricular failure), the second type is the haemodynamically stable PE, which is characterised by mild hypotension that can be resolved by fluids therapy (Kucher et al., 2005). Parenteral anticoagulants such as, low molecular weight heparin (LMWH), fondaparinux, or unfractionated heparin (UFH) are the mainstay for treatment of PE. Oral anticoagulants VKA and DOACs are safe options for pharmacotherapy in PE (Meyer et al., 2014). Selection of anticoagulant agents depends on the type of PE and on patients' probability of the condition (low, intermediate, and high) using designated scores such as Wells' score, and Geneva score. These scores stratify the risk of developing PE among suspected patients. It has therapeutic value as it is used to identify patients who are candidates for anticoagulation therapy (Bertoletti, 2011; Silveira, 2015).

1.5. Oral anticoagulants

Oral anticoagulants are drugs utilised for the prevention of blood clot formation by hindering the clotting factors involved in the coagulation cascade. There are two primary categories of oral anticoagulants: VKA and DOACs (Zhang et al., 2021).

1.5.1. Vitamin K Antagonists (VKA)

Warfarin is the main VKA which has been in use for more than 60 years (Laupacis et al., 1995). It is the mainstay for treatment and prophylaxis of thrombosis in conditions such as DVT, PE, and stroke prevention in AF (Hirsh, 1992). It acts by inhibiting vitamin K epoxide reductase (VKOR), which is needed for the gamma-carboxylation of vitamin K-dependent factors (factors 2, 7, 9, 10, protein C and S) (Johnson et al., 2011). Use of warfarin as anticoagulant is maintained by evidence from Randomised Controlled Trials (RCTs). Six RCTs, five in primary prevention and one secondary prevention trial supported the use of warfarin as an anticoagulant treatment for thromboprophylaxis in AF patients (Hart et al., 2007; Lip and Lim, 2007). A meta-analysis of these trials revealed that adjusted-dose warfarin was associated with an overall 64% (95% CI, 49%-74%) reduction in the relative risk of stroke compared to placebo. Furthermore, all-cause mortality was significantly reduced (26%; 95% CI, 3%-43%) with adjusted dose warfarin compared to placebo or control (Hart et al., 2007). However, use of warfarin was correlated with a relatively small absolute increase in major extra cranial haemorrhage (≤0.3% per year) (Hart et al, 2007; Lip and Lim, 2007).

1.5.2. Direct Oral Anticoagulants (DOACs)

1.5.2.1. Dabigatran

Dabigatran etexilate is a reversible direct thrombin inhibitor. The drug is metabolised to its active ingredient dabigatran in the gastrointestinal tract (GIT) (Ageno, 2012). The drug is excreted through the kidneys, its half-life is 12 to 17 hours. The key characteristic of dabigatran

is that it doesn't necessitate ongoing monitoring for anticoagulation. In addition to its use in VTE, the medication was used in several randomised studies of AF (Connolly, 2009), acute coronary syndromes (Oldgren ,2011), and prevention of thrombosis following orthopaedic surgery (Eriksson, 2009), and in patients with mechanical heart valves (Van de Werf, 2012). Randomied Evaluation of Long-Term Anticoagulation Therapy (RE-LY) clinical trial was published in 2009. The trial enrolled 18113 patients with non-valvular AF (NVAF) and at least one of the risk factors i.e. previous stroke/transient ischaemic attack TIA, systemic embolism, left ventricle ejection fraction less than 40% LVEF, symptomatic heart failure, New York Heart Association NYHA Class >2, > 75 years, or age > 65 y and with one or more of diabetes mellitus (DM), coronary artery disease (CAD), and hypertension. The trial included 951 centres in 44 countries (Ezekowitz et al., 2009).

The RE-LY trial's primary outcome was as follows: systemic embolism was 1.53% per year in patients receiving 110 mg dabigatran, 1.11% per year in patients who were receiving 150 mg. It was 1.69% per year in patients receiving warfarin. The risk of haemorrhagic stroke was 0.38% per year with warfarin compared to 0.12% with 110 mg and 0.10% per year with 150 mg of dabigatran. Both doses of dabigatran were non-inferior to warfarin, moreover, dabigatran is related to a lower incidence of intracranial haemorrhage (compared with warfarin) (Conolly *et al*., 2009). While the findings did not reach statistical significance, Baetz (2008) observed that the utilisation of dabigatran in the atrial fibrillation (AF) studies was linked to a trend indicating a slightly increased incidence of myocardial infarction.

1.5.2.2. Rivaroxaban

Rivaroxaban is a reversible direct factor Xa inhibitor. The plasma half-life of the drug is estimated to be 8 to 10 hours (Spyropoulos, 2012). The recommended dosage of rivaroxaban for the initial treatment of acute PE is 15 mg twice daily for the first 21 days followed by 20 mg once daily for prevention of recurrence (NICE, 2012). The Rivaroxaban Once Daily Oral

Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) was published in 2011. This randomised double-blind clinical trial was in 1178 sites in 45 countries. The primary outcome for this trial was: stroke or systemic embolism 1.7% in rivaroxaban group compared to 2.2 % with warfarin. The rates of major bleeding were similar in both drugs. The major bleed in rivaroxaban was 3.6%, compared to 3.4% in warfarin (Patel *et al*., 2011). In patients with atrial fibrillation, compared with warfarin an increased risk of all-cause mortality was observed in patients taking rivaroxaban. In contrast, in patients without atrial fibrillation, compared with warfarin, rivaroxaban was associated with a decreased risk of intracranial bleeding (0.54, 0.35 to 0.82). Increased risk of all-cause mortality was observed in patients taking rivaroxaban (1.51, 1.38 to 1.66) (Vinogradova, 2018).

1.5.2.3. Apixaban

Apixaban is a selective factor Xa inhibitor. The plasma half-life of this drug is 8 to 15 hours for twice daily doses (Eriksson et al., 2009). The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial was a randomised, double-blind, international trial comparing apixaban 5mg twice daily with warfarin (INR 2.0-3.0) in over 18,000 patients (Granger et al., 2011). The results of this trial showed that the rate of stroke or systemic embolism was significantly lower with apixaban compared to with warfarin (1.27% vs. 1.60% per year, respectively). This outcome was mainly motivated by a reduction in haemorrhagic stroke (Granger et al., 2011). Moreover, apixaban also significantly reduced all-cause mortality compared to warfarin (3.52% vs. 3.94% per year, respectively) (Bahit et al., 2017). The outcomes of the ARISTOTLE also showed that apixaban was safer than warfarin as it significantly reduced the risk of major bleeding (2.13% vs. 3.09% per year, respectively) (Granger et al., 2011). In patients with AF, compared with warfarin, apixaban was linked with a decreased risk of major bleeding (adjusted hazard ratio 0.66, 95% confidence interval 0.54 to

0.79) and intracranial bleeding (0.40, 0.25 to 0.64). An increased risk of all-cause mortality was observed in patients taking lower doses of apixaban (1.27, 1.12 to 1.45). In patients taking apixaban for indications other than AF, compared with warfarin, apixaban was associated with a decreased risk of major bleeding (0.60, 0.46 to 0.79), any gastrointestinal bleeding (0.55, 0.37 to 0.83), and upper gastrointestinal bleeding (0.55, 0.36 to 0.83). Increased risk of all-cause mortality was observed in patients taking lower doses of apixaban (1.34, 1.13 to 1.58) (Vinogradova, 2018).

1.5.2.4. Edoxaban

Edoxaban is a reversible direct factor X inhibitor. Like other DOACs, edoxaban is indicated for reducing the risk of stroke and systemic embolism in non-valvular AF in individuals with at least one risk factor of the following: congestive heart failure, hypertension, aged 75 years and over, diabetes mellitus, previous stroke or transient ischaemic attack (NICE, 2021). The drug is also indicated for treatment of DVT and PE and for the prevention of recurrent DVT and PE in adults. The participants of the ENGAGE AF-TIMI 48 study (an event-driven, Phase 3, multi-centre, randomised, double-blind double-dummy parallel-group study) were randomised to either edoxaban 30 mg once daily treatment group, or edoxaban 60 mg once daily treatment group or warfarin. The primary efficacy endpoint was the composite of stroke and systemic embolism events. Secondary efficacy endpoints included: composite of stroke, systemic embolism events, and cardiovascular mortality; major adverse cardiovascular event, which is the composite of non-fatal myocardial infarction (MI), non-fatal stroke, non-fatal systemic embolism events and death due to cardiovascular cause or bleeding; composite of stroke, systemic embolism events, and all-cause mortality (Giugliano et al., 2013).

The median study medicinal product exposure for both the edoxaban 60 mg and 30 mg treatment groups was 2.5 years. The median study follow-up for both the edoxaban 60 mg and 30 mg treatment groups was 2.8 years. The median subject-year exposure was 15,471, and

15,840 for the 60 mg and 30 mg treatment groups, respectively; and the median subject-year follow-up was 19,191 and 19,216 for the 60 mg and 30 mg treatment groups, respectively. In the warfarin group, the median TTR (time in therapeutic range, INR 2.0 to 3.0) was 68.4%. The main analysis of efficacy was aimed to show the non-inferiority of edoxaban versus warfarin on first stroke or systemic embolism events that occurred during treatment or within 3 days from the last dose taken in the modified intention to treat (mITT) population. Both regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes (Giugliano et al., 2013).

1.6. Impact of introducing of DOACs in clinical practice

Data from NHS BSA (Business Services Authority) showed that in England, the introduction of DOACs resulted in a decrease in prescribing of warfarin between 2009 and 2019. The data also illustrated that in England, there was a significant decline in use of warfarin compared to its prescribing in 2015. In 2019, prescribing of DOACs was 61.8% of all recommended OACs. In addition, apixaban was the most prescribed OAC in 2019 (38.9% of all prescribed OACs) (Afzal et al., 2021). Figure 4 illustrates use of OACs in England between 2009 and 2019.

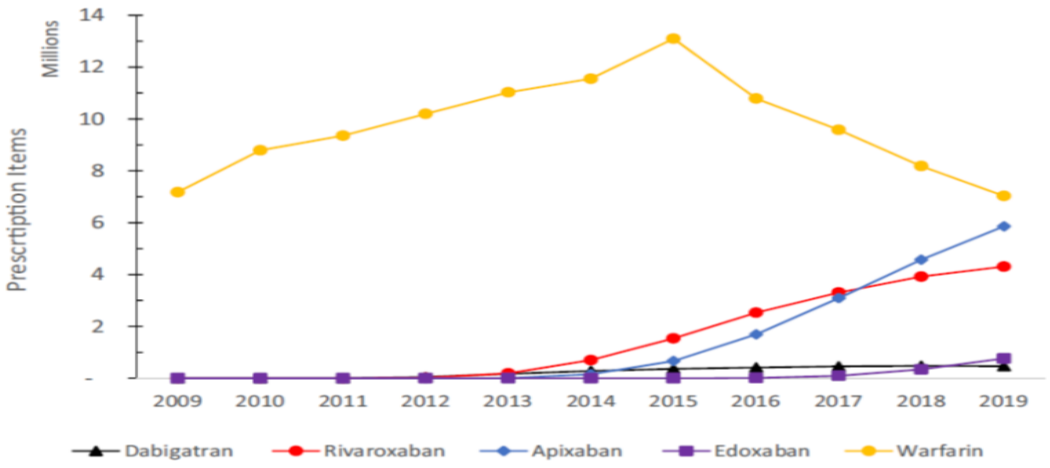

Figure 1.4. Trends of use of OACs in England between 2009 and 2019 (Afzal et al., 2021).

Regarding the reported side effects and Adverse Drug Reactions (ADRs) data from the Medicines and Healthcare Products Regulatory Agency (MHRA) between January 2009 and December 2019 showed that there were 643 events reported for apixaban and considered as serious ADRs. In the same year 2019, dabigatran had the least number of ADRs reports. The drug also showed a steady decline in the number of ADR reports from 2013 onwards, from 338 serious or fatal events reported in 2013 to 52 events reported in 2019 (Afzal et al., 2021). Figure 5 shows incidence of reported ADRs and side effects for OACs between 2009 and 2019.

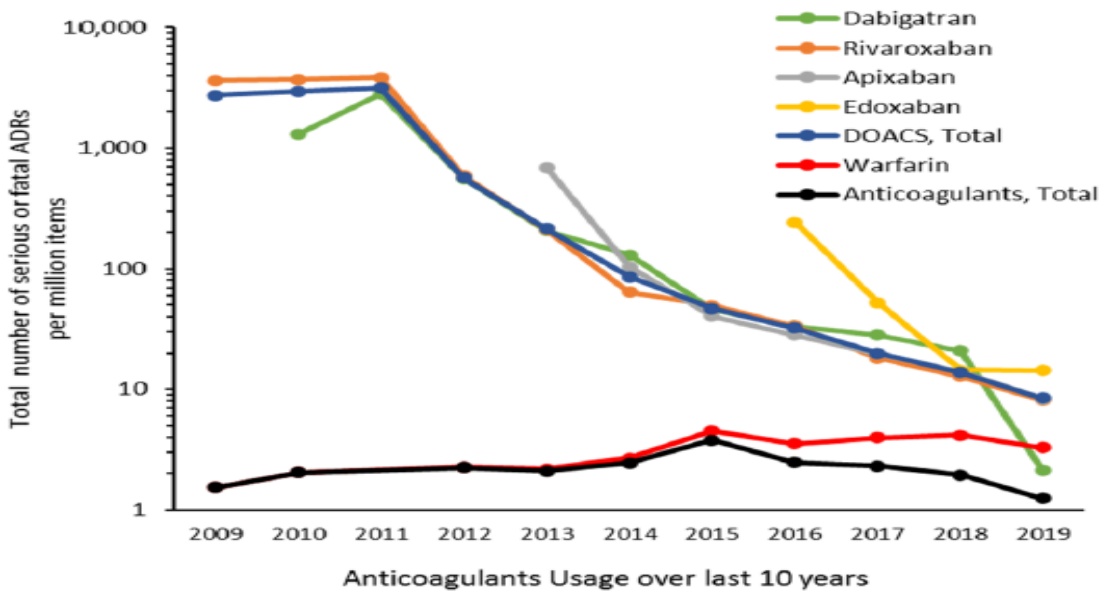

Figure 1.5. Reported serious ADRs for prescribed OACs between 2009-2019 (Afzal et al., 2021)

In the meta-analysis by Malik et al., (2019) of randomised controlled trials, which analysed the safety and effectiveness of DOACs and warfarin in older adults with AF, the results indicated that DOACs outperformed warfarin in terms of both efficacy and safety. The hazard ratio was 0.76 with 95% confidence intervals of 0.67 to 0.86 and a p-value of less than 0.01. The research findings also indicated that DOACs were similarly effective as warfarin in reducing the risk of stroke or systemic thromboembolism. Additionally, apixaban was found to be associated with the lowest risk of major bleeding compared to other DOACs. Dabigatran and apixaban were also linked to lower rates of intracranial haemorrhage compared to rivaroxaban or warfarin. Through the analysis of RCTs, it was observed that apixaban was the most favourable choice for both efficacy and safety in older patients with nonvalvular AF (Malik et al., 2019). It is worth noting that there is currently no published data available that compares the use of DOACs in the Middle East and Saudi Arabia regarding the same factors and timeframe.

1.7. Patients' compliance to medication regimens

In the literature, the term "compliance" has been used to describe the relationship between patients and their medication-taking behaviour. However, this concept primarily focuses on patients' behaviour without considering the various factors that may impact it. The study conducted by Haynes et al. (1976) was pioneering in its definition of compliance. They articulated compliance as the degree to which a patient's actions, such as adhering to medication regimens, dietary guidelines, or lifestyle modifications, align with the clinical recommendations. This concept has faced criticism for portraying a one-way relationship between HCPs and patients, where patients are merely passive recipients (Horne, 2006).

1.8. Patients' persistence with using medications

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group defined persistence as "the duration of time from initiation to discontinuation of therapy" (Cramer et al., 2008, P.1509). Figure 1.6. illustrates the differences between the two terms: compliance and persistence.

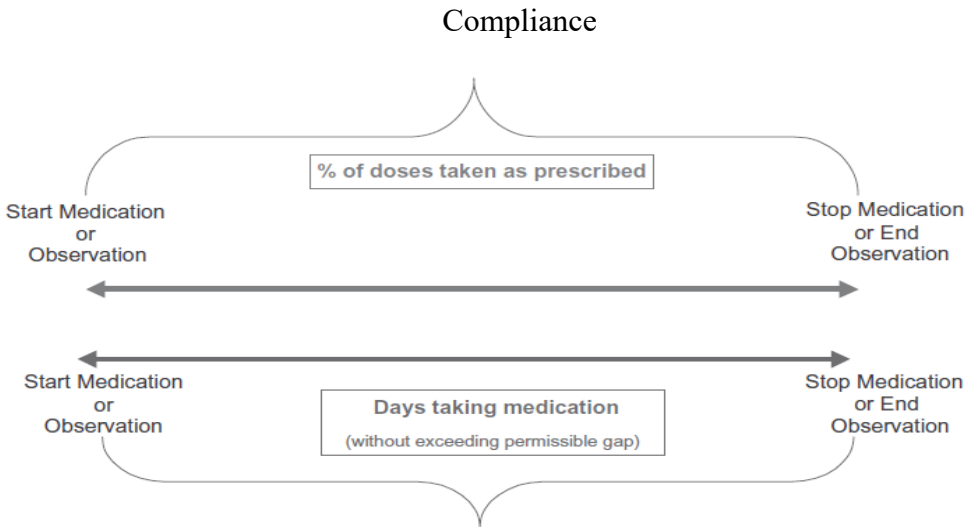

Figure 1.6. Differences between compliance and persistence (Cramer et al., 2008)

1.9. Patients' adherence to medication

The World Health Organisation (WHO) approved the following definition of adherence: "the extent to which a person's behaviour- taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider" (WHO, 2003, P.3). This description recognises the partnership between patients as users of medications and health care providers as supporters for patients to achieve the ultimate objectives either eradication or control of diseases (Garfield et al., 2011).

1.10. The influential factors that affect adherence to medications

Taking medication as prescribed is affected by several factors as described by the WHO, which identified five domains that influence adherence to medications. These factors are socioeconomic factors, factors associated with the health care team and to health system in place, disease-related factors, therapy-related factors, and patient-related factors (WHO, 2003). These factors were re-categorised into three domains: patient-related factors, physician-related factors, and health system/team building–related factors (Brown and Bussell, 2011).

1.10.1. Patients related factors

Patients related factors include, health literacy, patients' education, patients' health beliefs and attitudes towards medications, and economic status of patients. Health literacy which is defined as patients' ability to obtain, process, communicate and understand basic health information and services needed to make appropriate health decisions (Baker, 2006). Low health literacy is significantly associated with poor health outcomes such as low adherence to medications, suboptimal use of medical services, delays in diagnoses, higher rates of hospitalisation, and increased risk of mortality among adults (Gazmararian et al., 2003). Increasing patients' health literacy empowers patients, as providing patients with sufficient information and clear explanation of their conditions and their role in the management of their diseases makes them

able to play their role in the plans to manage these conditions. Consequently, they will be more adherent to their medications (von Wagner et al., 2009).

Improving patients' education is a key to improving adherence to medications (Balamurugan et al, 2006). Patients' education should be effective, personalised, and conducted in a various range of methods and settings (Schillinger et al., 2003). Roumie et al., (2006) reported that education of both physicians and patients compared to educating only physicians improved the outcomes among hypertension patients and resulted in better control of blood pressure. The patient's health beliefs and attitudes regarding the benefits of the treatment, their previous experiences with pharmacotherapeutic agents, and lack of motivation are also important patients' related factor that affects the extent of medication adherence (Gatti et al., 2009).

1.10.2. Physicians related factors

These factors can include insufficient explanation of advantages and disadvantages (for example side effects) of using the medications, prescribing complex drug regimens which can be difficult to obtain and follow, and underestimation of the impact of the financial element of the cost of treatment on the patients (Kripalani et al., 2007). Another physicians' related factor is the communication between physicians on different care levels (primary and secondary) (Steiner and Ernest, 2000).

1.10.3. Health Systems related factors

This group of factors is related to the infrastructure of the health systems through which health care is provided. Variations and complexity of health care systems can limit accessibility of patients to such organisations, in addition to that, it undermines the coordination of patients' health management between these variable systems (Gordon et al., 2007). Another element is the use of health information technology which facilitates sharing patients' information between health care providers in different levels of care. Lack of such technology can be a barrier for exchanging information (García-Pallarés et al., 2009).

Adherence to medication is complex, it is difficult to be evaluated based on a single factor or a group of factors, inclusion of all the affecting elements is necessary for reflecting a true picture on the status of medication taking behaviour of the patients (Stirratt et al., 2015).

1.11. Patients' non-adherence to medication

Non-adherence occurs when patients deviate from taking their prescribed medication as advised. Reasons for non-adherence can be divided to intentional and unintentional reasons (Wroe et al., 2002; Blaschke et al., 2012). It has been documented that about 50% of patients with chronic conditions such as hypertension and diabetes mellitus show some sorts of non-adherence to medications during the long-standing duration of taking prescribed medications to treat their conditions (De Geest and Sabaté, 2003). Non-adherence is a significant problem as it has severe outcomes on patients' health, it is also a big barrier towards achieving the maximum benefits of medications. Moreover, it increases the burden of treatment on health systems. Results of investigating the rationale behind non-adherence revealed that substantial numbers of patients do not get the expected benefits from their medications because of non-adherence (Sokol et al., 2005). It has also been shown that non-adherence to medications participates in poor clinical outcomes and increases morbidity and mortality (Roebuck et al., 2011).

1.11.1. Strategies to reduce patients' non-adherence to medications

There is a need to tackle non-adherence to medications particularly in developing countries as reports have indicated that about 50% of individuals who are taking medications for chronic conditions are classified as non-adherent (Naderi et al., 2012). Non-adherence is divided into intentional and unintentional non-adherence (WHO, 2003). This classification provides an approach for addressing the barriers for each category, hence, employing it to resolve the issues related to each type with the aim of increasing adherence to taking medications as prescribed.

Intentional non-adherence is characterised by the deliberate choice of patients to not take prescribed medications. Such behaviour reflects their attitudes and beliefs about medications. In addition, it highlights their concerns about the treated conditions (Horne et al., 1999). For instance, in 2014, Foster and colleagues successfully pinpointed factors connected to the utilisation of salbutamol inhalers among individuals with asthma (Foster et al., 2014). These factors included: hospital admission of patients, the chronicity of the condition, continuous need for the medication, patients' satisfaction with effectiveness of the treatment, and patients' beliefs about the safe use of the treatment. Such parameters can be used to predict the level of adherence to medications in patients with chronic conditions as other research reported similar findings (Osterberg, 2005; Morisky et al., 2008; Lehane and McCarthy, 2009). Additional predictors can include beliefs of friends and family, and patients concerns about the profile of adverse events for the prescribed medications (Lowres et al., 2019). These findings support the importance of patients own beliefs about medications on their adherence to medications. Subsequently, patient tailored interventions are a key for reducing intentional non-adherence to medications. Such interventions involve patients' education, shared decision making, and provision of multi-disciplinary support by team members such as pharmacists (Kuntz et al., 2014).

In contrast to intentional non-adherence, unintentional non-adherence occurs because of barriers that are beyond patients' ability such as cognitive impairment, intolerance of patients to cost of medications, language barriers that prevents patients from following directions of using medications, and complex nature of drug regimens (Sabaté et al., 2003). In order to reduce inadvertent barriers to adherence, it is necessary to identify these obstacles and implement patient-specific interventions to facilitate medication adherence. For example, generic prescribing lowers the cost of treatment, subsequently patients can afford high-cost medications and their adherence could improve (Sinnott et al., 2013).

1.12. Assessment of patients' adherence to medications

Measuring adherence is a challenging process mainly because of the absence of a clear definition of parameters for acceptable adherence. To perform a reliable measurement of adherence some factors should be considered in the tool. Such factors should be acceptable, consistent, and sensitive to change (Vermeire et al.,2001). Several methods are available to measure adherence, however, there is no favourite method for this purpose. Selection of a suitable method to measure adherence primarily depends on the personal characteristics which emphasises the goals of the intended study. The WHO classified the methods for measuring adherence into two main groups, subjective and objective methods (WHO, 2003).

1.13. Subjective methods for measuring adherence to medications

In these approaches, patients assess their own medication taking behaviour, or alternatively, healthcare professionals can assess it through patient involvement. The aim of such activity is to evaluate adherence of patients to their medications (Velligan et al., 2007). The disadvantages of these methods are under reporting of non-adherence as patients fear disapproval from their healthcare providers (Vik et al., 2004).

1.14. Objective methods for measuring adherence to medications

These methods use sources like pill counts, electronic monitoring, and secondary database analysis to measure adherence. Objective methods are favoured over subjective methods in some situations where healthcare practitioners were unable to obtain data about adherence and medication taking directly from patients or their carers (Vermeire et al., 2001; Velligan et al., 2007).

1.15. Direct methods for measuring adherence to medications

Some authors took a different approach to classify adherence methods. They classified these methods as direct and indirect approach (Ho et al., 2009; Jimmy and Jose, 2011). The direct

method classification is based on using drugs and its metabolites in the bodies of the subjects as quantitative markers for drug taking. Presence of these materials and observations from patients about their medication taking behaviour can give strong correspondence for adherence (Farmer, 1999). This method is characterised by high accuracy. However, disadvantages include their limitation on obtaining data. For example, it does not give data about reasons for non-adherence, it can only answer taking/not taking medication question. Another drawback is the cost and necessary expertise and training needed to perform the tests. Therefore, it is considered one of the expensive measures for assessing adherence (Vermeire et al., 2001). Metabolites of drugs can be quantified as in riboflavin; the quantities of these metabolites may vary because of inter individual metabolic variations such as in antipsychotics. Moreover, drug-drug interactions and drug-food interaction may give inconclusive results about medication taking behaviour. Another point about direct measurement of adherence is the bias expected in some circumstances especially when patients take their medications immediately before the expected tests, a behaviour which result in false estimation of adherence and known as white coat adherence (improved patient adherence to treatment around clinic visits) (Cramer et al., 1990; Jimmy and Jose, 2011; Modi et al., 2012).

1.16. Indirect methods for measuring adherence to medications

Indirect methods take the same approach of objective methods by utilising data obtained from sources such as pill counts and secondary database analysis to calculate adherence to medications using specific equations (Hess et al.,2006; Barner, 2010).

1.16.1. Pill count

This an indirect method for measuring adherence. In pill counting, the total number of dosage units taken between two scheduled visits (clinics) appointments is counted. Adherence of the patient ration is calculated by comparing taken dosage units with the total number of units

received by the patient (Farmer,1999; Vik et al.,2004). This method is simple and not expensive which makes it popular. However, the use of this method is limited by several factors. For example, Pro re nata (PRN) dosage forms are not feasible to assess. Moreover, it considers dispensing date as a denominator regardless the surplus of medications available to patient before dispensing date, consequently, it underestimates adherence (Vik et al., 2004).

1.16.2. Clinician assessments and self-reporting

This method is simple, cost effective, and gives real time feedback. It relies on structured interviews and real time feedback to obtain data about medication taking behaviour by patients. This method is undermined by several factors such as false input of data by respondents, miscommunication, and patients' psychological status about not taking medications. The most used are patient kept diaries and patients' interviews (Nguyen et al., 2014).

1.16.3. Patient kept diaries

This method for measuring adherence to medications documents how the patient follows their prescribed medications. A 30% increase in diary entries when compared with different methods like the Medication Events Monitoring System (MEMS) was reported (Farmer, 1999) reported. The author described self-reporting as an over estimating method when measuring adherence. The drawbacks of this method include loss of data if diaries are not returned by patient, higher levels of adherence can be calculated if false increase of data was entered. Therefore, these factors participate in making this method less reliable (Straka et al., 1997).

1.16.4. Patients interviews by clinicians

This is cost effective and easy to use method. In this method medication taking behaviour of patients is queried, particularly missed doses within specific period. In addition, questioning can be based on patients' knowledge about their prescribed medications such as names of the drugs, why they are taking these medications, and directions of use (Moral et al., 2015). The data acquired is subsequently employed by healthcare providers to assess patient adherence.

Nevertheless, according to (Vick et al., 2004), the proof supporting the connection between patients' understanding of their medications and their adherence is constrained.

1.16.5. Motivational interviews

Motivational interviews combine both of measuring adherence using classical interviews and the necessary interventions to tackle non-adherence to medications. It was described as a more effective approach than providing generic medication advice to patients (Rubak et al., 2005). Motivational interviews are considered a patient-centred method. Some authors consider them as means to assist patients in comprehending and making decisions to encourage non-adherent individuals to adhere to their medication regimens (Miller and Rollnick, 1991). Furthermore, motivational interviews have also been successfully applied in addressing substance abuse (Ekong and Kavookjian, 2016). The method is favoured by clinicians as it integrates measuring adherence and the necessary interventions to tackle non-adherence in a single tool. Motivational interviews can be used to improve adherence, however, the authors recommended further studies to clarify their benefit in this area (Palacio et al., 2016).

1.16.6. Questionnaires and scales

These methods use subjective principles to reduce limitations to self-reported methods. Moreover, the method considers variabilities within the studied population and conditions (Farmer, 1999). The disadvantage of these tools that sometimes they might be difficult for patients with low literacy levels due to the design of the questionnaires (Tan et al.,2014). Nguyen et al. (2014) identified three validated self-reporting adherence measuring scales. The authors categorised these tools into five groups that can be used to evaluate the following: limited to medication taking behaviour, limited to barriers to adherence, limited to beliefs associated with adherence to medications, barriers to adherence and beliefs related to adherence, and medication taking behaviour and barriers to adherence. This classification by the authors is based on certain definitions: medication taking behaviour: missing doses and

frequency of repeat dispensing of prescriptions. Barriers to adherence were defined as forgetfulness, disease related excuses, regime complexity, and side effects of prescribed medications. Beliefs associated with adherence include personal concerns on the medication safety and importance of following the directions.

The authors also agreed that a patient who takes 80% of the doses of the prescribed medications can be described as adherent while less than this percentage is classed as non-adherent. In other words, the authors established a cut off value for measuring adherence. Furthermore, some scales measure adherence by ranking the degree of adherence rather than using a cut off value, as in medication adherence questionnaire (MAQ), and the 8-item Morisky Medication Adherence Scale (8-MMAS) (Nguyen et al., 2014). Clinicians or researchers can do the interpretation of this ranking outcome. Currently, commonly used scales include those who consider medication taking behaviour, barriers to adherence, and beliefs associated with adherence. These tools include:

1.16.6.1. Brief Medication Questionnaire (BMQ)

The BMQ explores medication taking behaviour and barriers to adherence. It consists of three different screens which examines how patients took their medication in the past week, efficacy of drugs, and factors that may affect drug taking. It is characterised by its ability to allow self-taking medications, assess multiple drugs, and reduce clinicians training. The scale was validity of the scale was assessed in 20 patients using the Medication Events Monitoring System (MEMS). Results showed regimen and belief questions having 80–100% sensitivity and the recall questions having 90% sensitivity for non-adherence. (Svarstad et al., 1999).

1.16.6.2. Hill-Bone Compliance Scale (Hill-Bone)

Used to measure patients' medication taking behaviour and barriers to adherence. It was used with patients who are taking antihypertensive medications. The tool has 3 subscales namely medication taking behaviour, ability to keep appointments, and sodium intake. The scale is

rated on a 4 point Likert type scale. Fourteen item (validated for urban black ethnicity) and 9-item (validated for community dwelling populations) tests are available (Lavsa et al., 2011). The validation process demonstrated sensible internal consistency (item-total correlations all >.31, and a standardised Cronbach alpha of 0.79), with an average inter item correlation of .26. In addition, the modified scale had significant predictive validity in that noncompliance predicted higher diastolic blood pressures (p=.21, P<.05) and medication noncompliance tended to predict higher systolic blood pressures (p=.20, P<.06) (Labert et al., 2006).

1.16.6.3. Eight-item Morisky Medication Adherence Scale (MMAS-8)

This scale was developed by Morisky et al., 2008. It consists of 8 items closed questions (yes/no response) and the last item is a 5 point Likert response. The rest of the items concentrate on medication taking behaviour, particularly under use therefore barriers can be identified (Tan et al., 2014). The scale is characterised by 93% sensitivity and 53% specificity when validated, moreover, validation of the scale showed that the item-total correlations were >0.30 for each of the 8 items composing the scale. The internal consistency (Cronbach's alpha reliability) was 0.83 (Morisky et al., 2008). MMAS-8 has significant high popularity when a self-reported method is needed to measure adherence.

1.16.6.4. Medication adherence questionnaire (MAQ)

Also known as 4-item Morisky medication adherence scale 4-MMAS (Tan et al.,2014). The scale has advantage that it is quick to distribute and score and it also can identify barriers to adherence. MMAS-4 is widely used in research purposes as it was validated among low literacy patients and in wide range of diseases. However, psychometric properties of MMAS-4 are poor compared to MMAS-8. The sensitivity and specificity for MMAS-4 were 81% and 44% respectively and the Cronbach's alpha reliability was 0.61 (Morisky et al., 1986). Consequently, the MMAS-8 is more popular.

1.16.6.5. Self-efficacy for appropriate medication uses scale (SEAMS)

This scale consists of 13-item, 3- point Likert type scale for using on self efficacy in management of chronic conditions when measuring barriers to adherence. It is characterised by its lengthy content which make it impractical to conduct during care. Psychometric properties for this scale were assessed among 436 participants with CHD and other comorbid conditions. Reliability was assessed through internal consistency reliability and test-retest reliability. The scale had good internal consistency reliability (Cronbach's α 0.89) (Risser, Jacob and Kripalani, 2007; Lavsa et al., 2011).

1.16.6.6. Medication adherence report scale (MARS)

This self-reporting scale was developed by UK researchers (Horne and Weinman, 1999). The Medication Adherence Report Scale-10 (MARS-10) consists of 10 items that are used to assess both intentional and non-intentional behaviour. The questionnaire was successful in assessing non-adherence to medications in several chronic conditions (Horne and Weinman, 2002). MARS-10 was validated among asthma patients who use inhaled corticosteroid. Participants were from Hispanic, black, and white backgrounds. The scale showed good internal consistency among white and Hispanic background (Cronbach 0.85 and 0.86, respectively) and good test-retest reliability (r 0.65, P.001) (Cohen et al., 2009). A shorter version of this scale is also available, the MARS-5 contains 5 common patterns of non-adherent behaviour that patients score on a 5-point Likert scale (1 = always, 2 = often, 3 = sometimes, 4 =rarely, and 5 = never). Validation of the MARS-5 demonstrated acceptable reliability (internal and test-retest) and validity (criterion-related and construct validity). Internal reliability (Cronbach's α) ranged from 0.67 to 0.89 and test-retest reliability (Pearson's *r*) was 0.97 (Chan et al., 2020). Some studies described the MARS-5 scale as to have a low sensitivity and specificity, when compared to other self-reporting methods such as medication refill adherence (MRA).

Therefore, the MARS-5 scale can be mistaken in identifying non-adherent patients as it tends to overestimate patients' adherence (Van DeSteeg et al., 2009; Tommelein et al., 2014).

After going through the above mentioned commonly used methods and tools for measuring adherence it is clear there is no single tool that meets all the requirements for measuring adherence as every mentioned method has its pros and cons. Self-reported questionnaire style with a reasonable predictive power is more useful in a busy, literate community with limited resource and limited clinical settings. Pill count requires trained staff which make it used in clinical settings although it is objective method. Balancing the cost and accuracy is a key factor, for example pharmacy refill method is preferred in large studies over electronic medication packaging EMP. Worth mentioning, direct measures are rarely used due to the excessive cost and intrusiveness of these tools. Utilising accessible resources is crucial to enhance pharmacotherapy and address non-adherence, which poses a barrier to effective treatment for both patients and healthcare systems. Table 1.2. Summarises the methods used for measuring adherence.

Table 1.2. Summary of the methods for measuring adherence (Anghel et al., 2019).

Method of assessment	Advantages	Disadvantages	Disadvantages
Direct methods			
Measurement of drug/ metabolite levels	Accurate Objective, proving the ingestion of the drug	Costly Invasive Inter individual differences	Concentration of the drug/metabolite
Indirect methods			
Pill counts	Simple Mostly used in clinical trials	No evidence of ingested medication	Number of doses missed
Electronic databases	Easy to use, inexpensive	Evidence of the drug being dispensed but not ingested	Medication possession ration (MPR) Proportion of days covered (PDC)

	Non-invasive, patients not aware that they are being monitored Especially specific to identify non-adherent patients		
Electronic monitoring systems	Objective Additional information on degree of adherence One of the most accurate methods	The patient is aware of the evaluation No actual evidence that the medication is being ingested	Overall percentage of doses taken Dosing regime
Self-reported (questionnaires, visual analogue scales)	Easy to use Inexpensive	Overestimate adherence Subjective, influenced by recall or reporting bias	A value that is interpreted regarding a pre-established cut-off point

1.17. Adherence to medications in the Middle East

Published research on adherence and non-adherence to medications in the Middle East showed results of studies which were conducted mainly among patients who suffered chronic conditions such as diabetes mellitus, hypertension, and asthma (Hashmi et al., 2007; Fahey et al., 2006; Roaeid and Kablan., 2007). The design of these studies were cross-sectional studies that employed self-reported methods either alone or in combination with other methods such as pill counts (Abdul Jabbar and Al-Shammari, 1993). Studies on adherence to medications in the Middle East varied in their definitions of adherence to medications, therefore mixed outcomes were reported. For example, in some studies, participants were classified as adherent to their prescribed medications when they take 80% of the pills as recommended (Elzubier et al., 2000; Al-Saffar et al., 2005), one study lowered this threshold to 75% to describe patients as adherent to recommended medications (Kamel et al., 1999). Moreover, clinical judgement was also used to determine and measure adherence to medications in the Middle East (Bassili et al., 1998). Studies which addressed non-adherence to medications in the Middle East relied on proportions of missed doses as a marker to classify non-adherence to the studied medications. For example, Al-Faris et al. (2002) considered patients as non-adherent if they

missed one dose of their prescribed medication per week, while Khattab et al., (1999) classified patients as non-adherent to antidiabetic drugs if they missed 4 doses per month. Furthermore, Youssef et al., (1999) considered patients as non-adherent to their antihypertensive medications if they were taking less than 90% of their monthly prescribed tablets. Abdul Jabbar et al., (1993) classified patients as non-adherent to anti epileptics if they missed doses of 3 days /month.

Outcomes of studies on non-adherence to medications in chronic conditions were variable. the documented rates of non-adherence to medications varied between 1.4% to 88% (Bassili et al., 1998; Khattab et al., 1999; Roaeid et al., 2007). Among patients who are taking medications to treat hypertension, non-adherence rates were between 23% to 49% (Hashmi et al., 2007). Lower non-adherence rates (between 1.4% to 27.1%) were reported among patients who are taking antidiabetic agents (El-Shazly et al., 2000). For anti-depressants, non-adherence rates were between 24% to 88% among patients in the Middle East (Fido et al., 1998).

Reasons for non-adherence in the Middle East were variable, forgetfulness and side effects of medications were the commonly documented reasons for non-adherence (Al-Saffar et al., 2005). Other explanations for not taking medications as prescribed included feeling of no need for the drugs, disbelief about medications, low health literacy, and social stigma (Gulbay et al., 2006). In conclusion adherence and non-adherence to medication in chronic conditions, like other parts of the world, are significant problems in Middle Eastern countries.

1.18. Health system in Saudi Arabia

Saudi Arabia is one of the largest countries of the Gulf Arab states in the Middle East, with a total area of 2.5 million squared km and total population of 30.7 million, 20.7 million are Saudi citizens and about 10 million are expatriates. The country is considered as a relatively high human development index (HDI) of (0.854) in 2019 (WHO, 2020). The average life expectancy is 78 and 74 years for females and males respectively in the country. In Saudi Arabia the per

capita total expenditure on health was US$1004 in 2015, this made it the 6th highest in the Middle East and African region. Total health care expenditure was predicted to increase to US$44 billion by 2019. According to the WHO, the top 10 causes of death in Saudi Arabia are: ischemic heart disease (21.7%), stroke (16%), lower respiratory tract infections (6.3%), road traffic accidents (5.8%), diabetes (4.6%), kidney disease (4.6%), hypertension (2.8%), chronic obstructive pulmonary disease (1.7%), congenital anomalies (1.7%), and preterm birth complications (1.7%) (WHO, 2020).

1.19. Adherence to medications in Saudi Arabia

Most of the studies about adherence to medications in Saudi Arabia are carried out on chronic conditions such as diabetes and hypertension. The studies were mostly cross-sectional in design. The studies report diverse results with different outcomes.

1.19.1. Adherence to antidiabetic medications in Saudi Arabia

Khan et al., 2012 reported a high level of non-adherence rate (67.9%) to antidiabetics among participants in Eastern Saudi Arabia. In southwestern part of the country, particularly Abha area, Khattab et al., (1999) documented 61.2% adherence rate to oral antidiabetics in the region. Alqarni et al., 2019 reported 35.8% overall adherence rate to diabetes mellitus type II medications in AL Khobar area in Eastern Saudi Arabia.

1.19.2. Adherence to antihypertensive medications in Saudi Arabia

Khalil and Elzubier, (1997) reported 53% adherence rate to antihypertensive agents in central Saudi Arabia. The study found a strong association between uncontrolled hypertension and adherence to medications. In addition, Khayyat et al., (2017) documented 54% were non-adherent to antihypertensive medications in Riyadh area; the authors justified the high non-adherence by the low health literacy of the participants. They stressed the importance of patients' education to increase adherence to medications. Moreover, Alotayfi et al., (2018) used

social media to collect data from all of Saudi Arabia about taking antihypertensive medications as prescribed. The results of this study showed that only 6.2% of the participants were adherent to medications that are used to treat high blood pressure. Furthermore, Alzahrani et al., (2019) revealed that only 7.58% of the patients in their study, which conducted in central Saudi Arabia, were adherent to medications. The authors justified this low adherence rate by the poor knowledge of the participants about the need to continuously take medications to control blood pressure. The authors also suggested educating patients about their medications to increase their adherence. In another study, Algabbani and Algabbani, (2020) reported that 42.2% of the participants were adherent to antihypertensive agents. The study concluded that patients with no comorbid factors are more adherent to antihypertensive medications. The study also added that knowledge about hypertension condition increases adherence to taking these drugs as prescribed.

1.20. Adherence to OACs in Saudi Arabia

Adherence to OACs in Saudi Arabia is an area where numerous studies have been conducted to assess relationships between adherence to OACs and patients' related factors. The total number of studies that targeted adherence to warfarin and patients' related factors such as knowledge about the drug were higher than studies that assessed the relationships between adherence to DOACs and patients' related factors. This is due to the long-standing prescribing of warfarin and the more recent introduction of DOACs in the country as DOACs were introduced in 2013 in Saudi Arabia (Almeman et al., 2014). In addition, the studies reported many confounding factors, therefore, every study should be taken on its own merits and therefore obtained results from one study should not be generalised. Below are some examples of studies which studied adherence to OACs in Saudi Arabia. In other words, prescribing of warfarin is more established than recommending of DOACs for patients; therefore, warfarin has had more chance to be investigated than DOACs. (Al-Omair et al., 2016) assessed the

impact of patients' knowledge about warfarin and their adherence to this drug in central Saudi Arabia. The results of this assessment revealed that 53.1% of the participants had poor quality of knowledge as described by the authors. Moreover, the results showed that among poor knowledge group, 24% of the participants were classified as adherent to the drug, while 14.5% of the patients in the good knowledge about warfarin group were described as adherent to taking the drug as recommended. The authors concluded that knowledge about the drug is not associated with adherence to the drug. The relationship between INR control and adherence to the drug was investigated by another study carried out by Mayet et al., (2016) in central Saudi Arabia, Riyadh area. The authors reported that 46.4% of the participants had high level of adherence to warfarin, while 38.2% had an acceptable INR control. In contrast, 53.6% patients who had low adherence, 33% showed a good INR control. Moreover, Blakhi et al., (2017) in Al Qasim area, central Saudi Arabia assessed the relationship between adherence to warfarin and satisfaction with taking this medication. They documented that adherence to warfarin was high among highly educated patients and those who are satisfied with the drug. They reported 31.8% adherence rate among the participants. In addition, they published that 45.6% of the patients were within their recommended INR target. The authors concluded that satisfaction with the medication is necessary to increase adherence to warfarin. The factors that affect knowledge about OACs in Riyadh area, central Saudi Arabia, were the subject of investigation by (Alajami et al., 2021). Knowledge about both warfarin and DOACs were included in the study. The results of this research highlighted that 67.2% of the study participants had adequate knowledge about OACs. The results also documented those participants showed more knowledge about warfarin than DOACs. Another finding in this study was the inverse association between knowledge about OACs and the advanced age as elderly patients had less information about OACs compared to younger patients.

1.21. Conclusion

Although there is high variability in published studies examining adherence to medications from the different studies in different parts of Saudi Arabia, it seems clear that poor medication adherence to prescribed medication is common in Saudi Arabia. Multiple factors have also been shown to influence adherence/non-adherence to medications in Saudi Arabia, and it is not limited to certain areas, conditions, or medications. Further investigations of OAC adherence are needed in Saudi Arabia, from both patient and healthcare professional perspectives.

1.22. Purpose of conducting this study

This study aims to address a pressing need for a comprehensive investigation into the adherence to OACs in Eastern Saudi Arabia, encompassing both a quantitative assessment of patients' adherence and an in-depth exploration of the perspectives held by HCPs. Currently, there is a lack of published data on adherence to OACs and the associated factors in the study area. While some reports have touched upon the issue of adherence to OACs in Saudi Arabia, none have provided data specific to the study area. Furthermore, there is a notable absence of published data examining the perspectives of HCPs and the roles played by pharmacists in promoting adherence to OACs in the region. These knowledge gaps include the absence of localised data, limited comprehension of cultural influences, and the ongoing evolution of healthcare dynamics. These gaps hold significant consequences on patients' outcomes and healthcare expenditure. By concurrently measuring adherence rates to OACs and investigating the perspectives of HCPs, this research aims to offer a comprehensive understanding of adherence to OACs. Ultimately, this understanding will inform the development of culturally tailored interventions and contribute to enhancing the quality of care in Eastern Saudi Arabia.

1.23. Research aims and objectives

1.23.1. Aims

This DPharm research aims to assess adherence to OACs in Eastern Saudi Arabia and explore views of HCPs and their role in supporting OACs' users in taking these medications as prescribed with a focus on the pharmacist role.

1.23.2. Objectives

The objectives of this research are to:

1. Measure adherence to OACs by patients in Eastern Saudi Arabia who are taking these medications and examine patients' related factors on adherence to OACs among their users by conducting a cross sectional study and use of Hill-Bone self-reporting scale.
2. Identify the prescribed OACs and conditions for which these medications were prescribed in Eastern Saudi Arabia using cross-sectional approach.
3. Explore the role performed by hospital pharmacists including activities undertaken, scope of practice, working status and the practice environment for pharmacists at a secondary care setting. In addition, to evaluate their satisfaction of integration within the HCPs team and clinical practice, and to explore barriers to integration in the team. This will be achieved through conducting a thematic analysis qualitative approach and semi-structured interviews.
4. Explore the role of HCPs in supporting patient adherence to OACs, and potential barriers to their practice in this area by conducting a qualitative study using a thematic analysis qualitative approach and semi-structured interviews.

CHAPTER TWO

RESEARCH METHODOLOGY

This chapter provides the justification of design of the research and the theoretical and methodological approaches used in this thesis. It also discusses the techniques used to increase reliability and validity, in addition to the ethical considerations in this research.

2.1. Theoretical framework

Swanson, (2013) described a theoretical framework as the framework that can provide a foundation for or accommodate a theory within a research study. It is a synthesis of the ideas in the specified field of research. The objective of a theoretical framework in a research project is to provide an intellectual foundation for all the meanings contained in the obtained data by a researcher (Neuman, 1997). Furthermore, it offers a structure for examination of the collected data and helps researchers to discuss their findings more clearly in the light of the available theories. It also enables reporting of findings of a research project in a creative, evaluative, and analytical manner. A theoretical framework therefore adds to the depth of the analysis and discussion of findings (Bryman, 2016; Bowling, 2014).

2.2.Theoretical paradigms

A research paradigm, as defined by Crotty**,** (1998), encompasses fundamental beliefs about knowledge, reality, and research methodology. Theoretical paradigms serve as frameworks for researchers to articulate their hypotheses, investigate phenomena, and challenge educational practices. Researchers can choose a positivist approach when seeking definitive conclusions, requiring rigorous adherence to research criteria. Conversely, post-positivist researchers embrace flexibility and acknowledge the influence of prior knowledge on observations. Interpretive methods are commonly employed to understand social phenomena, while the transformative paradigm guides critical theory evaluation. Pragmatic researchers prioritise addressing questions and use multiple approaches, favouring relevance over strict adherence

to quantitative or qualitative paradigms, making pragmatism an ideal context for employing mixed methods to achieve research objectives.

2.3.The theoretical framework for this research

The theoretical framework underpinning this study was thoughtfully constructed to ensure its alignment with the research questions and the overarching aims and objectives of the investigation. The motivation for this research stems from the critical imperative to address the prevalent issue of suboptimal adherence to OACs within the Middle East, a region where empirical evidence consistently points to low adherence rates among OACs' users. This concern is further substantiated by an extensive which has revealed that adherence to medication regimens, particularly those as complicated as OACs, is intertwined with a multitude of complex factors, encompassing patient-related variables, prescriber dynamics, and systemic particulars within the healthcare environment (Davari et al., 2018).

Considering the complicated nature of this research landscape, a pragmatic research paradigm was carefully selected to serve as the foundational framework. This paradigm was thoughtfully complemented by the adoption of a mixed-methods research design, which seamlessly integrates both quantitative and qualitative methodologies. The quantitative aspect of the study, conducted within the Eastern region of Saudi Arabia, takes the form of a comprehensive cross-sectional investigation. This component is fundamentally descriptive, primarily focused on quantifying and assessing adherence rates among OACs' users through the utilisation of the validated HB scale. Beyond this quantification, the quantitative dimension investigates into the details of patients' lived experiences with adherence to OACs. It scrutinises the drivers behind non-adherence and scrutinises whether these drivers can be categorised as formidable barriers to adherence, thereby contributing valuable empirical evidence. Complementing the quantitative component, the qualitative dimension of the research, characterised by its thematic analysis methodology, seeks to unearth the perspectives of HCPs. This inquiry extends across

multiple dimensions, encompassing HCPs' viewpoints on various sides of adherence to OACs, encompassing patients' adherence behaviours, the prescribing landscape, and the prevailing support mechanisms geared towards augmenting patient commitment to OACs' regimens. This qualitative exploration unfolds the complexities of the barriers that often obstruct adherence to OACs, while simultaneously exploring the potential for pharmacists to exercise an expanded role in the holistic management of patients undergoing OACs therapy. By linking both quantitative and qualitative methodologies, this research attempt aims to provide a comprehensive understanding of the challenges surrounding adherence to OACs. It is poised to identify innovative pathways for enhancing patient outcomes within the complex realm of OACs therapy, contributing substantively to the body of knowledge in this critical domain.

2.4. Mixed methods research

The concept of mixed methods research is characterised as a comprehensive approach wherein both quantitative and qualitative data are collected and analysed simultaneously or sequentially within a single study, with an emphasis on integrating these data at various stages of the research process (Creswell, 2007). Various categorisations of mixed methods research exist, such as those proposed by Steckler et al. (1992). For instance, the sequential explanatory design prioritises quantitative data collection and analysis, followed by qualitative data collection and analysis. Its primary objective is to utilise qualitative findings to elucidate and interpret results obtained primarily through quantitative research (Ivankova, 2006). Similarly, the sequential exploratory design places initial emphasis on qualitative data collection and analysis, succeeded by quantitative data collection and analysis. This approach primarily aims at exploring a phenomenon and may be employed to test components of an emerging theory or generalise qualitative findings to different samples (Creswell, 2013). Furthermore, the sequential transformative design offers flexibility in the order of quantitative and qualitative phases and integrates their outcomes during the interpretation phase, guided by a theoretical

perspective like a conceptual framework or ideology, underscoring its significance in guiding the study (Kroll, 2009). Additionally, concurrent triangulation design, another mixed methods design, involves concurrent data collection employing both quantitative and qualitative methods to validate or support findings within a single study, with possible prioritisation of one method over the other, and their results are integrated during the interpretation phase (Castro, 2010). For this research, we have selected the sequential explanatory mixed method design, which focuses on using qualitative insights to explain and interpret findings from the primarily quantitative study, aligning with our research objectives.

2.4.1. Sequential explanatory design in this study

The sequential explanatory mixed methods research design aims to enhance understanding by first prioritising quantitative data collection and analysis, followed by qualitative data collection and analysis, with the primary objective of using qualitative findings to clarify and interpret the results of the quantitative phase (Creswell, 2017). This design exploits the strengths of both quantitative and qualitative approaches, combining the statistical thoroughness of quantitative research with the richness of qualitative insights. By doing so, it provides a more comprehensive understanding of research questions, particularly when complex phenomena are involved. This approach allows to address research questions from multiple angles, fostering a deeper exploration and interpretation of the quantitative findings. It offers the advantage of triangulation, where different data sources converge to strengthen the overall validity of the study, making it a valuable choice for research projects seeking to gain holistic insights into a particular subject or phenomenon (Ivankova, 2006).

The sequential explanatory mixed methods design stands out among other mixed methods approaches due to its specific aim of enhancing quantitative findings through the incorporation of qualitative insights. While other mixed methods designs like concurrent triangulation or sequential transformative also offer valuable insights, the sequential explanatory design

provides a clear advantage in that it prioritises quantitative rigor and allows for a deeper exploration and interpretation of those results through qualitative data. This design's sequential approach enables researchers to address the "how" and "why" questions, adding depth and context to quantitative findings, making it particularly suitable for research seeking a comprehensive and robust understanding of complex phenomena. Its triangulation of data sources strengthens the overall validity of the study, making it a powerful choice for research aiming to achieve both breadth and depth in its findings (Creswell, 2005).

The rationale for opting for the sequential explanatory design in this study lies in its capacity to provide a holistic comprehension of the research problem. This dual-phase strategy facilitates a multidimensional exploration of the research question, permitting a thorough examination from diverse angles. Moreover, employing this design allow for substantiation and validation of quantitative findings through qualitative data. This validation process assumes vital importance as it contributes to the establishment of the reliability and credibility of research outcomes. The qualitative element likely produces insights and clarifications that either strengthen or clarify the patterns or relationships recognised in the quantitative dataset, thereby reinforcing the robustness of the findings.

2.5.Quantitative research

Quantitative research involves data collected in numeric or quantified forms, with a focus on establishing statistical relationships, measuring, and describing. It emphasises objective measurement and observation, along with examining correlations and causations. The main purpose of quantitative data is to test relationships between variables and assess objective theories. Variables in quantitative research are categorised as dependent (affected by another variable), independent (causing an effect), and extraneous (confounding the relationship between dependent and independent variables) (White and Millar, 2014; Hamer and Collinson, 2014; Polit and Hungler, 2013; Wong, 2014; Moxham, 2012). There are several categories of

quantitative research such as descriptive, correlational, experimental, and Quasi experimental (Borbasi and Jackson, 2012; Burns and Grove, 2010). The selection of a specific design allows variables to be measured or manipulated in the study (Burns and Grove, 2010; Polit and Hungler, 2013). For this research, we will focus on the cross-sectional study design which is used to conduct the quantitative study in this study.

2.5.1. Cross-sectional study design

Cross-sectional study design is a research approach widely used in epidemiology, public health, and social sciences to gain insights into the characteristics and prevalence of specific phenomena within a given population or sample. Additionally, they offer valuable insights into the distribution of variables and potential associations between them (Polit and Hungler, 2013; Moxham, 2012). One of its notable advantages lies in its ability to efficiently capture a snapshot of a population's status at a single point in time. Moreover, it is useful for estimating the prevalence of diseases, risk factors, or societal trends, helping policymakers and healthcare professionals make informed decisions about resource allocation and interventions (Bushman and Huesmann, 2001). However, due to their limitations in determining cause-and-effect relationships, cross-sectional studies are often complemented by other study designs, such as qualitative methods when the research demands a deeper understanding of causal mechanisms and temporal sequences (Polit and Hungler, 2013).

Overall, cross-sectional study design serves as a valuable tool for researchers and policymakers in assessing the current state of a population's health, behaviour, or attributes and guiding further investigations in the field of public health and social sciences (White and Millar, 2014; Hamer and Collinson, 2014; Wong, 2014).The selection of a cross-sectional study design for this thesis is driven by the need to efficiently capture a snapshot of the population's characteristics, behaviours, and conditions at a specific point in time, to provide insights into prevalence, group comparisons, and potential associations between variables. This approach

offers a cost-effective and ethical means to gather data for hypothesis testing and policy formulation.

2.5.2. Collection of data for cross-sectional study in this thesis

Quantitative data collection methods aim to establish statistical relationships, measure variables, and test hypotheses. Key approaches include surveys and questionnaires, which involve structured, standardised questions administered to a sample or population; experiments, where variables are manipulated to assess cause-and-effect relationships; observations. These methods enable researchers to quantify phenomena, assess objective theories, and analyse data through statistical techniques, contributing to the empirical foundation of the research (Atkinson et al., 2001; Polit and Hungler 2013).

Selecting questionnaires as the method for quantitative data collection in this study is justified for several reasons. Firstly, questionnaires offer wide data coverage, structured and standardised questions, ease of administration, efficient data processing, and objective measurement. They also provide control over the research environment, facilitate hypothesis testing. Questionnaires also address ethical considerations and are cost-effective. However, potential limitations, such as response bias and limitations in capturing nuanced responses, should be acknowledged, and mitigated. Overall, the use of questionnaires aligns with the research objectives, allowing for the collection of precise quantitative data essential for hypothesis testing and statistical analysis in the thesis.

2.6.Qualitative research

Qualitative research involves a thorough investigation of phenomena. It is characterised by the collection of comprehensive narrative data using a flexible research design, allowing for an in-depth exploration of the subject matter (Polit and Beck, 2017). Furthermore, as highlighted by Barbour, (2000), qualitative research shines in documenting challenges and obstacles,

exploring how they are perceived and addressed, and shedding light on the factors influencing the success or failure of interventions and implementation efforts. Moreover, qualitative research can be employed as a standalone approach or integrated into mixed-methods research, combining both qualitative and quantitative data to provide a comprehensive perspective (Huston and Rowan, 1998). There are several types of qualitative research such as ethnography, Ground theory, narrative research, and observational research. For this thesis, we will focus on thematic analysis, the method of qualitative research methods that is used to conduct the qualitative aspect of this thesis.

Thematic analysis

Thematic analysis is a widely used qualitative research method that provides a structured framework for uncovering and interpreting patterns within qualitative data. This approach allows researchers to explore the richness of participants' experiences, narratives, or responses by identifying recurring themes or patterns that emerge from the data. Thematic analysis is particularly valuable in fields like psychology, sociology, and healthcare, where understanding the complexities of human behaviour, attitudes, and perceptions is essential.

One of the strengths of thematic analysis is its flexibility, making it suitable for a wide range of research questions and data sources. Thematic analysis provides a systematic way to identify, analyse, and report meaningful themes that contribute to a deeper understanding of the research topic. It also allows for the exploration of both manifest and latent content within the data, helping researchers gain insights into not only what participants say but also what may be implied or hidden in their responses. Through this rigorous process of data exploration and interpretation, thematic analysis enables researchers to distil complex qualitative data into coherent and insightful findings that can inform theory, practice, or policy.

Opting for thematic analysis as the qualitative research method for this thesis offers several distinct advantages. Firstly, it provides a structured and systematic approach to thoroughly

examine the richness of the data that can be collected from interviews with HCPs. Furthermore, thematic analysis allows for a systematic and comprehensive review of the qualitative data collected during the study. Moreover, the flexibility of this design is valuable in accommodating the variability in the perspectives of the interviewed HCPs. In addition, the data collected from HCPs' narratives can be effectively analysed through thematic analysis, ensuring that a holistic understanding of their views on patients' adherence to oral anticoagulants and its related factors and rigorous analytical techniques, thematic analysis ensures that the findings are derived systematically, reducing the potential for bias or subjectivity in the interpretation of the data. Ultimately, the insights gained from thematic analysis in this research context can serve as a valuable resource for updating healthcare practices and interventions. By revealing frequent themes, patterns, and nuances in HCPs' viewpoints, this study can contribute to the development of recommendations aimed at improving patients' adherence to oral anticoagulants, thus enhancing the overall quality of care in eastern Saudi Arabia healthcare system.

Collection of data for thematic analysis in this thesis

Various techniques can be employed in data collection in qualitative research, for example, semi-structured interviews are used with the flexibility to adapt questions based on participants' responses. Structured interviews are also utilised for exploring collective perspectives on a subject, with researchers potentially adopting participant-observer or detached observer roles. Another method for collection of data in qualitative research is observational data collection which involves detailed observation of individuals and events to understand behaviours and interactions, making it valuable for studying cultural aspects (Dicicco-Bloom and Crabtree, 2006; Foley and Timonen, 2015; Moser and Korstjens, 2017). We will focus on semi-structured interviews as it is the method of collection of data which is selected in this research.

Semi-structured interviews combine elements of both structured and unstructured interviews. These interviews utilise a pre-defined set of open-ended questions or topics to guide the conversation with participants while allowing flexibility for follow-up questions and exploration of emerging themes (Pope and Mays, 1995). This approach provides a balance between structure and spontaneity, enabling gathering in-depth insights, perspectives, and experiences from participants. Semi-structured interviews are widely used in various fields, such as social sciences, psychology, and healthcare, to explore complex phenomena, understand participant viewpoints, and generate rich qualitative data for analysis (Lambert and McKevitt, 2002).

The reason for selecting semi-structured interviews as the method for collection of data in this research lies in their ability to provide rich and context-specific data. Semi-structured interviews offer a flexible approach, allowing participants to express their views and experiences in their own words. Moreover, this method enables the gathering of valuable insights and perspectives that may not be readily apparent from textual or document sources alone. By combining semi-structured interviews with content analysis, the research can achieve a comprehensive understanding of the subject matter, enriching the depth and validity of the findings by incorporating both qualitative and quantitative data (Creswell, 2013).

2.7.Methodological Framework in this Thesis

The objective of this thesis is to evaluate the medication adherence of individuals prescribed OACs in the eastern region of Saudi Arabia and to delve into patients' experiences with OAC usage. Additionally, the thesis aims to gain an in-depth understanding of healthcare HCPs perspectives on adherence to and prescription of OACs in this geographical area. To accomplish these goals, a mixed methods research approach, specifically the sequential explanatory design, was employed. In this research, a quantitative study was conducted using a cross-sectional design and questionnaires to collect data from patients, focusing on their

adherence to OACs and their experiences with these medications. The questionnaire included questions about demographics of patients such as age, sex, education level, and comorbidities. It also included questions about their awareness of the reasons for which they were prescribed OACs, their convenience with OACs, and missing doses of OACs and reasons for missing OACs.

Furthermore, a qualitative study employing thematic analysis research design was carried out, involving the collection of data through semi-structured interviews schedule with HCPs. The questions were about perspectives of HCPs on patients' adherence to OACs, factors influence prescribing OACs, and support for OACs' users. Participating pharmacists were asked about their involvement in supporting patients and their role in increasing adherence to OACs. The rationale for selecting these research designs and data collection methods has been previously elucidated.

This overarching aim was realised through a series of four distinct studies: 1) A systematic literature review to assess OAC adherence among patients in the Middle East (Chapter 3). 2) An evaluation of patients' adherence to OACs employing the Hill-Bone Medication Adherence Scale (Chapter 4). 3) A survey designed to gauge patients' experiences with OACs (Chapter 5). 4) An exploration of HCP perspectives regarding patients' adherence and the prescription of OACs (Chapter 6). Table 2.1. provides an overview of the research aim, approach, qualitative and quantitative studies, and the justifications for your chosen methodology and data collection methods.

Table 2.1. Methodology overview

Research Aims	- Assess medication adherence of patients prescribed OACs in eastern Saudi Arabia - Investigate patients' experience with OACs - Provide insights from HCPs on adherence to and prescribing of OACs in eastern Saudi Arabia
Research Approach	Mixed methods (sequential explanatory)
Quantitative Phase	Cross-sectional study design
Data Collection for quantitative study	Measuring adherence to OACs: HB scale. Patients' experience with taking OACs: questionnaires administered to patients.
Qualitative Phase	Thematic analysis research design
Data Collection for qualitative Phase	Semi-structured interviews with HCPs

2.8. Reliability of the study

For the reliability of this research, careful adherence to the study protocols was maintained. The researcher conducted in-person interviews with patients, rigorously adhering to the prescribed interview structure to minimise potential biases. Additionally, these interviews were scrutinised by the supervisors to ensure consistency and reliability. To further strengthen the research's reliability, the questions of the interviews underwent scrutiny from experts in psychology and experienced pharmacists. Moreover, supervisors reviewed the questions to confirm their alignment with established interviewing techniques, collectively enhancing the overall reliability of this study.

2.9.Validity of the study

In this research, a triangulation approach was employed, which entails the utilisation of multiple data collection methods. This methodological triangulation aimed to merge findings from different sources, thereby enhancing the overall validity of the study. The research included both interviews and questionnaires, embracing a combination of quantitative and qualitative data collection approaches. Specifically, the study incorporated two distinct quantitative measures to assess medication adherence: the HB scale, a well-validated tool for measuring adherence, and a self-report question, and semi-structured interviews with HCPs. The inclusion of these dual measures was undertaken to boost the validity of the study's primary outcome, which focused on assessing patients' adherence to OACs and exploring views of HCPs on patients' adherence to OACs.

2.10. Research ethical considerations

The University of Birmingham Code of Practice for Research and the information and guidance provided on the University's ethics webpages was followed (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx). This research obtained full ethical approval from the University of Birmingham (Protocol number: ERN_19-0689). This research was also approved by the ethics committee in the site of the study (Prince Sultan Cardiac Centre PSCC) (Appendix I). Confidentiality of the interviews was sought through conducting the interviews in a private location offered by the study site. Obtained data was kept securely in a designated location in the PSCC, no access to the information was given to unauthorised individuals. Anonymity of the participants was an issue of high importance and no personal identification materials were exposed under any circumstances. Local protocols for patients' confidentiality were followed to safeguard rights of participants.

CHAPTER THREE

A SYSTEMATIC REVIEW OF ADHERENCE TO ORAL ANTICOAGULANTS AMONG ATRIAL FIBRILLATION PATIENTS IN THE MIDDLE EAST

3.1. Introduction

3.1.1. Prevalence and incidence Atrial Fibrillation

AF is the major type of arrhythmia that affects the human heart. It affects about 1% of the world population (Miyasaka *et al.,* 2006). The condition is an independent risk factor for stroke, which can be a disabling condition and can cause death. It has been reported that about 36% of all strokes in patients over 80 years are related to AF (Psaty *et al*., 1997). In the United Kingdom, AF is responsible for about 3% to 6% of acute hospital admissions (Zarifis *et al*., 1997; Lip *et al*., 1994). Recent studies reported that AF is affecting 1 in 10 of the elderly population in the UK (Burdett and Lip, 2020). The total number of individuals affected by the condition is increasing around the world (Camm *et al*., 2010). By 2050 the total number of patients who suffer (AF) is expected to be about 16 million in the United States alone (Krijthe *et al*., 2013; Marillo et.al.2017).

The United Nations (UN) classifies countries, based on data from the organisation's agencies, into developed economies, economies in transition, and developing economies. In developing countries, data about the epidemiology of AF is less available compared to developed world (Lip *et al*., 2015). Studies during the 1990s and mid 2000s reported varied incidences of the condition. For example, studies from Taiwan revealed a 1.16-0.76 in women, and 1.37-1.68 per in men (1,000 person-years) while studies from China reported more than 7% incidence of AF, corresponding to 0.7 cases per 1000-year (Chien *et al*. 2010). According to various large-scale studies in UK, such as the UK Biobank and the Health Survey for England, it is estimated that around 1-2% of the UK population is affected by atrial fibrillation, resulting in approximately 10-20 cases per 1000 individuals. Nevertheless, Moreover, the prevalence of AF tends to rise with age, indicating that certain age groups may experience a higher prevalence. For instance, individuals aged 65 or older are estimated to have a prevalence of AF of approximately 5-6%.

3.1.2. Prevalence of AF in the Middle East

The Middle East region represents one of the areas where the prevalence of AF is least studied. In addition, there are no official published statistics about the numbers of AF patients in the Middle East region (Alsheikh-Ali et al., 2014; Al-shamakhani *et al*., 2018). Dabdoob *et al.*, (2007) commented on the epidemiology of AF among the Qatari population. They reported 12% incidence of AF among Qatari patients, with an associated burden of comorbidities such as hypertension and diabetes mellitus. There is a need for further prevalence studies, or routine collection of diagnoses, in healthcare systems in the region.

3.1.3. Use of OACs for management of AF and for prevention of ischaemic stroke

Treatment of AF depends mainly on using OACs. Warfarin used to be the main treatment for AF and has been in use since the early 1950s (Verhoef *et al*., 2014). It acts in the liver by inhibiting the synthesis of four vitamin K-dependent coagulant proteins. Warfarin significantly reduces the relative risk of stroke by 64% compared to 22% when using antiplatelet such as aspirin (Hart *et al*., 2007). Disadvantages of warfarin include major bleeding incidences, the need for regular monitoring, drug-food interactions, and drug-drug interactions (Amin, 2013).

DOACs are a type of oral anticoagulant medication used to prevent blood clots in patients who are at risk of thromboembolic events, including pulmonary embolism and stroke. They offer a more effective and convenient treatment option compared to traditional anticoagulants like warfarin, as they directly target specific clotting factors in the blood (Dentali et al., 2012).

The four main DOAC drugs are dabigatran, rivaroxaban, apixaban, and edoxaban, and they are approved for various indications such as prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, treatment and prevention of deep vein thrombosis and pulmonary embolism, and prevention of venous thromboembolism in patients undergoing orthopaedic surgery (Connolly et al., 2009).

Clinical studies have shown that DOACs have similar or lower bleeding risks compared to traditional anticoagulants, and they are more convenient to take as they do not require frequent monitoring or dose adjustments. However, DOACs may not be suitable for all patients, and healthcare providers should carefully consider individual patient factors before prescribing these medications (Patel et al., 2011).

In terms of the reversibility of DOACs, they have a relatively short half-life compared to traditional anticoagulants, which allows for a faster reversal of their anticoagulant effects (Ageno et al., 2016). In cases where urgent reversal is needed, DOAC-specific reversal agents are available, such as idarucizumab for dabigatran and andexanet alfa for rivaroxaban and apixaban (Almegren, 2017).

Clinical trials have demonstrated that these reversal agents can effectively and rapidly reverse the anticoagulant effects of DOACs, leading to improved haemostasis in patients who experience bleeding events or require urgent surgery (Seigal et al., 2015). However, these reversal agents are expensive and not widely available, which may limit their use in certain settings (Pollack et al., 2015).

Overall, the reversibility of DOACs is an important consideration when using these medications, and healthcare providers should be familiar with the available reversal agents and their indications in order to effectively manage bleeding events or urgent surgery in patients on DOAC therapy (Glund et al., 2015).

The clearance of DOACs from the body can be affected by renal function, as these medications are primarily eliminated through the kidneys. Patients with impaired renal function may have reduced clearance of DOACs, leading to higher drug concentrations and an increased risk of bleeding (Gomez-Outes et al., 2016). To account for this, DOACs' dosing guidelines typically recommend dose adjustments or avoidance in patients with reduced renal function. For

example, dabigatran and edoxaban require dose reductions in patients with moderate or severe renal impairment, while rivaroxaban and apixaban are contraindicated in patients with severe renal impairment (Mavrakanas et al., 2017). Table 3.0. Summarises the dosing guidelines of DOACs.

Table 3.0. Prescribing of DOACs for patients with impairment of renal function

OAC	Indication	Dose
Dabigatran	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation	150 mg twice daily for CrCl > 50 mL/min; 75 mg twice daily for CrCl 30-50 mL/min
	Treatment and prevention of DVT and PE	150 mg twice daily after 5-10 days of parenteral anticoagulation
Rivaroxaban	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation	20 mg once daily with the evening meal; 15 mg once daily with the evening meal if CrCl 15-50 mL/min
	Treatment and prevention of DVT and PE	15 mg twice daily for the first 21 days, followed by 20 mg once daily thereafter
	Prevention of recurrent DVT and PE	20 mg once daily after 6 months of initial treatment
Apixaban	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation	5 mg twice daily; 2.5 mg twice daily if at least two of the following criteria are met: age ≥ 80 years, body weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL
	Treatment and prevention of DVT and PE	10 mg twice daily for 7 days, followed by 5 mg twice daily thereafter
	Prevention of recurrent DVT and PE	2.5 mg twice daily after at least 6 months of initial treatment
Edoxaban	Prevention of stroke and systemic embolism in non-valvular atrial fibrillation	60 mg once daily; 30 mg once daily if CrCl 15-50 mL/min or patient meets one of the following criteria: body weight ≤ 60 kg, age ≥ 75 years, or serum creatinine ≥ 1.5 mg/dL
	Treatment and prevention of DVT and PE	60 mg once daily after 5-10 days of parenteral anticoagulation
	Prevention of recurrent DVT and PE	30 mg once daily after at least 6 months of initial treatment

In clinical practice, HCPs should regularly monitor renal function in patients taking DOACs and adjust dosing as necessary to ensure safe and effective treatment. Additionally, patients

with impaired renal function should be closely monitored for bleeding events or other adverse effects related to DOAC therapy (Boriani et al., 2021). Dabigatran functions as a direct thrombin inhibitor by blocking thrombin, a crucial enzyme in the process of blood coagulation, to prevent the formation of blood clots. Its primary purpose is to prevent systemic embolism and stroke in individuals with AF, treat deep vein thrombosis and pulmonary embolism, and prevent venous thromboembolism after hip or knee replacement surgery (Connolly et al., 2009).

According to the NICE guidelines, dabigatran is recommended for use in patients with AF and at least one risk factor for stroke, based on evidence showing similar efficacy to warfarin but with a lower risk of bleeding. In addition, the drug is endorsed to treat DVT and PE, and to prevent VTE following hip or knee replacement surgery (NICE, 2014). Rivaroxaban is a DOAC that works by blocking factor Xa, a key enzyme involved in the blood clotting process, thus preventing the formation of blood clots. Rivaroxaban is indicated for a variety of medical conditions, including the prevention of stroke and systemic embolism in patients with AF, the treatment and prevention of DVT and PE, and the prevention of VTE after hip or knee replacement surgery. The NICE guidelines 2014 recommend the use of rivaroxaban for the prevention of stroke and systemic embolism in patients with AF and at least one risk factor for stroke. Clinical trials showed that this drug is non inferior to warfarin in AF patients for prophylaxis of stroke (Patel et al., 2011).

Apixaban is a factor Xa inhibitor that has been approved for stroke prevention. The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial was published in 2011. It was a multicentre double blind comparative trial. The primary outcome of the trial was as follows: stroke or systemic embolism 1.27%/year with apixaban and 1.6% with warfarin ($P<0.001$ for non-inferiority and 0.01 for superiority). The rate of haemorrhagic stroke was 49% lower in the apixaban group. The trial also showed that

major bleeding risk was 2.13% with apixaban and 3.09% per year with warfarin (Granger et al., 2011).

Edoxaban is another factor Xa inhibitor that has been approved for stroke prevention. The ENGAGE AF-TIMI 48 trial showed that edoxaban in 60 mg and 30 mg daily doses is noninferior for stroke prophylaxis in patients with AF compared with warfarin. The trial primary end point also showed that edoxaban was non inferior to warfarin for the primary endpoint of stroke or systemic embolic event (1.5% warfarin vs. 1.18% edoxaban 60mg dose) , and warfarin and low-dose edoxaban (1.5% warfarin vs. 1.61% edoxaban 30mg dose).(Giugliano *et al*., 2013).

Now many clinical guidelines now recommend use of OACs lifelong for AF patients to reduce the risk of stroke (Camm *et al*., 2010). OACs are therefore a lifelong therapy for the majority of patients experiencing AF (Brass, 1997; Gage *et al*., 2001), and therefore adherence to therapy is an important factor in their use.

3.1.4. Burden of AF and stroke on health systems

The risk of morbidity and mortality is increased in AF patients due to the significant increase in the risk of stroke (Lip et al., 2012). Studies have shown that AF increases the risk of stroke from 4.6% in 50-59 years old to 20.2% in 80-89 years, five times increase (Lip,2013). AF-related stroke results in more mortality, greater disability, longer hospital stays, poorer functional outcome, and reduces the chance of home discharge (Björck *et al*., 2013).

In developed countries, such as the USA, direct costs of stroke are expected to increase by 23% over the 20-year period up to 2030 to reach $95.6 billion from the US annual health care budget, and the indirect costs is expected to rise to $44.4 billion (Heidenreich *et al*., 2011). In the UK, it has been estimated that 1.4 million patients are at risk of stroke due to AF. About 4% of these patients are over 80 years old (Heidbuchel et al., 2015). In England alone, spending on

anticoagulants rose by more than £100 million in 2015/2016 and by around £400 million in 2017/2018. The cost of treatment is expected continue rising to reach about £1 billion per year by 2020 (Burn and Pirmohamed, 2018). These figures are important since in developing countries such expenditure may be unsustainable (Gaziano, 2005).

3.1.5. Adherence to medications

The concept of adherence to medication, as defined by the World Health Organisation (WHO), refers to the degree to which an individual's actions align with the prescribed recommendations from their healthcare provider, which may include taking medication, adhering to a specific diet, or implementing lifestyle changes (WHO, 2003). This definition considers several factors, including the patient's initial engagement with pharmacotherapy, their ongoing compliance over time, any instances of temporary or permanent discontinuation, and resuming medication usage after a break. Thus, adherence to medications encompasses all these components (Sabate, 2003).

3.1.6. Rationale for importance of adherence to OACs in AF patients

Adherence to OAC medications is crucial for successful treatment of patients with atrial fibrillation AF and other conditions that require OACs therapy (Ho et al., 2019). Non-adherence to OACs has been associated with significant health problems for patients, including an increased risk of stroke and damage to different organs affected by stroke (Platt et al., 2010, Yao et al., 2018). Failure to adhere to OACs has been linked to severe health issues such as an increased risk of stroke and organ damage (Zhang et al., 2018).

Numerous studies have investigated OACs' adherence rates among various patient populations, including Schulman (2014), who evaluated adherence patterns among OACs-naïve AF patients and those already on DOACs. Results revealed that adherence to OACs declined over time for patients who were already taking them, with DOAC patients exhibiting suboptimal drug levels when compared to the OACs-naïve group.

Moreover, Shore and colleagues (2014) conducted a study to explore the relationship between inadequate adherence to dabigatran and clinical outcomes over time in patients with atrial fibrillation (AF). Their analysis was based on the RE-LY trial, which compared two different doses of dabigatran with warfarin in AF patients, and adherence was evaluated through pill counts at 3, 6, and 12 months. Out of the 18,113 patients enrolled, 80.6% demonstrated good adherence to the medication. The study findings revealed that maintaining good adherence to dabigatran therapy was linked to more favourable clinical outcomes for AF patients. The authors also suggested that implementing adherence-enhancing interventions could be a valuable strategy to improve patient outcomes. Several studies have demonstrated the negative impact of non-adherence to OAC medications on the health outcomes of patients with various conditions.

For instance, in their study, Yao et al. (2016) aimed to investigate the relationship between adherence to OACs therapy and the incidence of stroke and bleeding in individuals with AF. They employed a retrospective cohort study design and examined data from 64661 patients in the US. The findings revealed that patients who did not adhere to their OACs therapy had a considerably elevated risk of experiencing stroke and bleeding in the context of AF.

Furthermore, Jortveit, and colleagues (2019) undertook a systematic review and meta-analysis to assess the effect of not following the recommended OAC treatment on the incidence of stroke and all-cause mortality in patients with AF. The study analysed 14 research papers involving a total of 97,291 AF patients. The analysis revealed that not following the prescribed OAC treatment was linked to a higher risk of stroke (RR, 1.64; 95% CI, 1.38-1.94; I2=76%; P<0.001) and all-cause mortality (RR, 1.50; 95% CI, 1.31-1.71; I2=68%; P<0.001). Furthermore, non-adherence to vitamin K antagonists was associated with a higher risk of stroke (RR, 1.69; 95% CI, 1.47-1.94; I2=79%; P<0.001) and all-cause mortality (RR, 1.50; 95% CI, 1.30-1.73; I2=68%; P<0.001). Non-adherence to DOACs was also linked to an

increased risk of stroke (RR, 1.44; 95% CI, 1.05-1.98; I2=81%; P=0.02) and all-cause mortality (RR, 1.65; 95% CI, 1.20-2.29; I2=0%; P=0.002). In conclusion, the study established that not following the recommended OAC treatment leads to a higher incidence of stroke and all-cause mortality in AF patients. Therefore, enhancing medication adherence should be a top priority in managing AF.

Similarly, Yao et al. (2018) conducted a retrospective cohort study on adherence to OACs among AF patients. In their study, the researchers identified 23 relevant studies with a combined patient population of 60,674 individuals. They found that the collective prevalence of non-adherence to OACs was 31.5%. Non-adherence was also associated with a higher risk of stroke or systemic embolism, with a hazard ratio of 1.51 and a 95% confidence interval of 1.19-1.92. Based on these findings, the authors concluded that non-adherence to OACs is a widespread issue that increases the likelihood of adverse clinical outcomes. They suggest the need for the development and implementation of effective strategies to improve adherence in clinical practice.

In addition, McHorney et al. (2017) conducted a study to investigate the factors that are linked to adherence to OACs therapies for stroke prevention in patients diagnosed with AF. The study utilised data from 17,095 patients who were enrolled in a national managed care plan in the United States. The authors observed that adherence to OAC therapies was inadequate, with only 44.2% of patients achieving optimal adherence, which was defined as taking at least 80% of the prescribed doses. In addition, patients who were older, had higher income, and had better health status were found to be more adherent to their OAC therapy, whereas those with multiple comorbidities and taking multiple medications were less likely to be adherent. The authors suggest that addressing modifiable factors such as patient education, simplifying medication regimens, and addressing side effects and drug interactions could help to enhance adherence to OAC therapies for stroke prevention in AF patients. They also emphasised the importance of

further research to gain more insight into the underlying reasons for low adherence and to develop more effective interventions to improve adherence.

These studies highlight the importance of adherence to OAC medications in preventing serious health problems such as stroke. Healthcare providers should prioritise patient education and interventions to improve adherence to OACs. By understanding the factors that contribute to non-adherence and tailoring interventions to address patients' specific needs, healthcare providers can enhance patients' health outcomes and minimise the risks associated with non-adherence. Overall, healthcare providers should regularly monitor adherence levels and intervene promptly to prevent potential health problems associated with non-adherence to OAC medications.

In the Middle East, there have been several studies examining adherence rates to OACs. In 2016, Eltayeb and colleagues in Sudan discovered that only 5.7% of patients adhered to warfarin therapy. Their findings indicated that patients who were satisfied with and adherent to warfarin treatment had better control over their International Normalised Ratio (INR) levels. The study also revealed that non-adherence to warfarin therapy had negative consequences on patients' health-related quality of life (HRQOL) and daily activities. In addition, Elbur and colleagues conducted a cross-sectional study in western Saudi Arabia to evaluate patients' knowledge, satisfaction, and adherence to oral anticoagulant (OAC) treatment, and to identify predictors of these domains. Two groups of patients were recruited, with 208 patients in group A for knowledge assessment and 248 patients in group B for satisfaction and adherence measurement. The study found that only 14.9% of patients had adequate knowledge about OAC treatment, and patients with an intermediate educational level or above were more knowledgeable. The satisfaction rate with anti-clot treatment was 63.7%, and females were less satisfied than males. The study also revealed that the rate of adherence to oral anticoagulant treatment was 35.9%. The authors recommend that health education should be provided to

improve patients' knowledge about oral anticoagulant treatment, and that patients should be motivated to increase their satisfaction and adherence to therapy.

Low levels of awareness regarding cardiovascular diseases, lack of infrastructure, and low income are significant challenges in developing countries. These obstacles make it difficult to implement comparable measures for reducing risk factors and taking preventive approaches to conditions such as stroke and neurological disorders (Ghandehari, 2011).

Compared to other regions and Western countries, there is a limited number of studies on the prescribing patterns and utilisation of OACs in the Middle East (Lip et al., 2012). This has led to a lack of understanding of the burden of OAC use, patients' attitudes and perceptions towards these medications, and their adherence to prescribed OACs (Chugh et al., 2014).

3.1. 7. Measuring adherence to medications

It is crucial to assess medication adherence to ensure optimal health outcomes for patients. Findings of studies on adherence to medications suggested that accurately measuring adherence to medications is essential for determining the effectiveness of a treatment plan, identifying potential barriers to adherence, and tailoring interventions to improve patient compliance (Osterberg et al., 2005; Kripalani et al., 2007). Consequently, measuring adherence to medications is important for several reasons: to ensure effectiveness of treatment as adherence to medication or treatment regimen is crucial for its effectiveness. If a patient does not adhere to the prescribed medication or treatment plan, it can lead to the progression of the disease or condition, and may result in treatment failure (Cavanagh et al., 2013).

Moreover, adherence to medication and treatment is associated with improved patient outcomes, such as better symptom control, reduced complications, and improved quality of life. By measuring adherence, healthcare providers can identify patients who may be at risk of

poor outcomes and take steps to improve adherence and optimise their treatment (Shiovitz-Ezra et al., 2009).

In addition, measuring adherence can help identify barriers to adherence, such as side effects, forgetfulness, or difficulty understanding instructions. Healthcare providers can work with patients to address these barriers and develop strategies to improve adherence (Kardas et al., 2013)

Another benefit from measuring adherence is to facilitate communication between patients and healthcare providers. By discussing adherence and barriers to adherence, healthcare providers can better understand their patients' needs and tailor their treatment plans accordingly. Furthermore, non-adherence to medication and treatment is associated with increased healthcare costs, such as hospitalisations. By measuring adherence and improving adherence rates, healthcare providers can reduce healthcare costs and improve the overall quality of care (Aitken et al., 2012).

Table 3.1 provides an overview of the different methods that can be used to measure adherence to medications, including both direct and indirect methods.

Table 3.1. Summary of methods for measuring adherence (Osterberg,2005)

	Advantages	*Disadvantages*
Direct methods		
i. Directly observed therapy	Most accurate	Impractical, Patient can hide pills and discard later
ii. Measurement of drugs metabolites	Objective methods	Expensive, variability can occur in metabolites
iii. Measurement of biomarkers	Objective, suitable for clinical trials	Used tests are expensive
Indirect methods		
i. Patients' questionnaires, self-reported	Simple, inexpensive, mostly used in clinical settings	Susceptible to errors, results are sometimes inaccurate by patients

ii.	Pill count	Objective, quantifiable, easy to perform	Data affected by patients' behaviour (e.g. dumping)
iii.	Rates of prescriptions refill	Easy to obtain data, objective	Refill is not equivalent to taking tablets
iv.	Assessment of patient's clinical response	Easy to perform, simple	Confounding factors may affect response
v.	Electronic medications monitors	Accurate, tracks medication taking patterns	Requires frequent visits, need downloading the data, expensive
vi.	Measuring physiological markers	Easy to carryout	Markers may be absent for different reasons
vii.	Patients' diary	Help to correct poor recall	Easily altered by patients

This systematic review aimed to review the literature to determine levels of adherence to OACs in AF patients in the Middle East. The reason for selection of AF because it is the main condition for which OACs are prescribed and AF patients represents the main patient group who are taking these medications. For example, the data from the UK indicated that in 2017, the proportion of the prescribed and dispensed OACs for AF patients was 65.6%. Literature was searched for comparable data from the Middle East but no information was found.

Specific objectives for this systematic review are:

- To determine the level and rate of non-adherence to OACs in patients with AF in the Middle East.
- To determine factors affecting non-adherence to OACs in AF patients from the Middle East.
- To determine clinical and non-clinical outcomes that affect OACs usage among AF patients in the Middle East.

3.2. Materials and Methods

3.2.1. Search protocol

3.2.2. Eligibilty criteria

The protocol for this systematic review was registered on PROSPERO (CRD42019124610) (Appendix II). The search included primary studies into adherence to OACs within the Middle Eastern region. It included data obtained from both cross-sectional and cohort studies. To collect relevant articles on adherence to OACs and atrial fibrillation, we systematically queried several databases, namely Pubmed, Pubmed Central UK, Embase, ScienceDirect, and Google Scholar. Our search was guided by specific keywords, which included the names of individual OACs like warfarin, dabigatran, rivaroxaban, apixaban, and edoxaban. The search period was from January 1, 2009, to June 30, 2021, which was chosen due to the timeline of DOACs incorporation into clinical practice. The search was limited to studies conducted in middle Eastern countries, namely Saudi Arabia, Egypt, Sudan, Kuwait, Qatar, United Arab Emirates, Israel, Bahrain, Jordan, and Lebanon. Duplicate studies were excluded, and the references of the collected articles were reviewed to select relevant studies. Abstracts and titles of the articles were independently screened by the research team, and relevant studies were selected based on specific criteria such as studies describing adherence to OACs, articles assessing patients' related factors to adherence such as satisfactions with OACs, and papers commenting on adherence to prescribing guidelines for OACs. Published quantitative data articles in English language that included data about patients' adherence to OACs, knowledge of patients about OACs, satisfaction of patients with OACs, adherence to prescribing guidelines of OACs by prescribers, and pharmacovigilance studies about OACs were included in this review. Registries and studies which were conducted outside the Middle East region were excluded. Articles that included non-adherence, and adherence to OACs in conditions other than AF were also excluded. The PRISMA guidelines were followed in this systematic review (Figure 3.1).

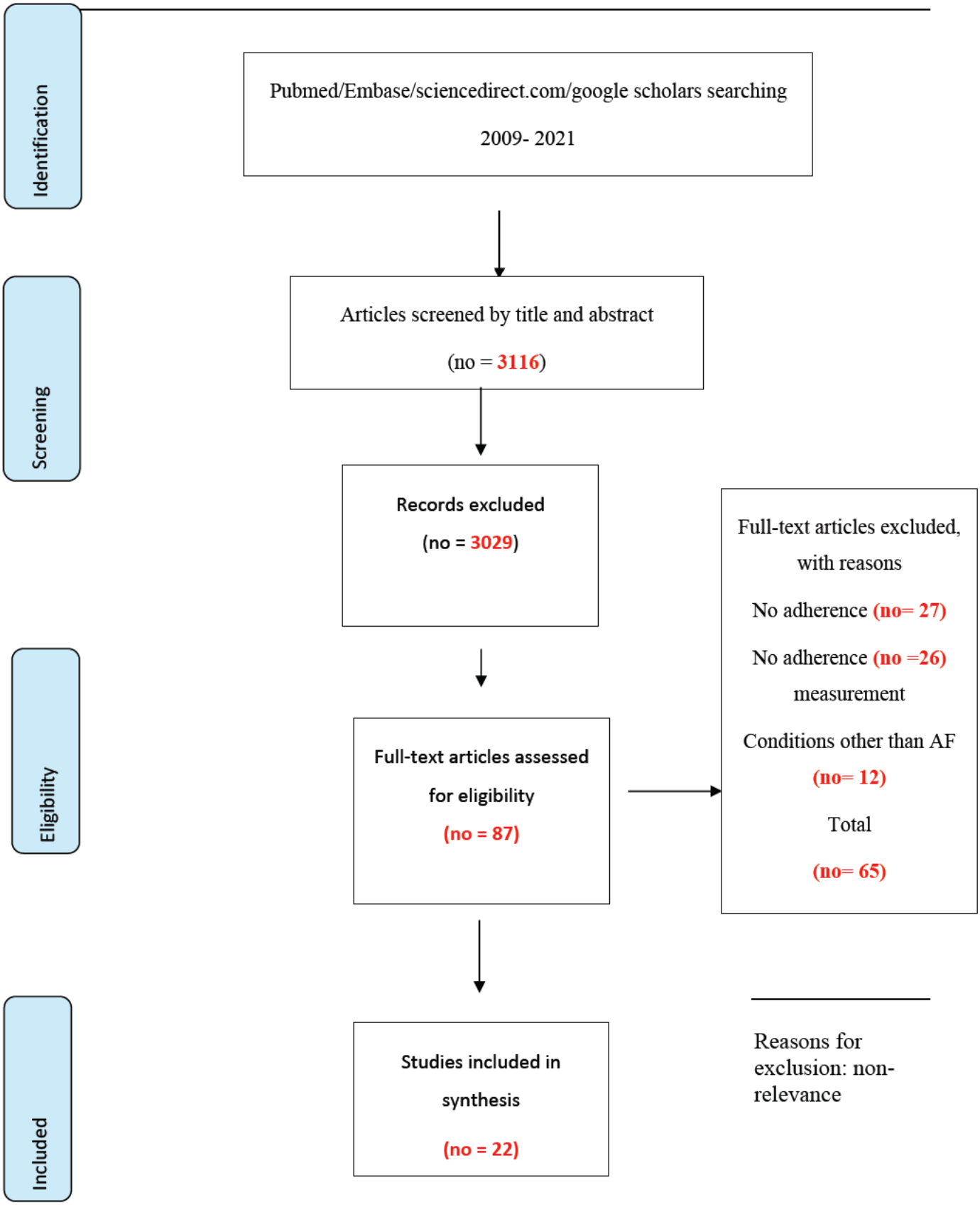

Fig. 3.1. Consort diagram for selection of studies

3.2.3. Evaluation of the studies

The Joanna Briggs Institute Critical (JBI) checklists designed for analytical cross-sectional studies and cohort studies were chosen to evaluate the quality of the selected cross-sectional and cohort studies in this systematic review.

The JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies consists of nine questions that assess the study's methodological quality. These questions address factors such as the representativeness of the sample population, the use of a reliable outcome measurement tool, the recognition and control of confounding variables in the analysis, and the applicability of the findings to the study population (Appendix II).

The JBI Critical Appraisal Checklist for Cohort Studies comprises of 11 questions addressing key aspects of cohort study methodology, including the clarity of study objectives, appropriateness of the study population selection, accuracy of exposure and outcome measurement, adequacy of follow-up data, appropriate statistical analysis methods, consideration of confounding factors, and the validity of study results and conclusions. JBI tools were carefully chosen because of its practicality and its appropriateness for the selected studies (Appendix II).

3.3.Results

Twenty two studies met the inclusion criteria were conducted across 11different countries in the region. There included Jordan (n=1), Kuwait (n=1), Qatar (n=5), Saudi Arabia (n=7), Sudan (n=1),Turkey (n=1), United Arab Emirates (n=3), and three multi-centre studies: Bahrain, Kuwait, Qatar, Oman, United Arab Emirates, and Yemen (n=2), and Bahrain, Jordan, Lebanon, Saudi Arabia, and United Arab Emirates (n=1). (see Appendix II for outcome of data extraction).

3.3.1. Evaluation of the selected studies

When applying the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies, it was observed that most studies provided comprehensive descriptions of the study population and setting. However, in the case of (Eltayeb et al., 2016) study, the site where the research was conducted was not adequately specified. The exposure was measured in a valid and reliable way in all studies excluding (Alshammari and Alhantoushi, 2018). The objective, standard criteria used for measurement of the condition are followed in the studies. However, confounding factors were not clearly identified in studies that discussed oral anticoagulant warfarin (Eltayeb et al., 2016), (Balkhi et al., 2017), (Elbur et al., 2015), (Ababneh et.al., 2016), (Alyousif and Almeman, 2016), (Salam et al., 2012), (Elewa et al., 2016 a), (Elewa et al., 2016), (Elewa et al., 2017). For example, drug interactions checks were not reported if it had been assessed. Consequently, it was not clear if strategies to deal with confounding factors were in place. This contrasts with studies that considered DOACs where confounding factors are clearly defined (Elewa et al.,2018), (Al-Meman and Almutairi, 2014), (Shehab et al., 2015), (Mayet et al., 2018), (Martínez et al., 2018), (Emren et al., 2018). The JBI critical appraisal tool for cohort studies was employed to assess the quality and relevance of the following cohort studies (Elewa et al.,2016 a), (Zubaid et al., 2013), (Zubaid et al., 2015), (Martinez et al., 2018), (Alyousif and Alsaileek, 2016), (El Kadri et al., 2021), (Anoussi et al., 2021), which are included studies. The evaluation process confirmed that the selected cohort studies successfully met the criteria for inclusion in the systematic review.

3.3.2. Study design

Two study designs were found in the selected studies, namely cross-sectional studies and cohort study designs. Cross sectional survey study design was used in 15 studies (Eltayeb et al., 2016), (Balkhi et al., 2017), (Mayet et al., 2018), (Elbur et al., 2015), (Alshammari and

Alhantoushi,2018), (Elewa et al.,2016), (Emren et al., 2018),(Ababneh et.al., 2016), (Al-Meman and Almutairi, 2014), (Salam et al., 2012), (Elewa et al., 2017), (Shilbayeh et al., 2018), (Shelbayeh et al., 2018 a), (Elewa et al., 2018), (Shehab et al., 2015). Cohort study design was found in 5 studies (Elewa et al.,2016 a), (Zubaid et al.,2013), (Zubaid et al., 2015), (Martinez et al.,2018), (Alyousif and Alsaileek,2016), (El Kadri et al., 2021), (Anoussi et al., 2021).

3.3.3. Settings of the selected studies

The studies were carried out in either anticoagulants clinics, specialised cardiac hospitals, or general practice (GP) centres. Anticoagulants clinics were the venue for collecting data in 15 studies (Eltayeb et al., 2016), (Mayet et al., 2018), (Elbur et al., 2015), (Zubaid et al., 2013), (Emren et al., 2018),(Ababneh et.al., 2016), (Shilbayeh et al., 2018), (Elewa et al., 2018), (Salam et al., 2012), (Elewa et al., 2016 a), (Elewa et al., 2016), (Elewa et al.,2017), (Zubaid et al., 2015), (Shilbayeh et al., 2018a) ,(Shehab et al., 2015). Three studies were conducted in primary care (Alshammari and Alhantoushi, 2018), (Balkhi et al., 2017), (Martinez et al., 2018). Specialised cardiac centres was the host of 2 studies (Alyousif and Alsaileek., 2016), (Al-Meman and Almutairi, 2014). Eleven studies were single-site studies (Al-Meman and Almutairi, 2014), (Shilbayeh et al., 2018), (Alyousif and Alsaileek., 2016), (Balkhi et al., 2017), (Eltayeb et al., 2016), (Shilbayeh et al., 2018a), (Elbur et al., 2015), (Mayet et al., 2018), (Elewa et al., 2016), (Elewa et al., 2016 a), (Salam et al., 2012), with 9 studies being undertaken in multiple centres (Elewa et al., 2017), (Martinez et al., 2018), (Zubaid et al., 2015), (Elewa et al., 2018),), (Emren et al., 2018), (Zubaid et al., 2013), (Ababneh et.al., 2016), (Alshammari and Alhantoushi, 2018), (Zubaid et al., 2015).

3.3.4. Duration of the selected study

Durations of data collection varied between the studies, in 4 studies, it was between 1 and 2 months (Eltayeb et al., 2016), (Elbur et al.,2015), (Balkhi et al., 2017), (Alshammari and

Alhantoushi, 2018). In other 4 studies, it was necessary to spend between 2.5 and 5 months to obtain the data (Mayet et al., 2018), (Shilbayeh et al., 2018), (Zubaid et al., 2013), (Shilbayeh et al., 2018a). Six to 8 months was the period for collecting data in 3 studies (Emren et al., 2018), (Ababneh et.al., 2016), (Zubaid et al., 2013). Moreover, studies needing between 12 and 19 months were 3 (Alyousif and Alsaileek, 2016), (Zubaid et al., 2015), (Elewa et al., 2016).

In addition, between 19 and 36 months was necessary for 3 studies (Elewa et al., 2016 a), (Al-Meman and Almutairi, 2014), (Martínez et al., 2018). Two studies retrieved data for 60 months (Elewa et al., 2017), (Elewa et al., 2018). Finally, only 1 study included data for (20 years) 240 months (Salam et al., 2012).

3.3.5. Tools to measure adherence to OACs

Different adherence measuring scales were used. Morisky 8-item Scale was used to measure adherence in 3 studies (Emren et al. 2018), (Ababneh et al., 2016), (Shilbayeh et al., 2018). In addition, Morisky 4-item Scale translated to Arabic language was used in 2 studies (Eltayeb et al., 2016), (Elbur et al., 2015) while the Medication Adherence Questionnaire (MAQ) translated to Arabic was used in 1 study (Balkhi et al., 2017). (Table 3.2).

Table 3.2. Adherence measures and authors of the publications

Type of measuring adherence scale	Authors of the studies
Morisky 8-item	(Emren et al.2018), (Ababneh et al.,2016), (Shilbayeh et al., 2018)
Morisky 4-item Scale translated to Arabic language	(Eltayeb et al.,2016), (Elbur et al., 2015)
Medication Adherence Questionnaire (MAQ) translated to Arabic language	(Balkhi et al., 2017)

3.3.6. Tools to measure patients' satisfaction with OACs

To measure patients' satisfaction with oral anticoagulants, Anti-Clot Treatment Scale ACTS was used in 3 studies (Eltayeb et al., 2016), (Balkhi et al., 2017), (Elbur et al., 2015). The 24-item Duke Anticoagulation Satisfaction Scale DSS was used in one study (Elewa et al., 2016 a). (Table 3.3).

Table 3.3. Satisfaction with oral anticoagulants measures and authors of publications

Type of satisfaction measure	Authors of studies
Anti-Clot Treatment Scale ACTS	(Eltayeb et al., 2016), (Balkhi et al., 2017), (Elbur et al.,2015)
The 24-item Duke Anticoagulation Satisfaction Scale DASS	(Elewa et al.,2016 a)

3.3.7. Measuring effectiveness and usage of OACs

Time in therapeutic range TTR was used in 4 studies (Zubaid et al., 2013), (Shilbayeh et al., 2018), (Elewa et al., 2016 a), (Alyousif and Alsaileek et.al., 2016).

3.3.8. Overview of the objectives of selected studies

The objectives of the selected studies were as follows: measuring adherence to oral anticoagulants, measuring adherence to oral anticoagulants and patients' satisfaction with oral anticoagulants, measuring adherence to oral anticoagulants and assessing knowledge about oral anticoagulants, assessing adequacy of anticoagulation with oral anticoagulants, assessing adequacy of anticoagulation with oral anticoagulants and knowledge about oral anticoagulants, assessing adequacy of anticoagulation with oral anticoagulants and patients' satisfaction with oral anticoagulants, describing adherence to prescribing guidelines of oral anticoagulants, developments in use of oral anticoagulants, describing reported adverse events related to oral anticoagulants. Table (3.4) summarises the objectives and the studies.

Table 3.4. Overview of the objectives of the studies

Objectives	*Studies*
Measuring adherence to DOACs	(Emren et al., 2018)
Measuring adherence to OACs and patients' satisfaction with oral anticoagulants	(Eltayeb et al., 2016), (Balkhi et al., 2017), (Elbur et al., 2015).
Measuring adherence to OACs and assessing knowledge about oral anticoagulants	(Ababneh et.al., 2016).
Assessing adequacy of anticoagulation with the oral anticoagulant warfarin	(Elewa et al., 2016), (Alyousif and Alsaileek, 2016), (Zubaid et al., 2013).
Assessing adequacy of anticoagulation and knowledge about OACs	(Shilbayeh et al., 2018).
Assessing adequacy of anticoagulation and patients' satisfaction with oral anticoagulants.	(Elewa et al.,2016 a), (Shelbayeh et al.,2018 a)
Describing adherence to prescribing guidelines of OACs	(Elewa et al.,2018), (Mayet et al., 2018), (Alshammari and Alhantoushi,2018), (Anoussi et al., 2021).
Trends in use of OACs was the objective of 3 studies	(Zubaid et al., 2015), (Elewa et al.,2017), (Salam et al., 2012), (El kadri et al., 2021).
Describing reported adverse events related to OACs	(Martinez et al.,2018), (Al-Meman and Almutairi, 2014), (Shehab et al., 2015).

3.3.9. Outcomes of the objectives of the selected studies

Studies, which investigated adherence to warfarin, reported low levels of adherence among patients (31.8%, 35.9%, and 54%). These studies were carried out in different countries, used different methods to measure adherence, and reported variable limitations to their results (Balkhi et al., 2017; Elbur et al., 2015; Ababneh et. al., 2016). Adherence to DOACs was the objective in only one study (Emren et al., 2018). The results of this study were stratified in three levels of adherence: (23%) of the participants showed high adherence to DOACs, (51%) were classified as low adherence. Table (3.5.) summarises the outcomes of these studies.

Table 3.5. Outcomes of the objectives of the selected studies

Authors	Outcomes	
Eltayeb et al., 2016	□ Adherence rate (5.7%), patients were satisfied (47%) □ No association between adherence and satisfaction	
Balkhi et al., 2017	□ Adherence rate was 31.8%. □ Satisfaction level was 51%. □ higher education, and being non-Saudi are strong predictors for controlled INR □ adherence was significantly associated with INR control	
Shilbayeh et al., 2018	□ Rate of adherence was 32.6%. □ 48.5% of patients showed satisfactory knowledge of warfarin, however, only □ 57.1% had good anticoagulation control (TTR ≥ 75%). □ no correlation was found between anticoagulation control and knowledge about warfarin. □ No significant association between MMAS-8 category adherence/non-adherence and level of knowledge based on a cut-off point of 50%.	
Elbur et al., 2015	□ Rate of adherence was 35.9%, □ Satisfaction level was 63.7%, □ No association between adherence and background characteristics of the participants	
Alshammari and Alhantoushi, 2018	□ Family physicians knowledge about use of anticoagulants by patients varies between physicians. □ Barriers to knowledge defined as lack of follow-up system and lab investigations. □ educational programs are necessary to provide follow-up system and □ facilitate performing of lab investigations to decrease parries and aid practice of use of anticoagulants.	
Emren et al., 2018	□ The adherence to NOAC was found to be low (49%), □ Reasons for non-adherence were high CHADVASC score, low levels of education, advanced age, knowledge about their drug and disease, and living in rural areas with limited access to a specialist.	
Ababneh et.al., 2016	□ Rate of adherence was 54 %. □ Advanced age educated patients are factors associate with adherence. □ No association was found between adherence and gender,	□ 58 % knew how frequent they should check INR levels. □ MMAS-8 adherence scores were significantly associated. □ with warfarin knowledge

	BMI, warfarin weekly dose, number of medications, or duration of warfarin use. • 22 % reported knowledge about warfarin drug interactions. • 37 % reported knowledge about warfarin food interaction,	• Mean TTR range was 38.94 ± 32.57,15 % were considered in a good anticoagulation control group (TTR[70 %). • Significant association between adherent groups (adherent vs. non-adherent) and INR control groups was found in this study. • 50 % knew their INR target
Shilbayeh et al., 2018	• Rate of adherence was 32.6%. • 48.5% of patients showed satisfactory knowledge of warfarin, however, only • 57.1% had good anticoagulation control (TTR ≥ 75%). • no correlation was found between anticoagulation control and knowledge about warfarin. • No significant association between MMAS-8 category adherence/non-adherence and level of knowledge based on a cut-off point of 50%.	

Other patients' related factors, which may affect adherence such as patients' knowledge about OACs, patients' satisfaction with OACs, effectiveness of OACs, and adherence of the prescribers to the prescribing guidelines, have also been assessed in the studies. Inconsistent outcomes in terms of association between adherence and knowledge, patients' satisfactions, and effectiveness of oral anticoagulants were documented. Table (3.6) summarises the outcomes of the studies.

Table 3.6. Outcomes of the assessment of patients' related factors and adherence to OACs in the selected studies

Authors	Outcomes
Mayet et al., 2018	56% of rivaroxaban prescriptions met at least one inappropriate criterion. Inappropriate dosing per patient's creatinine clearance (CrCl) was recognised in 42% of rivaroxaban prescriptions. Majority of rivaroxaban prescriptions (82.9%) issued for 15mg strength. Non-approved indications identified in 14% of rivaroxaban prescriptions.
Elewa et al., 2018	Dabigatran and rivaroxaban were prescribed for inappropriate indication in (3.3%) of the patients. Inappropriate dosing was found in (33.6%) prescriptions. There were significantly more inappropriate dabigatran prescriptions compared to rivaroxaban. Logistic regression analysis confirmed that dabigatran prescribing was the only factor associated with inappropriate indications. Factors associated with inappropriate dosing included dabigatran prescriptions and poor renal function. DOACs have been gradually replacing warfarin in Qatar; however, they are not always prescribed appropriately specially in patients on dabigatran and those with renal impairment.
Zubaid et al., 2014	AF patients in the Middle East are relatively young with high burden of atherosclerotic risk factors. 10% of patients spontaneously cardioverted to sinus rhythm. 75% of patients were managed with rate control strategy. Amiodarone is usually used in pharmacological cardioversion.

	• Sinus rhythm was restored in 43% of patients when pharmacological cardioversion compared to 76% of patients when electrical cardioversion was attempted. • 40% of patients with CHADS2 score 2 were not on warfarin at discharge. • patients who were discharged in AF rhythm, • 62% of patients were prescribed warfarin at the time of discharge. • Reasons for discharge without warfarin were physician preference/decision, high bleeding risks, anticipated noncompliance, and other reasons. • INRs at 1, 6, and 12 month follow-up, 28% were <2, 56% were between 2 and 3, and 16% were >3.
Salam et al., 2012	• The study reported suboptimal use of oral anticoagulation. • On admission, there was no ethnic preference in the use of anticoagulant warfarin. • On discharge Asian patients were more likely than arabs to be prescribed warfarin. • Non treatment patients declined from 90% to 48% between 1991 to 2010. • 44.1% of the patients used oral anticoagulants.
Shehab et al., 2015	• The main indication for dabigatran use was AF. • Rate of bleeding with dabigatran was (23.7%). • Melena was the leading cause of bleeding (10.7%). • Hospitalisation rate was (67.1%) • Dabigatran withdrawal rate was (0.01%), and mortality rate was (6.5%). • Dabigatran represents a suitable alternative to warfarin; however, it may need plasma drug monitoring.
Zubaid et al., 2013	• The TTR was 47% for traditional method and 52.6% for poor TTR. • Study did not comment on effect of non-adherence on this result, but was reported as a limitation that need to be studied
Al-Meman and Almutairi, 2014	• 26% of those receiving a dose of 150 mg experienced adverse events including 2 cases of minor bleeding and 1 case of stroke. • 8% of those receiving a dose of 110 mg experienced adverse events, including 1 case of major gastric bleeding and one case of death.

	• The most common adverse event was gastric distress. • Treatment with dabigatran was considered as safe, however, high risk patients need to be evaluated before starting treatment
Elewa et al., 2016 a	• Mean number of (INR) tests/month was 65, the average testing frequency was 2.7 weeks. • The average %TTR was 76.8 to22.9%. • There was one major bleeding event (0.67%/year), 12 minor bleeding events (8%/year) and two thromboembolic events (1.35%/year) recorded during the study period. • 76% of the patients indicated 'a lot to very much' in terms of their overall satisfaction with the anticoagulation treatment. • The participants who were naïve to anticoagulation treatment reported a significantly greater satisfaction and better QoL than the experienced patients
Elewa et al., 2016	• Pharmacist-based clinics had a superior TTR compared to those managed at the doctor-based clinics. • The % of visits within therapeutic range was significantly higher in the pharmacist's group compared to doctor's group (76.5% vs. 71.2%). • Percentage of visits with extreme sub-therapeutic INR was reduced in the pharmacist-managed clinic (5.17% vs. 7.05%). • Pharmacist-based anticoagulation has better INR control when compared to the traditional anticoagulation management.
Elewa et al., 2017	• 84% of patients were on warfarin and 16% were on DOACs. • 78% of patients prescribed warfarin for AF, 22% was on DOACs. • For VTE patients 79% were on warfarin, 21% on DOACs. • Prescriptions of DOACs increased from 0.5% to 23% between 2011 and 2015. • Rivaroxaban prescriptions increased significantly compared to dabigatran (40.9%) in 2014 vs. (64.1%) in 2015. • 23.9% of DOACs patients were on warfarin while (16.9%) of DOACs users were switched back to warfarin.

	• Rapid uptake of DOACs in Qatar as they currently account for more than 20% of all anticoagulant use. • A shift towards more use of rivaroxaban compared to dabigatran since its approval in the country in 2014. • Despite DOACs adoption, warfarin remains the main anticoagulant prescribed
Martínez et al., 2018	• confirmed findings from previous studies that Middle Eastern AF patients are youner than those in other parts of the world, • Middle East AF patients have significantly high figures of AF alone without comorbidities compared to rest of the study population. • Rates of DM and HF are higher in the area. • Rates of major bleeding was 1% when using rivaroxaban
Alyousifet.al., 2016	• 28.2% had a history of stroke. • The mean TTR was 59%. • 32.7% had poor anticoagulation control; TTR of <50%. Poor anticoagulation control was significantly associated with higher CHADS2 score. • TTR was not significantly different between men and women. • TTR was not associated with age or duration of anticoagulation. • There was no adequate information to assess the effect of other factors such as diet, compliance, and level of education on anticoagulation. • The overall quality of anticoagulation was not significantly different between patients with and without stroke.

3.3.10. Limitations to studies

The included studies reported several limitations which may have affected their outcomes. The majority of studies were single site (Eltayeb et al., 2016), (Balkhi et al., 2018), (Elbur et al., 2015), (Shilbaya et al., 2018 a), (Ababneh et al., 2016) which reduces the generalisability of the outcomes to all populations. Another limitation is the limited sample sizes, some studies reported that the size of the sample was not representative to the population and minimising the utility of the data, these studies were (Alshammari and Alhantoushi, 2018), (Elewa et al., 2016a), (Shilbaya et al., 2018 a). Studies that reported problems with risk of bias and under/over estimation of adherence rates as well as problems with using questionnaires and design of studies included (Eltayeb et al., 2016), (Emren et al., 2018), (Alshammari and Alhantoushi, 2018), (Balkhi et al., 2018), (Elewa et al., 2016). In the clinical aspect, accuracy of diagnosis of AF, missing data about use of medications, and clerking and documentation errors were reported as limitations to the studies in the following studies (Salam et al., 2012), (Zubaid et al., 2015), (Zubaid et al., 2013), (Alyousif and Alsaileek, 2016), (Elewa et al., 2017), (Elewa et al., 2018).

3.3.11. Key findings

The systematic review of the literature revealed that adherence to OACs in the Middle East is low, compared to other parts of the world. Awareness about the medical conditions for which OACs are prescribed such as AF among patients varied between patients in the region. The systematic review also indicated that health system related factors such as inappropriate prescribing of OACs can play a role in reducing patients' adherence to OACs.

3.4. Discussion

The aim of this review is to assess the level of adherence to oral anticoagulants in the Middle East and highlight related factors that affect adherence to OACs in the area.

The results of the selected studies documented variable adherence rates which ranged between 5.4% and 54% in the region. This wide variation can be explained by differences in the prescribing patterns of OACs, the differences in the employed tools to measure adherence, confounding factors associated with the design of the studies, and variations between the populations in these studies. Similar adherence rates to OACs were reported in other parts of the world, however, results of studies from developed countries showed adherence rates > 80% (Zhao et al., 2017; Borne et al., 2017; Brown et al., 2017; Han et al., 2019). It is worth mentioning that these studies had employed different strategies to measure adherence to OACs in terms of design of the studies and use of different methods to measure adherence to OACs such as proportion of days covered (PDC). The variations in the methods used to measure adherence and the differences between the health systems in the Middle East and the developed countries, and the cultural variations in the two populations, all these factors make the results about adherence to OACs from the two areas incomparable.

The included studies revealed that self-reporting methods were the main tools to evaluate adherence to OACs and the main method to assess the relationships between adherence to OACs and the impact of non-clinical factors on adherence to these medications in the Middle East. Nevertheless, these methods are disadvantaged by the possibility of biased limitations and inability of some participants to assess themselves accurately (Pannucci et al., 2010; Althubaiti, 2016).

Moreover, the studies in this review had a cross-sectional study design, which is known as cost effective, easy to conduct, and it measures the prevalence of a phenomenon successfully

(Carlson and Morrison, 2009). At the same time, cross-sectional designs have some shortcomings such as their susceptibility to biases and they are challenging to find reasoning (Austin, 2011). Therefore, the results of the studies should be interpreted with caution due to these limitations and confounding factors, considering that the Middle Eastern population high heterogeneity, levels of literacy/ illiteracy, and the variable availability of medical services within the region. Such variations may contribute to the complexity of the analysis of the adherence phenomenon in the Middle East.

The WHO identified five domains which can be considered as determinants to adherence. These dimensions are the interaction between healthcare providers, patients, and healthcare systems; socio-economic factors; patients related factors; condition related factors; and therapy related factors (WHO, 2003). The selected studies in this review were focused on investigating the VKA warfarin and on some of the non-clinical factors, mainly therapy and patients' related factors. Despite their ability to elucidate some relationships between adherence to OACs and non-clinical factors in taking medications, such as warfarin, these studies were fallen short of interpreting the non-clinical factors, such as knowledge of patients about their conditions.

The results of this systematic review showed that the studies were conducted on patients who were taking warfarin which indicated that prescribing of warfarin is still more common than recommending of DOACs in the Middle East, this finding can be justified by availability of warfarin in drugs' formularies in the Middle East for longer time compared to DOACs. Therefore, outcomes of research on warfarin are widely available. Moreover, indications, cautions on prescribing, and dosing recommendations when prescribing warfarin in the Middle East are not different to other parts of the world where warfarin is still widely used (Rodwin, 2019). From another point of view, looking at the speed of which DOACs are incorporated in the prescribing systems for cardiovascular conditions showed that this rapidity varies between Middle Eastern countries. Studies from the gulf state Qatar for example reflected a higher speed

(Elewa et al., 2017) in adding DOACs to their formulary compared to other countries such as Jordan and Sudan (Ababneh et al., 2016; Eltayeb et al., 2016). This can be justified by the availability of the financial resources and the necessary expertise to these health systems to make DOACs available to patients.

The results of this review showed that studying adherence to OACs in the Middle East addressed clinical and non-clinical factors related to use of OACs. The non-clinical factors that may influence adherence to OACs can be patients' related factors such as patients' satisfaction with OACs, knowledge about the therapy, and it can also be therapy/physician/health system factors such as assessing elements associated with the prescribing process and reporting of ADRs and side effects (Eltayeb et al., 2016; Balkhi et al., 2018; Mayet et al., 2018; Ababneh et al., 2016; Elbur et al., 2015). In the Middle East, the investigation of the above factors was mainly among patients who were using warfarin as an OAC. The selected studies were carried out as cross-sectional studies using self-reporting scales. This resulted in high heterogeneity and variability which make generalisation of these results slightly difficult. Therefore, the significance of the association between adherence to OACs and these factors should be interpreted with caution due to the nature of the studies. For example, in these selected studies, the patients' satisfaction with warfarin ranged between 47% in Sudan and 63.7% in western Saudi Arabia (Eltayeb et al., 2016; Elbur et al., 2016). These results reflected an average level of convenience with the medication in the two countries. Therefore, the low patients' satisfaction with warfarin could be significantly correlated with the low adherence rates to warfarin reported in these studies (5.7% adherence rate reported by Eltayeb et al., 2016 and 35.9% documented by Elbur et al., 2016). Noteworthy that Eltayeb et al., 2016 reported insignificant association between adherence to warfarin and patients' satisfaction with the drug. However, this result could be undermined by the small sample size (n=93) in the study. Elewa et al., 2016a reported that satisfaction with warfarin was high among individuals who were

naiive to anticoagulation treatment. Results of investigating satisfaction with warfarin from Spain reported a significant correlation between this factor “patients’ satisfaction”? and INR control. The authors reported an increase in the INR control when the perceived benefits are high among the therapy users (Fernandez et al., 2017).

The results of investigation of the relationship between knowledge of the patients about OACs in the Middle East and the adherence to these drugs documented variable outcomes. While Eltayeb et al., 2016 documented a non-significant association between patients’ knowledge about OACs and adherence to these medications in Sudan, in contrast, Elbur et al., 2016 reported a positive relationship between adherence to OACs and knowledge of OACs’ users about these medications. The authors reported that adherence rate to warfarin was risen as a result of the increase of patients’ knowledge. Furthermore, significant association between knowledge about warfarin and rates of adherence was documented in Jordan (Ababneh et al, 2016). Some studies from outside the Middle East region have investigated the effect of increasing patients’ knowledge about anticoagulation therapy on their adherence to this treatment. In Iran, the interventions of Farsad et al., (2019) to increase patients’ knowledge about warfarin had a positive impact on increasing adherence of patients’ adherence to warfarin. The authors assessed the effect of their educational interventional material on adherence to warfarin. They documented a significant association between knowledge about warfarin and adherence to this medication. Similar outcome was also reported by Souza et al., (2018) in Brazil who assessed the correlation between adherence to OACs and quality of patients’ information about the drugs. They concluded a significant relationship between adherence to these medications and patients’ knowledge about it.

Few researchers in the Middle East investigated the patterns of prescribing of DOACs and reporting of side effects and ADRs. The limited availability of the systems for reporting side effects in some countries in the region undermines expressing the real scale of these events in

a consistent manner. Nevertheless, issues related to the prescribing guidelines cannot only be attributed to the prescribing process, but other factors can be involved such as inaccuracy in documentation of the conditions and parameters related to patients such as kidneys' function status (Elewa et al., 2017). In other words, the health systems as a whole might be involved in such events in the Middle East. Further studies are needed to highlight such impact.

Mayte et al., 2018 documented that the prescribing guidelines for prescribing OACs are not followed on some occasions in the Middle Eastern Countries. The authors of this publication documented that, in some cases, the indications for which DOACs were prescribed do not match the recommendations of the prescribing guidelines for these medications. The authors recommended more adherence to the prescribing guidelines in terms of the cautions and contra indications which expose the patients to the ADRs. Furthermore, Shehab et al., 2015 reported on use of dabigatran by AF patients in UAE. They recommended monitoring of plasma level of the drug due to high incidences of ADRs related to the use of the drug among their cohort. Moreover, in Saudi Arabia, the prescribing of the two strengths of the DOAC dabigatran (110mg and 75mg) was reviewed by Al-Meman and Almutairi, 2014. The authors found that prescribing of the 110mg was associated with major gastric bleeding and death. The most common adverse event linked with taking this medication was gastric distress. Additionally, cases of minor urethral and optic nerve bleeding, major gastric bleeding, stroke, and death were also observed. The study concluded that treatment with dabigatran is primarily successful in low-risk profile patients (Al-Meman and Almutairi, 2014). The results of this study are comparable to the findings of Hernandez et al., 2015 who reported that risk of bleeding is significantly associated with use of Dabigatran. Similar results about the risk associated with the use of dabigatran were also reported in Iran by (Ganji et al., 2016) and by (Beshir et al., 2017) in Malaysia. In general, the results from the selected studies showed that the reported concerns associated with taking these medications by OACs' users such as side effects and

ADRs were similar to those documented in the rest parts of the world. However, because of the recent introduction of DOACs in the Middle East the full magnitude of the impact of this group of drugs is not well documented.

3.5. Recommendation for the practice and policy makers

Current studies focus on using self-reporting methods to measure adherence to OACs, it provides insight into the prevailing patterns of OACs' adherence in the area. However, large scale studies are needed to identify levels of adherence to OACs, such studies will minimise the bias in the responses and in the selection of participants. Such large studies will enable the health authorities in these countries to plan and adopt evidence-based health policies that target increasing the benefits of OACs and minimising the consequences of low adherence to the drugs such as stroke and hospitalisation. Employing advanced methodologies like the Proportion of Days Covered (PDC) to measure adherence to OACs is poised to enhance the robustness and precision of the acquired findings, offering a more reliable dataset on OACs' adherence due to its heightened sensitivity and specificity. The examination of non-clinical determinants linked to OAC adherence should not be restricted solely to patient-related factors like satisfaction with OACs; instead, it should encompass a broader spectrum, including health system-related variables and factors tied to the patient-physician dynamic. Such effort is instrumental in shedding light on the extent of the issue and plays an integral role in characterising the problem comprehensively.

3.6. Conclusion

The selected studies reported low levels of adherence to OACs in the Middle East. These studies were successful in demonstrating links between adherence to OACs and non-clinical factors such as therapy related factors and patients' related factors. The reasons behind these links were not investigated. Very few studies investigated the connection between the health

systems/patients/physican relationships and their impact on adherence to OACs. The outcomes of selected studies are confounded by the reliance of these studies on small cross-sectional studies that used self-reporting tools to assess adherence to OACs. Consequently they reflected an incomplete picture of adherence to OACs and its related non-clinical factors in the region. Worth mentioning, without a full clarity of determinants of adherence to OACs in the region, it will be difficult to describe the nature of non-adherence to OACs as intentional or non-intentional phenomena to suggest explanations. Measuring adherence to OACs in the Middle East requires large studies to identify the depth of the phenomenon and report on suitable solutions.

CHAPTER FOUR
ASSESSMENT OF ADHERENCE TO ORAL ANTICOAGULANTS IN EASTERN SAUDI ARABIA

4.1. Background

OACs is an important group of medications, which is used in prevention of ischaemic stroke (Yao et al., 2016). The World Health Organisation (WHO) has reported that more than 13 million people around the world experience ischaemic stroke annually, of whom, about 61% are under the age of 70 years (WHO, 2019). In Saudi Arabia stroke incidences are increasing, studies have shown a rise in the incidence of ischaemic stroke between 1993 and 2018 from 43.80 to 57.64 per 100,000 (Al-Rajeh et al., 1993; Alhazzani et al., 2018).

Warfarin is the gold standard OAC that is being used since 1950s. It exhibits its effect by inhibiting the vitamin K dependent synthesis of clotting factors, therefore it is also known as VKA (Hirsh, 1995). The drug has a narrow therapeutic index, subsequently, it requires regular monitoring to ensure it remains within the recommended therapeutic level. The drug also has significant drug-drug and drug-food interactions (Hirsh, 1992). All these features affect patients' continuous use of this medications.

The above-mentioned disadvantages of VKA, were overcome by the development of the DOACs with the aim of being as effective as VKA and with lesser side effects and adverse events than VKA (Eriksson et al., 2011). DOACs are relatively new to the market, and they are used in patients who are diagnosed with several cardiovascular diseases (CVD). Currently there are four DOACs that are licensed and approved as options for prophylaxis of stroke and systemic embolism. These DOACs are apixaban, dabigatran, edoxaban, and rivaroxaban, which exert their therapeutic effect either through direct thrombin inhibition as in dabigatran or through inhibition of factor Xa in the coagulation cascade without using antithrombin as a mediator (apixaban and rivaroxaban) (Connolly et al., 2009). The main advantage of this group of drugs that they do not need monitoring. Other advantages of DOACs include they have simple regimens, fewer drug-drug interactions, and less dietary restrictions (Connolly, 2009).

Compared to warfarin, the well-established anti-coagulant since 1954, DOACs can play a significant role in managing coagulation in the future (Davis et.al., 2005; Hart et.al., 2007).

In both VKA and DOACs, taking these drugs as prescribed is necessary for achieving the anticipated therapeutic benefits. Studies have shown that adherence is important for patients who are taking OACs, particularly those with clinical prediction score of risk based on congestive heart failure, hypertension, age, diabetes, vascular diseases, and sex (CHA2DS2-VASc) score ≥2 (Yao et.al., 2016). Emren et al.,2018 reported that non-adherence to DOACs in patients who were prescribed OACs for AF can result in adverse drug reactions (ADRs). These ADRs can include bleeding and thromboembolic events (Lip et al., 2012), moreover, the authors identified factors that may contribute to non-adherence to DOACs such as increased age, psychological and physiological conditions such as depression and dementia respectively, as well as associated other co-morbidities. Adherence to OACs is essential for achieving their therapeutic benefits. Adherence to DOACs varies between the drugs. Brown et.al.,2016 in their evaluation to adherence to DOACs found that Rivaroxaban had the highest adherence rate compared to other licensed DOACs.

To the best of our knowledge, little is known about the use of OACs and adherence of OACs' users in the Eastern Saudi Arabia despite the published data about preventative therapy for AF patients in the area (Alalwan et al., 2021).

4.2. Aim of the study

The study aim was to measure adherence to OACs among patients who are taking these drugs in Alhassa area, Eastern Saudi Arabia.

The objectives of the study are:

- to determine prescribing patterns of OACs in the study area (Alhassa area).

- to identify the conditions for which OACs are prescribed for patients in the study area.
- to assess the effect of patient related factors on adherence to OACs in the study area.

4.3. Method of the study

4.3.1. Design of the study

For this study, a cross-sectional study approach was chosen as the research methodology. This method enables the gathering of information regarding the patients' adherence to OACs, as well as the collection of data concerning patients' experiences with these medications. Furthermore, this approach is both economical and capable of yielding dependable and valid findings. Additional rationale for opting for this quantitative research design was elaborated upon in Chapter 2 of this thesis.

4.3.2. Location of the study

The research was carried out at the PSCC, a specialised cardiac hospital situated in the Al Ahsa region of the Eastern Province in Saudi Arabia. PSCC is dedicated to the diagnosis and treatment of heart and vascular disorders within this region. It boasts a total of 174 beds specifically designated for patients with cardiac conditions, encompassing both adults and children. The facility is staffed by a highly skilled and experienced healthcare team, which includes cardiologists, cardiac surgeons, nurses, and pharmacists collaborating to deliver comprehensive patient care. Moreover, PSCC offers an extensive array of cardiac services such as cardiac surgery, interventional cardiology, electrophysiology, cardiac imaging, heart failure management, and cardiac rehabilitation. Furthermore, the hospital actively engages in research and educational initiatives aimed at advancing the realm of cardiac care and enhancing patient outcomes.

4.3.3. Population of the study

This study recruited patients receiving cardiac care for conditions necessitating the prescription of OACs, such as atrial fibrillation (AF), at the PSCC. Patients were invited to take part in the study, and the study's objectives were elucidated to them. Upon their willingness to participate, a consent form was provided for them to sign, signifying their voluntary decision to join the study.

4.3.4. Inclusion/exclusion criteria

Inclusion Criteria: The study covered patients aged 18 years or older who were undergoing treatment with OACs and receiving follow-up care at the outpatient department of the PSCC. These participants had been prescribed warfarin, dabigatran (at doses of 110-150 mg), rivaroxaban (at doses of 15-20 mg), or apixaban (at doses of 2.5-5 mg) for conditions such as AF, DVT, PE, and other cardiac conditions requiring OAC treatment. Exclusion Criteria: Patients who declined to provide their consent for participation in the study were excluded from the research.

4.3.5. Informed consent

Before recruiting participants, they were provided with a document that outlined the purpose of the study, as well as any relevant details that could assist them in making an informed decision about whether to participate. This information was used to obtain the informed consent of the participants. (Appendix III).

4.3.6. Ethical approval by Institutional Review Board

The study was approved by the research committee at the PSCC (Appendix I). The study was also approved by University of Birmingham (ERN 19-0689, Appendix I).

4.4. Collection of data

4.4.1. Sample size calculation

The sample size was calculated using Raosoft sample size calculator (http://www.raosoft.com/samplesize.html). The confidence interval (CI) was 95%, margin of error was 5%. Based on estimation of 5000 population, the required total number of patients was 357.

4.4.2. Measuring adherence to OACs

Data on medication adherence was collected using the self-reporting Hill-Bone scale, a tool designed to gauge adherence behaviours. Originally comprising 14 questions assessing patient behaviour across three domains (appointment keeping, dietary habits, and medication adherence), the Hill-Bone questionnaire was later refined to include nine questions specifically focused on patients' adherence to their prescribed medications. Initially developed and validated for measuring compliance among individuals with high blood pressure, this tool was referred to as the Hill-Bone High Blood Pressure Scale (HB-HBP). Subsequently, the Hill-Bone Medication Adherence Scale (HB-MAS), which emerged as a subscale of the HB-HBP, expanded its applicability to cardiac conditions beyond hypertension. The HB-MAS serves as a valuable instrument for evaluating patients' medication adherence and guiding the formulation of appropriate interventions (Miller et al., 1997; Burt et al., 1995).

4.4.3. Assessment of patients' experience with taking OACs

Data about patients' experience with OACs was collected using questions about their prescribed OACs. Collected data from each participant included demographics: age, sex, reasons for prescribing anticoagulants, co-morbidities, and level of education. Other questions included reasons for taking OACs, beliefs of patients about therapeutic benefits, missing doses and reasons for missing doses, and awareness about international normalised ratio (INR) target for warfarin users (Appendix III).

4.4.4. Statistical analysis

Statistical Package for the Social Sciences (SPSS), (version 26) was used for the analysis of the data. Mean and standard deviation were used to present numerical data, while frequency and ratio were used for categorical data. To compare obtained data, the Chi squire (X^2) test was used. The factors which were found to be associated with medication adherence in univariate analysis ($P < .05$) were evaluated with multivariate logistic regression analysis. Odds ratio (OR) and 95% confidence interval (CI) were estimated with standard methods. The limit of statistical significance (type I error) was considered as $P < 0.05$ in all analyses.

In addition, the statistical analysis employed a multivariate binary logistic regression approach, which predicts relationships between dependent and independent variables and calculates the probability of specific outcomes occurring based on multiple sets of variables. This analysis aimed to identify independent variables associated with adherence to OACs, considering both demographic characteristics and patients' responses related to their experiences with OACs. Through the exploration of associations among independent variables like age and sex, valuable insights can be gained into the determinants influencing patients' adherence to OACs.

4.5. Results

4.5.1. Characteristics of the participants

4.5.1.1. Demographics of participants in the study

Three hundred and twelve patients were recruited to participate in the study. The minimum age of patients included in the study was 24 years and maximum age was 96 years. There were 163 (52.2%) females and 149 (47.8%) males. For the level of education, there were 141 (45.2%) participants who did not receive any form education. Eighty-six (27.6%) patients received education at primary level, 56 participants (17.9%) had secondary education, 27 (8.7%) continued their education until university, and 2 patients (0.6%) furthered their learning to postgraduate education (Table 4.1.).

Table 4.1. Demographic characteristics of the participants

Background characteristic	Frequency	Percentage %
Sex		
Males	149	47.8
Females	163	52.2
Total	312	100
Age (years) by gender		
Males <50 years	64	43
Males 50 years and above	85	57
Females <50 years	45	27.6
Females 50 years and above	118	72.4
Total	312	100
Level of education		
No education	141	45.2
Primary school	86	27.6
Secondary school	56	17.9
University graduate	27	8.7
Postgraduate	2	0.6
Total	312	100

4.5.1.2. Comorbidities among participating patients

Participants in the study had various diagnoses including cardiovascular diseases, hypertension, and DM type II (DMII). CVDs were present in 131 (42%) of the patients, hypertension was present in 165 (52.9%) of the patients, and DMII was a co-morbidity in 13 (4.1%) patients. There were 3 (1%) other co-morbidities presented in patients: rheumatoid arthritis in 2 cases (0.7%) and inflammatory bowel disease (IBD) in 1 (0.3%) case. Among males, there 62 (41.6%) CVD cases, 78 (52.3%) hypertension, 8 (5.4%) DMII, and 1 (0.7%) case of IBD. Within the female participants there were 69 (42.3%) cases of CVD, 87 (53.4%) hypertension, 5 cases of DMII, and 2 (1.2%) participants had IBD. (Table 4.2).

Table 4.2. Distribution of comorbidities among participating patients

	CVDs (%)	Hypertension (%)	DMII (%)	IBD (%)	Total (%)
Males	62 (41.6%)	78 (52.3%)	08 (5.4%)	1 (0.7%)	149 (100%)
Females	69 (42.3%)	87 (53.4%)	05 (3.1%)	02 (1.2%)	163 (100%)
Total	131 (42%)	165 (52.9%)	13 (4.1%)	03 (1%)	312 (100%)

4.5.1.3. Indications for prescribing OACs for the participants

Reasons for prescribing OACs for patients were variable. The majority of patients were prescribed OACs for valve disease conditions (47.8%, n=149) and AF (46.2%, n=144). Other justifications for prescribing an OAC were stroke (1.9%, n=6) patients, DVT (2.6%, n=8) patients, and PE (1.6%, n=5).

Among males there were 75 (50.3%) patients who had valve disease, 60 (40.3%) patients were diagnosed with AF, 7(4.6%) patients were suffered DVT, 2 (1.3%) patients experienced PE, and 5 (3.5%) participants complained of stroke. Indications for prescribing OACs among female patients were as follows: 74 (45.4%) of the female participants had valve disease conditions, 84 (51.5%) were complaining of AF, 3 (1.9%) of the female participants had PE, 1 (0.6 %) was experiencing DVT, and 1 (0.6%) have had stroke conditions (Table 4.3).

Table 4.3. Indications for prescribing OACs among the participating patients

	Valve disease (%)	AF (%)	DVT (%)	PE (%)	Stroke (%)	Total (%)
Males	75 (50.3%)	60 (40.3%)	07 (4.6%)	02 (1.3%)	05 (3.5%)	149 (100%)
Females	74 (45.4%)	84 (51.5%)	01 (0.6%)	03 (1.9%)	01 (0.6%)	163 (100%)
Total	149 (47.8%)	144 (46.2%)	08 (2.6%)	05 (1.6%)	06 (1.9%)	312 (100%)

4.5.1.4. Prescribed OACs for the participants

The two classes of OACs, namely VKA and DOACs, were prescribed for the participants. Two hundred and three (65.1%) patients were prescribed warfarin, while 109 (34.9%) patients were recommended DOACs as their OAC medication.

Among male participants, warfarin was prescribed for 100 (67.1%) patients, while DOACs were prescribed for 49 (32.9%) patients. For female patients, warfarin was the drug of choice for 103 (63.2%) participants and DOACs were the recommended OAC medication for 60 (36.8%) patients. (Table 4.4).

Table 4.4. Prescribing patterns of OACs among male and female patients

	Warfarin (%)	DOACs (%)	Total (%)
Males	100 (67.1%)	49 (32.9%)	149 (100%)
Females	103 (63.2%)	60 (36.8%)	163 (100%)
Total	203 (65.1%)	109 (34.9%)	312 (100%)

4.5.1.5. Duration of taking OACs by the participants

The period since patients have started taking OACs was also considered in the study. Eight (2.6%) patients were taking OACs for less than 3 months,11 patients (3.5%) were on OACs for 6 months, 15 (4.8%) patients were taking an OAC for 1 year, and 278 (89.1%) have been taking OACs for more than one year.

Among male patients, 5 (3.4%) patients were on OACs for less than 6 months, 4 (2.7%) patients were on OACs for 6 months, 8 (5.4%) patients were on OACs for 1 year, and 132 (88.6%) patients were on OACs for more than 1 year. For female participants, 3 (2.6%) patients were taking OACs for under 3 months, 7 (4.3%) participants were on OACs for 6 months, 7 (4.3%) have been taking OACs for 1 year, and 146 (89.6%) patients were on OACs for less than 1 year.

For participants who are taking warfarin, 3 (1.5%) patients were taking the drug for 3 months, 9 (4.4%) patients were on the medication for 6 month, 8 (3.9%) patients were taking warfarin for 1 year, and 183 (90.1%) were on the therapy for more than 1 year.

For patients who were prescribed DOACs, 5 (4.6%) patients were on DOACs for 3 months, 2 (1.8%) patients have been taking DOACs for 6 months, 7 (6.4%) patients were on the drug for 1 year, and 95 (87.2%) patients were taking DOACs for more than a year. (Tables 4.5, 4.5[a]).

Table 4.5. Duration on OACs among male and female patients

	< 6 months (%)	6 months (%)	1 year (%)	>1 year (%)	Total (%)
Males	05(3.4%)	04(2.7%)	08(5.4%)	132(88.6%)	149(100%)
Females	03(2.6%)	07(1.8%)	07(4.3%)	146(89.6%)	163(100%)
Total	08 (2.6%)	11 (3.5%)	15 (4.8%)	278 (89.1%)	312 100%)

Table 4.5a. Duration on OACs according to OAC type

	Warfarin (%)	*DOACs (%)*
3 months	3 (1.5%)	5 (4.6%)
6 months	9 (4.4%)	2 (1.8%)
1 year	8 (3.9%)	7 (6.4%)
1 year	183 (90.1%)	95 (87.2%)
Total	203 (100%)	00%)

Table 4.5.b summarises the bio-demographic data for the participants in the study.

Background characteristic	Frequency n=	Percentage %
Sex		
Males	149	47.8
Females	163	52.2
Age (years)		
Range 24-96		
mean 56.02 (S.D. ± 15.4)		
<50 years	109	34.9
>50 years	203	65.1
Age (years) by gender		
Males <50 years	64	43
Males 50 years and above	85	57
Females <5o years	45	27.6
Females 50 years and above	118	72.4
Level of education		
None-educated	141	45.2
Primary school	86	27.6
Secondary school	56	17.9
University graduates	27	8.7
Postgraduate	2	0.6
Level of education by age (years)		
Males <50 years	3	4.7
None-educated	14	21.9

Primary school	27	42.2
Secondary school	19	29.7
University graduates	01	1.6
Postgraduate	64	100
Males 50 years and above	48	56.6
None-educated	25	29.4
Primary school	11	12.9
Secondary school	01	1.2
University graduates	0	0
Postgraduate	85	100
Females <50 years	03	6.7
None-educated	21	46.7
Primary school	14	31.1
Secondary school	06	13.3
University graduates	1	2.2
postgraduate	45	100
Females 50 years and above	87	73.7
None-educated	26	22
Primary school	04	3.4
Secondary school	1	0.8
University graduates	0	0
postgraduate	118	100
Indications for OACs		
Valve disease	149	47.8
Atrial Fibrillation	144	46.2
DVT	08	2.6
PE	05	1.6
Stroke	06	1.9
Prescribed OACs		
Warfarin	203	65.1
Doacs	109	34.9
Co morbidities		

Hypertension	165	52.9
DM II	13	4.1
CVD	131	42
IBD	03	01
Duration on OACs		
< 6 months	8	2.6
6 months	11	3.5
1 year	15	4.8
> 1 year	278	89.1

4.5.2. Measuring adherence of the participants to OACs

4.5.2.1. Examination of reliability of the Arabic translated Hill-Bone scale

In the process of translating adherence measurement scales, various obstacles, including linguistic and cultural complexities, healthcare system differences, health literacy disparities, and resource limitations, can be encountered. To address these challenges, a careful and culturally sensitive translation approach was implemented, involving experts in cross-cultural psychology research and pilot testing with a small patient sample to maintain accuracy and validity. To overcome limitations, bilingual experts conducted cognitive interviews, expert reviews ensured cultural relevance and linguistic accuracy, and ethical considerations were upheld throughout the research process. Due to financial constraints and time limitations, extensive psychometric testing could not be conducted. These constraints may affect the reliability and validity of the study's results, requiring caution in interpretation. Despite these limitations, ethical standards were maintained, emphasising informed consent and cultural sensitivity. The study encourages future research to address these limitations to improve the quality of the Arabic translated version of the HB scale and enhance the validity of findings in similar contexts.

Reliability of the Arabic translated version of Hill-Bone scale was assessed using coefficient alpha (Cronbach's alpha) test. This test was used to examine the relationship between the elements of the scale as a group. A Likert scale was used to explain the values for Cronbach's Alpha (Table 4.6).

Cronbach's Alpha test results of the Hill-Bone Arabic translated version showed acceptable reliability value (α=0.788) (see table 4.6). All items appeared to be worthy of retention, resulting in a decrease in the alpha if deleted. The one exception to this was question no.8 (q.8), which would increase the alpha to α = 0.793 if omitted. Results of the reliability analysis are shown in Table 4.7.

Table 4.6. Likert scale for interpretation of Cronbach's Alpha

Cronbach's Alpha	Internal consistency
$\alpha \geq 0.9$	Excellent
$0.9 > \alpha \geq 0.8$	Good
$0.8 > \alpha \geq 0.7$	Acceptable
$0.7 > \alpha \geq 0.6$	Questionable
$0.6 > \alpha \geq 0.5$	Poor
$0.5 > \alpha$	Unacceptable

Table 4.7. Obtained responses for the Arabic translated version of the Hill-Bone questionnaire

	Scale Mean if Item Deleted	Scale Variance if Item Deleted	Corrected Item-Total Correlation	Squared Multiple Correlation	Cronbach's Alpha if Item Deleted
q1	29.89	4.415	.355	.187	.788
q2	29.73	4.377	.495	.364	.764
q3	30.06	3.759	.669	.642	.734
q4	30.07	3.899	.591	.585	.749

q5	29.66	4.571	.502	.462	.765
q6	29.68	4.477	.511	.503	.763
q7	30.05	3.939	.577	.467	.751
q8	29.57	5.191	.216	.113	.793
q9	29.60	4.935	.375	.248	.781

4.5.2.2. Calculation of adherence of the participants to OACs

The Hill-Bone Scales Team in the School of Nursing at Johns Hopkins University, Baltimore, Maryland, USA was contacted to confirm the interpretation of the obtained responses to the scale's questions and to verify method of interpretation of the scores. The team approved the method of analysis which was used in analysing the obtained data regarding adherence to OACs for this study.

Each question in the Hill-Bone scale has 4 options to respond to: none-of the time (4 points), some of the time (3 points), most of the time (2 points), and all of the time (1 point). The total score of the Hill-Bone scale is 36 points. Participants with Hill-Bone score of 36 points were considered as adherent to OACs. Respondents who scored less than 36 points were considered as non-adherent to OACs. Responses to each question of the Arabic translated version of Hill-Bone scale are shown in table (4.8). Total scores obtained by participants in our study are shown in Table (4.9).

Table 4.8. Responses to each question of the Arabic translated Hill-Bone scale

Questions	Mean score (out of 4)	Std. Deviation	N
How often do you forget to take your oral anticoagulants (OACs) medicine?	3.65	0.504	312
How often do you decide NOT to take your oral anticoagulants (OACs) medicine?	3.81	0.418	312
How often do you forget to get prescriptions filled?	3.48	0.532	312

How often do you run out of oral anticoagulants (OACs) pills?	3.47	0.531	312
How often do you skip your oral anticoagulants (OACs) medicine before you go to the doctor?	3.88	0.341	312
How often do you miss taking your oral anticoagulants (OACs) pills when you feel better?	3.86	0.372	312
How often do you miss taking your oral anticoagulants (OACs) pills when you feel sick?	3.49	0.526	312
How often do you take someone else's oral anticoagulants (OACs) pills?	3.97	0.194	312
How often do you miss taking your oral anticoagulants (OACs)pills when you are careless?	3.94	0.253	312

Table 4.9. Total points scored by respondents to Arabic translated Hill-Bone scale

Score	Frequency	Percentage (%)
36	93	29.8
35	31	9.9
34	29	9.3
33	64	20.5
32	53	17.0
31	15	4.8
30	6	1.9
29	7	2.2
28	6	1.9
27	5	1.6
26	2	0.6
23	1	0.3
Total	**312**	**100.0**

4.5.2.3. Adherence to OACs among warfarin users

Sixty-nine (34%) participants who were taking warfarin scored 36 points in the scale, consequently they were classified as adherent to the drug while 134 (66%) warfarin users scored less than 36 points. Therefore, they were considered as non-adherent. Adherence rate to warfarin among its users was 34%. (Table.4.10).

Table 4.10. Classification of responses to the Arabic translated Hill-Bone scale by warfarin users

	Frequency (%)
Participants classified as adherent to warfarin (scored 36 points in Hill-Bone scale)	69 (34%)
Participants classified as non-adherent to warfarin (scored < 36 points in Hill-Bone scale)	134 (66%)
Total	203 (100%)

4.5.2.4. Adherence to OACs among DOACs users

Twenty-four (22%) DOACs users scored 36 points in Hill-Bone scale, they were categorised as adherent to DOACs, while 85 (78%) patients who were using DOACs scored less than 36 points, thus they were considered as non-adherent to DOACs. Adherence rate among DOACs users was 22%. (Table 4.10[a]).

Table 4.10[a]. Classification of responses to the Arabic translated Hill-Bone scale by DOACs users

	Frequency (%)
Participants classified adherent to DOACs (scored 36 points in Hill-Bone scale)	24 (22%)
Participants classified as non-adherent to DOACs (scored < 36 points in Hill-Bone scale)	85 (78%)
Total	109 (100%)

4.5.2.5. Overall adherence among OACs users

The overall results showed that participants who responded (none of the time) to all questions in the questionnaire (scored 36 points in the Hill-Bone scale) were 93 participants (29.8%). Subsequently, 93 (29.8%) of the participants were classified as adherent to OACs. Two-hundred and nineteen (70.2%) participants (scored less than 36 points in the Hill-Bone scale) were classified as none-adherent to OACs. (Table 4.10[b]).

Table 4.10[b]. Overall classification of responses to the Arabic translated Hill-Bone scale by OACs users

	Frequency (%)
Participants classified as adherent to OACs (scored 36 points in the Hill-Bone scale)	93 (29.8%)
Participants classified as non-adherent to OACs (scored < 36 points in the Hill-Bone scale)	219 (70.2%)
Total	312 (100%)

Table 4.10[c] illustrates the adherence rates to warfarin, DOACs, and the overall adherence rate to OACs in the study.

Table 4.10[c]. Classification of responses to the Arabic translated Hill-Bone scale by DOACs users

	Percentage %
Adherent rate to warfarin users	34%
Adherent rate to DOACs users	22%
Overall adherence to OACS users	29.8%

4.5.3. Assessment of relationships between patients' characteristics and adherence to OACs

Chi-square test was used to examine the relationships between adherence to OACs and patients demographics including age of participants, sex of patients, education status, reasons for prescribing OACs, types of prescribed OACs, duration on OACs, and total number of comorbidities among patients.

4.5.3.1. Age of patients

The relationship between age groups of participants and adherence to OACs was assessed. Chi-square test results showed that there was a statistically significant difference between adherence to OACs and the age of participants χ^2 (1, N = 312) = 6.1, p = .014. Patients who are under 50 years old are more adherent to OACs compared to older patients (50 years and above). (Table 4.11).

Table.4.11. Age groups and status of adherence to OACs among participants

	Adherent (%)	*Non-adherent (%)*	*Total (%)*
Patients aged Under 50 years	42 (38.5%)	67 (61.5%)	109 (100%)
Patients aged 50 years and above	51 (25.1%)	152 (74.9%)	203 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

4.5.3.2. Sex of the patients

Chi-square (χ^2) test of independence was performed to examine the relationship between gender of participants and adherence to OACs. The outcome of the analysis revealed

statistically non-significant relationship χ^2 (1, N = 312) = 1.3, p = .256. There was no significant relationship between sex of the participants and adherence to OACs (Table 4.12).

Table.4.12. Adherence to OACs among male and female participants

	Adherent (%)	*Non-adherent (%)*	*Total (%)*
Males	49 (32.9%)	100 (67.1%)	149 (100%)
Females	44 (27%)	119 (73%)	163 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

4.5.3.3. Level of education

In contrast to the sex of patients, Chi-square χ^2 test revealed a statistically significant difference between illiterate and educated patients regarding adherence to OACs χ^2 (1, N = 312) = 10.5, p = .001. Educated patients are more adherent to OACs compared to uneducated patients. (Table 4.13).

Table.4.13. Level of education and adherence to OACs among participants

	Adherent (%)	*Non-adherent (%)*	*Total (%)*
Uneducated patients	29 (20.6%)	112 (79.4%)	141 (100%)
Educated patients	64 (37.4%)	107 (62.6%)	171(100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

4.5.3.4. Indications for prescribing OACs

The relationship between the condition for which OACs were prescribed and adherence to these medications was also assessed using Chi-square χ^2 test. The results of the statistical analysis of variables showed that there was a significant relationship between the indication for prescribing OACs and adherence to these drugs χ^2 (1, N = 312) = 11.95, p = .001. The proportion of subjects who reported adherence to OACs among patients with conditions such as valve disease, stroke,

DVT, and PE were more adherent to OACs compared to participants who were diagnosed with AF (Table 4.14).

Table 4.14. Indications for prescribing OACs and status of adherence to OACs

	Adherent (%)	*Non-adherent (%)*	*Total (%)*
Patients with AF	29 (20.1%)	115 (79.9%)	144 (100%)
Patients with other conditions	64 (38.1%)	104 (61.9)	168 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

4.5.3.5. Types of prescribed OAC

The link between type of prescribed OAC and adherence to these drugs was assessed. Chi-square χ^2 test of independence was performed to examine this relationship. Result of the analysis revealed a significant difference between type of OACs and adherence to these medications among participants, where the proportion of patients on warfarin were more adherent than patients on DOACs. X^2 (1, N = 312) = 4.95, p = .028. (Table 4.15).

Table 4.15. Types of prescribed OACs and adherence to OACs

	Adherent (%)	*Non-adherent (%)*	*Total (%)*
Patients on warfarin	69 (34%)	134 (66%)	203 (100%)
Patients on DOACs	24 (22%)	85 (78%)	109 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

4.5.3.6. Duration on OACs

Chi-square χ^2 test was used to assess the relationship between period that patients have been taking OACs and adherence to these medications. The result of the test revealed a significant

relationship between the duration of taking OACs and adherence to OACs χ^2 (1, N = 312) = 5.037, p = .025. Patients who have been taking OACs for one year and more were more adherent to OACs compared to patients who were on the drug for less than a year. (Table 4.16).

Table 4.16. Duration of time since patients have started taking OACs and adherence to OACs

	Adherent (%)	*Non-adherent (%)*	*Total (%)*
Patients on OACs for < 1 year	10 (10.8%)	9 (47.4%)	19 (100%)
Patients on OACs for ≥ 1 year	83 (28.3%)	210 (71.7%)	293 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

4.5.3.7. Total number of co-morbidities

The relationship between the multi-comorbid status among patients and adherence to OACs was also assessed using Chi-square χ^2 test. The results of this test showed there was no significant relationship between the total number of conditions within a patient and adherence to OACs χ^2 (1, N = 312) = 2.434, p = .119. Presence of one co-morbidity or more did not affect adherence to OACs among participants. (Table 4.17)

Table 4.17. Presence of co-morbidities and status of adherence to OACs

	Adherent	*Non-adherent*	*Total*
Patients with 1 co-morbidity	48 (34.3%)	92 (65.7%)	140 (100%)
Patients with > 1 co-morbidity	45 (26.2%)	127 (73.8%)	172 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

Table 4.18 summarises the relationships between the adherence to OACs and patients' characteristics in the study.

Table 4.18. Outcome of Chi square results for relationships between adherence to OACs and patients' characteristics.

	χ^2	df	N	p
Sex	1.3	1	312	.256
Age	6.1	1	312	.014
Education	10.5	1	312	.001
Indications for OACs	11.9	1	312	.001
Prescribed OAC	4.95	1	312	.028
Total number of comorbidities	2.434	1	312	.119

4.5.4. Patients' experiences with taking OACs

4.5.4.1. Awareness about indications for OACs

Participants were asked if they knew why they were prescribed OACs. Out of 312 participants, 306 (98.1%) stated they were aware of why they were taking OACs. Only 6 (1.9%) reported that they did not know why they were prescribed these drugs (Table 4.19).

Table 4.19. Awareness of participants about indications for taking OACs

	Frequency	Percentage %
Patients aware about indications for taking OACs	306	98.1
Patients NOT aware about indications for taking OACs	06	1.6
Total	312	100

4.5.4.2. Awareness about INR target for warfarin users

Patients on warfarin were queried about their awareness of the INR target by asking if they are aware about the INR target? Out of 203 patients who were taking warfarin in the study, 82 (40.4%) patients stated that they know their INR target, opposite to 121 (59.6%) who reported they were unaware of their INR target (Table 4.20).

Table 4.20. Responses to the question: do you know your INR target? (for warfarin users only)

	Frequency	*Percentage %*
Patients aware about INR target	82	40.4
Patients NOT aware about INR target	121	59.6
Total	203	100.0

4.5.4.3. Compliance with advice of prescribers about taking OACs

Patients were asked if they follow prescribers' advice. Out of 312 patients, 288 (92.3%) responded that they take OACs as prescribed, while 24 (7.7%) declared that they amend the advice sometimes. (Table, 4.21).

Table 4.21. Responses of participants to the question how you take OACs?

	Frequency	*Percentage %*
Patients reported taking OACs as prescribed	288	92.3
Patients NOT taking OACs as prescribed	24	7.7
Total	312	100

4.5.4.4. Experience of patients with missing doses of OACs

Missing doses of OACs was another investigated area with patients. Participants were asked how often they miss doses of their prescribed OACs. Out of 312 participants, 93 (29.8%) reported they do not miss a dose at all. Occasional missing of doses was reported by 211 (67.6%) of the participants. Patients who stated missing doses on regular bases was 8 (2.6%) patients. (Table 4.22).

Table 4.22. Responses to the question: how often do you miss a dose of your OAC?

	Frequency	Percentage %
Patients reported do not miss doses	93	29.8
Patients reported missing doses occasionally	211	67.6
Patients reported missing doses on regular bases	8	2.6
Total	312	100.0

4.5.4.5. Reported reasons for non-adherence to OACs

Participants were shown commonly documented reasons, which may deter them from taking OACs as prescribed. These reasons were forgetfulness, side effects, food-drug interaction, drug-drug interactions, and confusion about how to take OACs. Participants responses were as follows 114 (36.5%) patients stated forgetfulness, 91 (29.2%) patients reported side effects, 23 (7.4%) patients claimed they do not know how to take the regimen, 52 (16.6%) stated food interactions, and 32 (10.3%) patients reported drug interactions as reasons for not taking their OACs (Table 4.23).

Table 4.23. Responses to the question: do you have any reason for not taking your oral anticoagulant?

	Frequency	*Percentage %*
Forgetfulness	114	36.5
Side effects	91	29.2
I do not know how to take it	23	7.4
Food-drug interactions	52	16.6
Drug-drug interactions	32	10.3
Total	312	100.0

4.5.4.6. Perception of patients about therapeutic benefits of OACs

Patients were asked if they thought they were gaining benefits from OACs. The majority of the participants 298 (95.5%) confirmed they believe in the effectiveness of OACs for treatment of their conditions, however, 14 (4.5%) reported inconveniences with taking these drugs. (Table 4.24).

Table 4.24. Responses of patients to the question: do you think you are getting therapeutic benefits from oral anticoagulant?

	Frequency	*Percentage %*
Patients believe getting benefits from taking OACs	298	95.5
Patients DO NOT believe getting benefits from taking OACs	14	4.5
Total	312	100

4.5.4.7. Influence of patients' perception on adherence to OACs

The questionnaire used for data collection asked patients who were taking OACs about the obstacles they faced in consuming them. These obstacles included side effects, adverse drug reactions,

interactions with other drugs or food, and insufficient guidance regarding dosage. In addition, OACs' users were asked if their views on effectiveness of OACs are affected by the reported reasons for not taking OACs as prescribed (do you think the reported problems with OACs are affecting your beliefs these medications?). The majority of participants 295 (94.6%) confirmed they fully believe in the effectiveness of OACs and will continue taking OACs as prescribed, in contrast to 17 (5.4%) participants who reported they do not trust OACs when it is associated with reported barriers. (Table 4.25).

Table 4.25. Responses of patients to the question: do you think any of the reported barriers, if any, affect your beliefs about your oral anticoagulants?

	Frequency	*Percentage %*
Patients' beliefs on OACs are NOT affected by barriers to taking OACs	295	94.6
Patients' beliefs on OACs are affected by barriers to taking OACs	17	5.4
Total	312	100

4.5.5. Assessment of relationships between patients' experiences with taking OACs and adherence to OACs

Chi-square χ^2 test was used to examine the relationship between adherence to OACs and: awareness of participants about indications for taking OACs, following advice of prescribers on how to take OACs, missing doses of OACs, reported reasons for non-adherence to OACs, awareness about INR target among warfarin users, views of patients about therapeutic benefits of taking OACs, and effect of perception of patients about therapeutic benefits of OACs on adherence to these medications.

4.5.5.1. Patients' awareness about indication of taking OACs

Chi-square χ^2 analysis revealed a non-significant relationship between awareness of individuals about why they are taking and adherence to OACs χ^2 (1, N = 312) = 2.59, p = .107. Awareness

of patients in the study about the reasons for taking OACs did not affect adherence to these medications. (Table 4.26).

Table 4.26. Awareness of patients about indications for taking OACs

	Adherent to OACs	*Non-adherent*	*Total*
Patients who are aware about indications for OACs	93 (30.4%)	213 (69.6%)	306 (100%)
Patients who are NOT aware about indications for OACs	0 (0%)	6 (100%)	6 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

4.5.5.2. Awareness about INR target among warfarin users

Among warfarin users, the relationship between awareness about INR target and adherence to warfarin was also assessed. Statistical analysis using Chi-square χ^2 test showed a significant relationship between patients' awareness about INR target and adherence to warfarin χ^2 (1, N = 203) = 4.6, p = .031. The proportion of patients who were aware about the INR target were more adherent to warfarin compared to patients who did not know their INR target. (Table 4.27).

Table 4.27. Awareness about INR target among warfarin users

	Adherent	*Non-adherent*	*Total*
Patients aware about INR target	35 (42.7%)	47 (57.3%)	82 (100%)
Patients DID NOT know INR target	34 (28.1%)	87 (71.9%)	121 (100%)
Total	69 (34.7%)	134 (66%)	203 (100%)

4.5.5.3. Adherence to the advice of prescribers about taking OACs

Relationship between following prescribers' advice about taking OACs and adherence to these medications was also assessed. Chi-square χ^2 test revealed a significant relationship between compliance of patients and adherence to OACs χ^2 (1, N = 312) = 11, p = .001. Compliant patients with advice about how to take OACs were more adherent to OACs compared to non-compliant patients who do not usually follow recommendations of the prescribers about taking OACs. (Table 4.28).

Table 4.28. Patients following of prescribers' advice on how to take OACs

	Adherent	*Non-adherent*	*Total*
Patients who take OACs as prescribed	93 (32.3%)	195 (67.7%)	288 (100%)
Patients who DO NOT take OACs as prescribed	0 (0%)	24 (100%)	24 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

4.5.5.4. Missing doses of OACs by patients

The Chi-square χ^2 test was also used to evaluate the relationship between missing doses of OACs as reported by patients and adherence to OACs. The result of the test revealed that there was a highly significant relationship between the missing doses of OACs and adherence to these medications χ^2 (2, N = 312) = 134.9, p = .000. Patients who were adherent to OACs did not miss any dose of OACs in contrast to non-adherent patients who missed doses either occasionally or regularly (Table 4.29).

Table 4.29. How often participants miss doses of OACs

	Adherent	*Non-adherent*	*Total*
Patients do not miss doses	93 (83.8%)	18 (16.2%)	111 (100%)
Patients miss doses occasionally	0(0%)	198 (100%)	198 (100%)
Patients miss doses regularly	0 (0%)	3 (100%)	3 (100%)
Total	93(29.8%)	219 (70.2%)	312(100%)

4.5.5.5. Reasons for non-adherence of patients to OACs

Chi-square χ^2 test was also used to examine the relationship between the reported reasons by patients missing doses of OACs and the adherence to these drugs. The results revealed a significant relationship between adherence to OACs and the documented reasons by participants for missing doses χ^2 (4, N = 312) = 27.7, p = .000. (Table 4.30).

Table 4.30. Reported reasons for non-adherence as reported by participants

	Adherent	Non-adherent	Total
Forgetfulness	53 (46.5%)	61 (53.5%)	114 (100%)
Side effects	19 (20.9%)	72 (79.1%)	91 (100%)
Food interactions	11 (21.2%)	41 (78.8%)	52 (100%)
Drug interactions	9 (28.1%)	23 (71.9%)	32 (100%)
Do not know how to take OACs	1 (4.3%)	22 (95.7%)	23 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

4.5.5.6. Patients' perception on therapeutic benefits of OACs

Chi-square χ^2 test was used to examine the relationship between patients' perceptions about therapeutic benefits of OACs and adherence to OACs. There was no significant difference

between views of patients in therapeutic effectiveness of OACs and adherence to OACs χ^2 (1, N = 312) = 1.7, p =. 194. Patients views on therapeutic benefits of these drugs did not affect their adherence to OACs. (Table 4.31).

Table 4.31. Patients views on therapeutic benefits of OACs

	Adherent to OACs	Non-adherent	Total
Patients' perception of gaining benefits from OACs	91(30.5%)	207 (69.5%)	298 (100%)
Patients' perception of NOT gaining benefits from OACs	2 (14.3%)	12 (85.7)	14 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

4.5.5.7. Influence of patients' perception on adherence to OACs

The relationship between patients' perception of the therapeutic benefit of OACs and its effect on their adherence to OACs was examined using Chi-square (χ^2) test. The results of this test showed a non-significant relationship χ^2 (1, N = 312) = .26, p = .611. Adherence to OACs among participants was not affected by patients' perception of therapeutic benefits of OACs. (Table 4.32).

Table 4.32. Patients' perceptions on therapeutic benefit and adherence to OACs

	Adherent	*Non-adherent*	*Total*
My perceptions about OACs affect my adherence to OACs	6 (35.3%)	11 (64.7%)	17 (100%)
My perceptions about OACs DO NOT affect my adherence OACs	87 (29.5%)	208 (70.5%)	295 (100%)
Total	93 (29.8%)	219 (70.2%)	312 (100%)

Table (4.33) summarises the relationships between adherence to OACs and participants experience with taking these drugs.

Table 4.33. Outcome of Chi-square analysis of relationships between adherence to OACs and patients experience with OACs.

	χ^2	*Df*	*N*	*p*
Awareness about reasons for taking OACs	*2.6*	*1*	*312*	*.107*
How you take your OACs	*11*	*1*	*312*	*.001*
Missing doses of OACs	*134.9*	*2*	*312*	*.000*
Knowledge about INR target	*4.6*	*1*	*203*	*0.031*
Reported reasons for missing doses	*27.7*	*4*	*312*	*.000*
Views of patients in effectiveness of OACs.	*1.7*	*1*	*312*	*.194*
Beliefs about using OACs	*.26*	*1*	*312*	*.611*

4.5.6. Prediction of adherence to OACs among participants

Binary logistic regression was used to examine the predicting factors of adherence to OACs using patients experience with OACs and patients' characteristics variables. Selected dependent variable was adherence outcome, covariates were age of patients, sex of patients, education level, prescribed OACs, presence of co-morbidities, indications for prescribing OACs, knowledge about INR target, and duration on OACs. The results of this statistical analysis revealed that only age, sex, duration on OACs, missed doses, reported reasons for non-adherence, and knowledge about INR target, were predictors for adherence to OACs (Table 4.34).

Table 4.34. Outcome of binary logistic regression for predicting factors of adherence to OACs among participants

						95% CI FOR EXP (B)	
	B	SE	df	Sig.	Exp(B)	Lower	Upper
AGE	.034	.016	1	.033	1.035	1.003	1.068
SEX	.832	.419	1	.047	2.298	1.011	5.227
DURATION ON OACS	2.682	1.066	1	.012	.068	.008	.553
KNOWLEDGE ABOUT INR TARGET	.645	.301	1	.031	1.906	1.056	3.439
MISSED DOSES	-3.755	.459	1	.000	42.736	17.372	105.136
REPORTED PROBLEMS WITH TAKING OACS	3.065	1.234	1	.014	21.427	1.876	244.735

4.6. Discussion

There are several previous studies on adherence to OACs in Middle Eastern countries (Salam et al., 2012; Zubaid et al., 2015; Elewa et al.,2016; Shilbayeh et al., 2018; Alshammari and Alhantoushi, 2018). Published results from previous studies indicated variable levels of adherence to OACs in these countries. Saudi Arabia is no exception to these countries as most published data on adherence to OACs described adherence among OACs' users as being at low levels (Elbur et al.,2015; Mayet et al., 2018). Even though various justifications such as reduced knowledge about the drugs and low satisfaction with their benefits for the decreased adherence to OACs among their users in Saudi Arabia were provided, the authors of these publications suggested that urgent solutions are needed to increase adherence to OACs and to maximise the benefits from these drugs (Elbur et al.,2015; Elewa et al., 2018). Our study results agree with the necessity of urgently needed interventions to increase adherence to OACs taking into consideration that stroke and ischaemic heart disease, conditions for which OACs are the

mainstay for treatment, were reported among the top 3 causes of death in Saudi Arabia (Murray et al., 2020). Assessing adherence to OACs and identifying barriers to adherence are the first step to remedy the problem of low adherence to OACs. Below are the key findings of our study.

4.6.1. Key findings

A significant proportion of the participants of this study (95.5%) indicated that they are convinced with the benefits of taking OACs. This outcome reveals that patients in the study area are satisfied with taking OACs. A strong association between patients' satisfaction with OACs and level of adherence was reported in some studies in the Middle East (Ababneh et al., 2016; Balkhi et al., 2017). Our results suggests that patients' satisfaction with OACs is highly unlikely to be considered as a barrier to adherence to these drugs in the study area. Furthermore, our study revealed a significant increase in non-adherence to OACs with the rise of age of participants. The results showed that adherence to OACs among patients < 50 years old was (38.5%) compared to (25.1%) among participants who were > 50 years old. Emern et al., 2018, reported that advanced age is a reason for non-adherence among OACs users in the Middle East. The authors attributed the effect of age in decreased adherence to OACs as due to anticipated mental impairment and increased polypharmacy. However, this study did not report a cut-off age for non-adherence. Our results agree with this finding, advanced age of some of our participant can be a participating factor in their low adherence to OACs.

Another significant outcome from our result was the various identified barriers to adherence to OACs which were reported by the study participants. Reported reasons for non-adherence were side effects, food-drug interaction and drug-drug interactions, and other reasons such as personal beliefs and lack of motivations. However, a significant number of participants (94.6%) stated that their willingness to take OACs and that their willingness was not affected by these reasons. This finding reinforces our view of the urgent need for patient tailored and

personalised interventions to facilitate taking OACs as prescribed, rather than assuming pre-existing ideas about barriers.

Another important finding of our study is that it showed the positive impact of education on adherence to OACs among the population. The results of the study showed that educated patients were more adherent to OACs than non-educated (37.4%, 20.6% respectively). Taking into account that nearly half of the participants were non-educated (45.2%), these findings indicate that targeted interventions, such as patients' education to improve adherence to OACs, are needed. In addition, our results revealed that adherence among warfarin users was higher than among those who were taking DOACs (34% and 22% respectively). According to Witt et al., 2009 study, patients who take warfarin receive frequent monitoring. The study found that an anticoagulation service managed by clinical pharmacists substantially improved adherence to warfarin therapy.

When we looked at the indications for which these drugs were prescribed, the data showed that warfarin was prescribed for valve disease conditions in 47.8% of the participants while DOACs were prescribed for AF in 46.2% of the patients, DOACs were also recommended for VTE and stroke conditions in 6.1% of the participants. This finding suggests that patients' beliefs about their conditions can be an influential factor on adherence to OACs. DiMatteo et al., 2007 reported a significant correlation between seriousness of the condition and level of patients' adherence as patients believed that valve conditions are more serious and require regular taking of medications compared to their beliefs about AF and VTE that requires prescribing DOACs such as VTE and stroke as suggested.

The authors documented that patients' perception about severity of their condition and their awareness about this seriousness can predict adherence to medications. Another interpretation which may strengthen this finding is the well-established prescribing process of warfarin and

the recent and slow uptake of DOACs in healthcare systems including Saudi Arabia despite the preference of DOACs over warfarin by some prescribers. Currently warfarin is the only available therapeutic option for individuals who have valve(s) (aortic or mitral) replacement procedures. This may also strengthen the theory of increased adherence among warfarin patients who will be aware of the seriousness of valve replacement procedures. Furthermore, according to Witt et al., 2009 study, patients who take warfarin receive frequent monitoring. The study found that an anticoagulation service managed by clinical pharmacists substantially improved adherence to warfarin therapy.

Our results also revealed a noticeable increase in adherence among OACs users associated with the increase of duration of taking OACs. This finding contrasts the reported results by some authors who documented that adherence to OACs decreases with the increase of duration of taking medications. Chapman et al., 2005 who investigated adherence to antihypertensive and lipid lowering drugs reported a drop in adherence rates to these medications from 45% at 3 months to 36% at 12 months. We cannot attribute specific reasons for this phenomenon in our results as other factors need to be considered such as total number of daily tablets and other comorbidities. For example, survivor bias might be involved as it is conceivable that individuals who had a low level of adherence ceased taking their medication and attending clinic appointments, resulting in their exclusion from the study. Alternatively, they could have passed away.

4.6.2. Relating our findings to previous literature

The results of our study showed that overall adherence rate to OACs using Hill-Bone scale for measuring adherence is 29.8% among the participants of the study. Adherence among warfarin users (203) was 40.4% while adherence among patients who were taking DOACs (109) was 22%. In Saudi Arabia, adherence to warfarin was previously studied by Balkhi et al., 2018 who documented a 31.8% adherence rate in their investigation of patients' adherence to

warfarin in Qassim area, central Saudi Arabia (Balkhi et al., 2017). Shilbayeh et al reported 32.6% adherence rate to warfarin when they studied adherence to the drug in Riyadh area (Shilbayeh et al., 2018). Similarly, Elbur et al reported 35.9% adherence rate to warfarin in Taif, Western Saudi Arabia (Elbur et al., 2015). Our results indicates that adherence to warfarin in Eastern and Western Saudi Arabia is more or less the same but higher than in central parts of the country. Comparing our results to findings of comparable research results in the Middle East revealed that Ababneh et al. in Jordan documented 54% adherence rate among patients who were taking warfarin (Ababneh et al., 2016). Our results have reported lower adherence rate than the documented results from Jordan. However, in our study we used Hill-Bone scale to measure adherence to OACs, which classified participants into either adherent or non-adherent. Adherence to OACs in the other studies was measured by using self-reporting questionnaires (e.g. MMAS-8) that adopt different approaches in classifications of adherence (high adherence, medium adherence, and low adherence). The adherence rates are therefore not directly comparable.

Our results reported an overall 22% adherence rate to DOACs. Despite numerous publications examine the use of DOACs in Saudi Arabia, to our knowledge no published study investigated adherence to DOACs in the country. A study by Emren et al., 2018 in Turkey reported 49% adherence rate to DOACs. Our results indicate that the uptake of DOACs is still at early stages in Saudi Arabia and further investigations are needed to examine the use of these medications in this country as their uptake increases.

The results on adherence to OACs in the present study suggests a significant relationship between adherence to OACs and age of participants, education level, indications for prescribing OACs, and type of prescribed OAC ($P < .05$). Similar findings were reported in studies carried out by Shilbayeh et al, 2018 and Balkhi et al., 2018 who reported significant association between adherence to warfarin and higher education levels and nationality of participants ($P < .038$). Our results agree with these findings regarding the education level; however, nationality of participants was not investigated in our study. From a wider point of view, results by Middle Eastern investigators did not confirm a relationship between adherence to OACs and sex of the patient (Ababneh et al, 2016), a similar finding which is

documented by our study (P .256). In other words, this study did not find a significant difference between the sex of participants and adherence to OACs.

Our results indicated a significant relationship between adherence to OACs and following prescribers' advice on how to take OACs, missing doses of OACs, and knowledge about INR targets for warfarin users ($P < 0.05$, table 9). However, the results did not confirm any association between adherence to OACs and awareness of patients about their indications for taking OACs ($P > 0.05$).

Regarding knowledge about warfarin, Shilbayeh et al., 2018 reported insignificant association between knowledge about INR and adherence to warfarin (P 0.453), our findings agree with this result as our results showed insignificant relationship between the two elements.

Using regression analysis of the data revealed that there are certain characteristics that can influence adherence to OACs among its users in the study area. These characteristics are age of patients, level of education, and indications for prescribing these drugs. Our results are consistent with the findings of the study conducted by Liang et al. 2018, which found that factors such as age, educational attainment, and the reasons for prescribing OACs were significant determinants of the choice of the appropriate OAC therapy.

4.6.3. Strengths and limitations

The strengths of this research include its novelty in assessing adherence to OACs in the study area. This study is the first of its kind in Alhassa area, Eastern Saudi Arabia, it employed self-assessment method to examine adherence to OACs. The self-reported Hill-Bone scale for measuring adherence was the first time to be used in the area to assess adherence to OACs.

The use of a self-reported method to measure adherence (HB scale) is a limitation. This scale does not specify level of adherence like in other scales such as Eight-Item Morisky Medication Adherence Scale (MMAS-8) which classifies adherent population into highly, moderately and poorly adherent individuals. However, the scale was the most cost-effective method to be employed for the purpose of this research study.

Using more than one self-reporting scale to evaluate adherence offers several benefits. Firstly, it can enhance the precision of the assessment by minimising the risks of bias and inaccuracies associated with relying on a single scale. Moreover, it can assist in determining the most suitable scale for a particular medication or patient population. Additionally, it can provide a more complete comprehension of adherence by measuring various aspects or dimensions of medication-taking behaviour. Furthermore, it can facilitate the creation of customised interventions by identifying specific areas of non-adherence that necessitate attention.

The study was also limited by not calculating Time in Therapeutic Range (TTR) which reflects the INR control for patients who are taking warfarin. This was mainly due to lack of sufficient data as patients in the study did not carry information about history of taking warfarin in terms of their INR, dosages, and appointments. All this information is usually provided to patients verbally.

Another limitation to this research was the cross-sectional nature of the study design which can subject the study population to bias of selection. This problem was overcome in the selection criteria for participants as OACs users with cognitive impairment and patients who did not consent to participate in the study were excluded.

In addition to the limitations, the small sample size recruited for the study and the fact that the study was carried out in one centre in Eastern Saudi Arabia undermined the generalisability of its findings to all population in Saudi Arabia. However, this approach was aligned with the resources accessible and feasible for this study.

4.7. Conclusion

The study effectively accomplished its primary objectives, offering valuable insights into the landscape of adherence to OACs and prescribing patterns in Eastern Saudi Arabia. The research

revealed a troubling pattern of low adherence among patients, with less than one-third of participants classified as adherent to their OAC regimens. This underlines the need for targeted interventions and strategies to improve adherence rates and subsequently enhance patient outcomes. Additionally, the study elucidated that warfarin remained the predominant choice for OACs' therapy in the region, with a notably higher proportion of adherent patients receiving warfarin prescriptions compared to DOACs. These findings hold significance for healthcare practitioners and policymakers, highlighting the importance of optimising adherence strategies and exploring the potential benefits of alternative OAC therapies.

Furthermore, the study's comprehensive assessment of medical conditions warranting OAC prescription shed light on the diverse range of indications, including valve disease, AF, DVT, PE, and Stroke. This information provides valuable guidance for HCPs when considering OACs treatment options for patients with specific medical conditions. Moreover, the study identified key predictors of adherence, encompassing various demographic and clinical factors, along with patient-reported reasons for non-adherence. This nuanced understanding of adherence determinants can inform tailored interventions aimed at addressing the specific challenges faced by patients in the region. In conclusion, the study's successful achievement of its objectives contributes significantly to the knowledge base surrounding adherence to OACs and prescribing practices, offering a foundation for future research and interventions to improve patient care in Eastern Saudi Arabia.

CHAPTER FIVE: A QUALITATIVE STUDY OF PATIENTS' ADHERENCE TO ORAL ANTICOAGULANTS: INVESTIGATING THE PERSPECTIVE OF HEALTHCARE PROFESSIONALS AND EXAMINING THE ROLE OF PHARMACISTS IN PROMOTING PATIENTS' ADHERENCE TO OACS

5.1. Introduction

OACs, including warfarin and direct oral anticoagulants DOACs, are the drugs of choice for prevention of thromboembolic events such as VTE and stroke. Adherence to OACs is the cornerstone for effective treatment and for reaching the desired therapeutic outcomes (Lip *et al*., 1994; Lip et al., 2015). Research reports have documented variable results about the extent of adherence to OACs among their users in Saudi Arabia (Elbur et al., 2015; Shilbayeh et al., 2018). Despite the high variability of the results documented about adherence to OACs, these publications agreed that there are factors that can affect adherence (Zubaid et al., 2013). The factors that contribute to the classification of patients as adherent or non-adherent to OACs are not well understood in Saudi Arabia, as there is limited information available on the subject (Manzoor et al, 2017). This lack of understanding highlights the need for further research to identify the underlying reasons behind patient adherence to OACs in the region. In addition, little is known about how OACs' users are supported with taking these medications.

Variable levels of adherence to OACs were reported in different parts of Saudi Arabia (Elbur et al.,2015; Balkhi et al., 2018; Al-Saikhan, 2020). Although several studies have been conducted, they did not address important inquiries, including the prescription practices for OACs, the obstacles to adhering to OACs, and the extent of support provided by hospital and community pharmacists to ensure adherence to OACs. The papers published have primarily focused on the quantitative aspects of investigating adherence to OACs, with a particular emphasis on patient-related factors such as such as patients' perceptions about these medications. (Mayet et al., 2016). Studying adherence to OACs from a qualitative perspective is vital to underline the scope of the delivered health services for OACs' users and to identify challenges that face patients and care providers. Such studies can produce valuable data that can lead to a better understanding of medication taking behaviour and in Saudi Arabia, in turn open the door for suggesting patient-tailored interventions that can lead to increasing the

support for adherence to OACs and ultimately improving treatment outcomes in the country. HCPs are the cornerstone for the delivering health services as they are equipped with the essential knowledge and technical skills, therefore they can play a significant role in providing significant information about use of OACs.

5.2. Aim of the study

To provide in depth views and experience of HCPs on adherence to and prescribing of OACs in Eastern Saudi Arabia. Specific objectives of the study are:

To explore views of HCPs on patients' adherence to OACs in the study area

To identify impediments to improve patients' adherence to OACs in view of HCPs

To investigate role of pharmacists in supporting patients' adherence to OACs

To determine factors that influence prescribing of OACs as expressed by interviewed HCP

5.3. Design of the study and collection of the data

Thematic analysis, which falls under the umbrella of qualitative research methods, was selected as an approach in this study. employed for data collection involved the use of thematic analysis approach, The utilisation of thematic analysis as the chosen methodology for exploring HCPs perspectives on adherence to OACs is grounded in its capacity to provide an in-depth and examination of the qualitative data. Adherence to OACs is a complex phenomenon influenced by various clinical, social, psychological, and contextual factors. Thematic analysis aligns with an interpretative approach, allowing for the exploration of the complex interaction of these factors within the narratives of HCPs. By employing thematic analysis, the study aims to reveal the intricate themes and patterns that underlie HCPs' perspectives, ultimately contributing to a more comprehensive understanding of the factors influencing adherence to OACs (Braun and Clarke, 2006; Joffe and Yardley, 2004).

Data for this study was collected through semi-structured interviews featuring open-ended questions. These interviews were structured into four key sections encompassing: (1) background information regarding the interviewed HCPs such as their roles within the hospital and years of work experience; (2) the specific roles of HCPs within the hospital setting; (3) the assessment of patients' adherence to OACs by HCPs, with a particular emphasis on AF and VTE conditions; and (4) the involvement of pharmacists in evaluating adherence to OACs and conducting medication reviews (interview schedule Appendix IV). To enhance the reliability and validity of the interview questions, a review process was undertaken by academic experts and pharmacists, in line with principles of face and content validity as suggested by Bowling, 2014 and Smith, 2002. As a result of the feedback received from these experts, one question was rephrased to enhance its clarity. The rationale for selecting thematic analysis as the study design and for employing semi-structured interviews for data collection was elaborated upon in Chapter 2 of this thesis.

5.4. Conduction of the interviews

The selection of interviewees for this study was conducted through a purposive sampling approach. The researcher specifically targeted HCPs employed at the study centre (PSCC) who were closely involved in the care of patients taking OACs. These HCPs were personally invited to participate in the research. A total of 15 HCPs expressed their willingness to be part of the study, including a diverse group comprising physicians, pharmacists, and nurses. The rationale behind choosing this group of HCPs lay in their substantial knowledge and expertise concerning adherence to OACs and the behaviours of patients in this context. Further justification was provided in chapter 2 of this thesis.

5.5. Ethical clearance

Ethical clearances were obtained from the University of Birmingham Science, Technology, Engineering and Mathematics Ethics Committee for conducting the study and from the research committee in the study centre (PSCC, Saudi Arabia) before conducting the interviews. Consent of the interviewed HCPs was sought before interviewing, (Appendix I). Files and transcripts of the interviews will be destroyed after submission of the thesis.

5.6. Location of the interviews

The interviews were conducted at the (PSCC) where all the interviewed HCPs were full timely employed by the centre. Time of the interview was selected by the HCPs according to their schedule of work. A private room in the centre was designated for face-to-face interviews. Prior to each interview the objectives of the study were described, and an opportunity to ask any questions about the study was given. Consent of participants was sought before starting the interviews using a consent form. (Appendix. IV).

5.7. Data management and analysis

An inductive methodology was employed for the analysis of the collected data, with a primary focus on the perspectives expressed by the interviewees. This inductive approach allowed for the emergence of themes through a systematic process of open coding applied to the dataset. Furthermore, this approach emphasises the extraction of insights directly from the data itself, fostering a deeper understanding by permitting unexpected or innovative themes to emerge, ultimately leading to a more comprehensive data interpretation. To perform this, themes were generated by identifying codes within the interview transcripts, following the guidelines established by Braun and Clarke, 2006. The process involved an initial familiarisation with the data through regular transcript reviews, creating preliminary code sets, and using color-coded markers to group similar codes. Within the inductive framework, codes that were comparable

were consolidated to form meaningful themes, each carefully reviewed to ensure the consistency of its constituent codes, and accurately labelled to reflect its content. The resulting findings were then synthesised into a comprehensive report.

5.8. Findings of qualitative interviews with HCPs

5.8.1. Characteristics of the HCPs

Fifteen HCPs including doctors, nurses, pharmacists, and pharmacy technicians were interviewed. The breakdown of the total number of interviewed professionals is as follows: 8 physicians, 2 nurses, 3 pharmacists, and 2 pharmacy technicians. Characteristics of the interviewees and duration of each interview are summarised in table.5.1.

Table.5.1. Characteristics of HCPs who participated in the qualitative interviews

Interviewee serial number	occupation	Duration of the interview (minutes)
1	Physician 1	54
2	Pharmacy technician 1	46
3	Pharmacist 1	41
4	Staff nurse 1	42
5	Pharmacists 2	43
6	Pharmacists 3	48
7	Pharmacy technician 2	42
8	Staff nurse 2	41
9	Physician 2	52
10	Physician 3	46
11	Physician 4	48
12	Physician 5	45
13	Physician 6	44
14	Physician 7	45
15	Physician 8	40

5.8.2. Extracted themes from the interviews with HCPs using thematic analysis

The thematic analysis of the semi-structured interviews for collection of data had yielded 6 primary themes and several subthemes as shown in table 5.2.

Table 5.2. Themes and subthemes produced from analysing the HCPS interviews using thematic analysis.

Theme no.	Themes	Subtheme
1	Viewpoints of HCPs on factors influence prescribing of OACs	- HCPs perspectives on patients' illness perception when prescribing OACs - Relationship between adherence to OACs and illness perception - Effect of patient safety considerations when prescribing OACs - Clinical factors influence selection of OACs - Non-clinical factors that affect selection of OAC - Concordance about OACs - Effect of cost factor on prescribing OACs
2	Assessment of adherence to OACs among OACs users	- Utilisation of scales to measure adherence in routine practice - Assessment of adherence among warfarin users - Assessment of adherence among DOACs users
3	Perspectives of HCPs on patients' adherence to OACs	- Perspective of interviewees on overall adherence to OACs - Variations in adherence to OACs between hospitalised and discharged patients
4	Impediments for adherence among OACs users	- Viewpoints of HCPs on identification of non-adherent patients - Perception of HCPs on reasons for non-adherence among OACs' users
5	Viewpoints of interviewed HCPs on supporting adherence of patients who are taking OACs	- Counselling of OACs' users - Counselling of warfarin users - Counselling for DOACs patients - Availability of adherence aids for OACs users - Social care input in facilitating adherence to OACs
6	Role of pharmacists and pharmacy technicians in resolving	- Accreditation of pharmacists and pharmacy technicians for pharmaceutical services

issues related to adherence to OACs	- Perceptions of pharmacists and pharmacy technicians in monitoring warfarin users - Input of pharmacists and pharmacy technicians in supporting polypharmacy patients - Use of validated scales in routine pharmacy practice - Barriers to patients' education by pharmacists and pharmacy technicians - Availability of pharmaceutical services for OACs users in community pharmacies - Sales of OTC medicines to OACs users in community pharmacies

5.9. Outcomes of the extracted themes

5.9.1. Theme 1: Viewpoints of HCPs on factors influence prescribing of OACs

In this theme, the interviewed HCPs discussed various factors that could influence the prescribing of OACs, including the assessment of illness perception, clinical factors affecting OAC selection, patient safety considerations, non-clinical factors such as socio-economic factors that could affect OAC selection, concordance about OACs, and cost factors in OAC prescribing. The interviewees were asked about their opinions and perceptions regarding the prescription of OACs. They expressed that the introduction of DOACs has expanded the treatment options for OAC users. However, they also acknowledged that the availability of DOACs has brought new challenges to the selection and prescription of OACs.

> *"prescribing of warfarin is well established, launching of DOACs has increased treatment options for patients."* (Phys. 3).

5.9.1.1. HCPs perspectives on patients' illness perception when prescribing OACs

The HCPs who were interviewed were specifically asked if they took into consideration the perceptions of patients who were prescribed OACs about their medical condition. In response to this question, the HCPs confirmed that they did indeed investigate this aspect with their patients.

"I always to discuss with patients their thoughts and their experience about their conditions". (Phys. 8)

During the interviews, HCPs were questioned regarding the topics they address with their patients. Respondents highlighted that they consider patients' personal traits, underlying factors contributing to their condition, potential impact of the illness on their daily activities, as well as strategies for disease management.

" I describe to my patients what the disease is, why and how it occurred, impact of the condition on their future, and how and why we treat the condition". (Phys. 7)

5.9.1.2. Relationship between adherence to OACs and illness perception

HCPs expressed that adherence to OACs improves with the increase in patients' perceptions about the seriousness of their illness among majority of patients.

"When patients know more about their illness, they comply with the advice about OACs". (Phys. 5).

The HCPs who participated in the interviews emphasised the relationship between OAC adherence and patients' perception of their condition.

"I notice better adherence among patients who know more about their conditions". (Pharm. 1).

5.9.1.3. Effect of patient safety consideration when prescribing OACs

Some interviewees believed that regular monitoring of anticoagulation and INR checks provided patients with some safety compared to patients on DOACs. However, interviewees expressed poor control of anticoagulation associated with use of warfarin discourages some physicians from prescribing warfarin for some patients.

"when I prescribe warfarin, I feel patients will be safe to some extent, because of the monitoring, not like when I prescribe a DOAC as it is not monitored". (Phys. 4)

"checking anticoagulation effect in warfarin protect patients compared to DOACs". (Phys. 1)

"warfarin is monitored but DOACs are not, it is much safer to prescribe warfarin". (Phys. 7)

Some of the HCPs who were interviewed raised concerns regarding the limited safety data available for DOACs in Saudi Arabia, particularly among elderly patients. In addition, they expressed apprehension about the lack of readily available antidotes for DOACs, except for dabigatran and rivaroxaban.

DOACs are relatively new in the market, we do not have enough data about the magnitude of their safety in Saudi Arabia, we rely on the internationally reported side effects and incidents more". (Phys. 4).

" local data about adverse events is scarce; we use Datex® system to report incidences, we hope to increase the information in the future". (Phys. 5).

Interviewees were asked if any scheme to report suspected side effects and ADRs with OACs or with other medications is available. They highlighted that Saudi Food and Drug Administration (SFDA) is responsible for pharmacovigilance and that all health care practitioners are advised to report side effects and ADRs. They added that because of the work pressure they may forget to communicate incidences with SFDA.

" SFDA deals with vigilance issues, we inform them about problems with medications". (Pharm.1)

"sometimes we are busy to report incidents related to DOACs". (Phys. 3).

5.9.1.4. Influence of clinical factors on selection of OACs

During the interviews, the selection of OACs was a topic of discussion, including the preferences for prescribing them. A few respondents mentioned that they prefer DOACs over

warfarin due to the lack of need for monitoring and a lower risk of adverse events associated with its use compared to warfarin.

> *"I prefer DOACs because they do not need monitoring and the risk of adverse events is lower than warfarin."* (Phys. 5)

> *"when I have a choice; I will choose DOACs, the risk of side effects and food restrictions is minimum compared to warfarin"*. (Phys. 1)

The HCPs who were interviewed held varying opinions regarding their preferred OAC when choosing between warfarin and DOACs.

> *"there is no general consensus about warfarin or DOACs, we take each case on its own merits."* (Pharm 2).

In the study, healthcare professionals were asked about the factors that influenced their decision-making process when selecting an appropriate OAC for their patients. They identified several determinants that played a significant role in their decision-making, including patient age, mental health status, contraindications, and potential risks associated with OAC use, such as the risk of falls. Additionally, the HCPs considered the use of other medications by their patients and their adherence to medication, as these factors could impact the effectiveness of the prescribed OAC. By taking all of these factors into account, the HCPs were able to make well-informed decisions about the most appropriate OAC to prescribe for each patient based on their individual medical history and unique circumstances. This personalised approach to prescribing has the potential to result in better health outcomes for the patients.

> *"I look into the general condition and check for risk associated with use of OACs, risk of fall for example, when prescribing any OAC"*. (Phys. 6)

> *"I consider the psychological and cognitive status of patients before prescribing an OAC."* (Phys. 2)

HCPs added that patients' health beliefs about medications also participated in their decision to prescribe OACs.

> *"beliefs of patients about taking medications are also important for the decision to prescribe OACs, some patients do not belief on taking tablets"*. (Phys. 1).

The use of risk calculators such as CHA2DS2-VASc, CHADS2, and HAS-BLED was discussed with interviewed HCPs. They confirmed use of these tools is a common practice, however, only physicians reported using it when prescribing OACs.

> *"we use risk assessment tools such as CHA2DS2-VASc, CHADS2, and HAS-BLED in routine practice when prescribing OACs"*. (Phys 8)

> *"it is used by physicians as they are the prescribers"*. (Phys. 4).

Figure 5.1. summarises influential factors for recommending of OACs for patients.

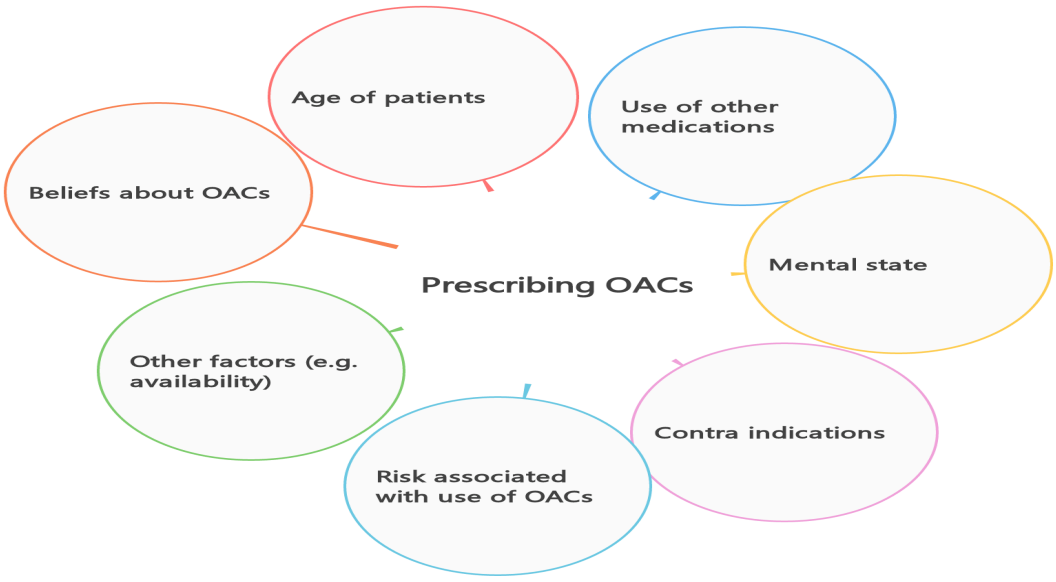

Figure 5.1. Identified factors which influence prescribing of OACs as perceived by HCPs

5.9.1.5. Non-clinical factors that affect selection of OAC

Interviewees also acknowledged the importance of patients' non-clinical factors such as social care circumstances as a determinant for selection of appropriate OAC.

> *"from my experience, some patients are expected to have social or medical problems with monitoring of INR if prescribed warfarin; it will be difficult to visit the hospital for regular appointments. Appropriateness of the OACs for their circumstances is essential".* (Phys. 3).

Interviewed HCP also reported feeling anxious about possibility of causing harm to patients and being held accountable.

> *" OACs are started and monitored in hospitals, this makes physicians fully responsible for prescribing and monitoring".* (Phys. 2)

During the study, HCPs were interviewed about how patient characteristics and opinions affect the process of prescribing OACs. The results revealed that patient characteristics and opinions do have an impact on the healthcare professionals' prescribing decisions. In fact, some of the interviewed HCPs mentioned that many of their patients dislike being prescribed warfarin due to the need for frequent blood monitoring, which has led them to prefer DOACs as a first choice.

> *"some patients express their concerns about warfarin due to the regular INR checks required, DOACs would be their choice".* (Phys. 1)

> *" If a patient proves to have low awareness about the condition and shows less adherence to medications, then prescribing warfarin may be a risk for this patient".* (Phys. 6)

5.9.1.6. Concordance about OACs

As part of the study, HCPs were asked about the importance of informed discussions with patients when prescribing OACs. Additionally, they were questioned about their willingness to respect a patient's decision to decline a suggested OAC. The HCPs confirmed that they place significant value on informed discussions with patients and that they fully respect a patient's decision to decline a suggested OAC, as long as the decision is well-informed.

> *"I accept what my patients decide after we discuss it on condition that they know why it was suggested".* (Phys 2).

> *"If my patients understand the rationale of the selection of OACs, I accept their decision, otherwise they will not be adherent to their OAC treatment".*

Some interviewed HCPs highlighted that mutual agreement with patients about OAC and ability of patients to make informed decisions influence their willingness to prescribe OACs.

> *"discussing options with Patients is important, it helps with the selection of the right OAC".* (Phys. 8)

> *"I make sure the patients have full information about OACs to enable them to make decisions about the right option".* (Phys. 3).

5.9.1.7. Effect of cost as a factor on prescribing OACs

When discussing the role of cost as a factor influencing prescribing or adherence to OACs, interviewees noted that the supply of VKA and DOACs is free of charge in Saudi Arabia.

> *"Cost of OACs is not a barrier in Saudi Arabia, it is provided free of charge to the patients".* (pharm. 1)

5.9.2. Theme 2: Assessment of adherence to OACs among OACs users

In the preceding theme, the focus was on the prescribing of OACs and the factors that influence it. The subsequent theme revolves around adherence to OACs, which was discussed with HCPs. This included adherence to both VKAs and DOACs.

5.9.2.1. Utilisation of scales to measure adherence in routine practice

The interviewees were asked about the use of validated scales like the Morisky (MMAS-8) or other comparable self-reported scales to assess patient adherence to OACs in their regular clinical practice. The interviewees noted that such scales were not commonly employed in their routine practice. They explained that this was mainly due to time limitations and insufficient knowledge and expertise among some HCPs.

> *I don't use these scales in routine practice, they are excellent, but our time is limited ".* (Phys.3)

> *" I focus more on clinical issues; I need to see many patients plus these scales need training "*. (Phys. 7)

" These scales need training, not everyone can use it". (Phys. 2)

The HCPs who were interviewed were questioned regarding their methods for assessing adherence. They reported that they evaluate adherence by examining the patient's compliance with dosage instructions, adherence to the prescribed schedule for taking medication, and reviewing the patient's attendance record for appointments and visits to clinics.

> *" I ask my warfarin patients about the dose, and when they take warfarin, I also ask if they have any problems with taking warfarin "*. (pharm. 1).

> *" T*he *computer tells me about the patients record of visits, I check if a patient missed INR check"*. (Phys. 7)

5.9.2.2. Assessment of adherence among warfarin users

During the study, HCPs were asked about the methods they use to assess adherence

in patients taking warfarin. The participants stated that they review symptoms and check INR levels as tools for assessment. They also mentioned using INR as a marker for patients' adherence to warfarin.

> *"I ask the patients about their condition and if there is any concern, also I check the readings of the INR".* (Phys. 1)

> *"If the patient is adherent, I do not see problems with the INR".* (Phys. 6)

The interviewees reported that some healthcare providers, including dentists and community pharmacists, do not communicate information about the coagulation status of warfarin patients when needed, such as for dental procedures or over-the-counter medication purchases.

> *"dentists and community pharmacists do not have access to INR results of a warfarin user, we do not have means of communication like in other countries".* (pharm. 1)

5.9.2.3. Assessment of adherence among DOACs users

The interviewees were questioned regarding their approach to assessing patient adherence to DOACs. According to the HCPs, they evaluate the presence of symptoms, frequency of medication intake, and potential barriers to tablet administration.

> *"We assess the patient's complaint for which a DOAC was prescribed, for instance if an ECG is fine, we conclude that the patients is more likely to be adherent, it gives a hint"*(phys. 5)

5.9.3. Theme 3: Perspectives of HCPs on patients' adherence to OACs

The theme focused on the opinions of HCPs regarding the adherence of OAC users. The discussion included two perspectives: the HCPs' views on patient adherence and the differences in adherence between hospitalised and discharged patients.

5.9.3.1. Perspective of interviewees on overall adherence to OACs

The HCPs who were interviewed shared their experience regarding patients' adherence to OACs. Some HCPs expressed satisfaction with the level of adherence among patients, while others raised concerns about the adherence of some patients who are taking warfarin.

> *"Most of my patients are adherent to OACs in my experience"*. Physician (Phys.1) .

> *"There are some of my warfarin patients who are not adherent, but they are few."* (phys. 5)

"Some of *my warfarin patients are not adherent as they should be their INR is never within the range ".* (Phys. 8).

Moreover, some HCPs believed that adherence of patients to DOACs is higher than warfarin

"Most of patients are adherent to DOACs". (Phys. 6).

*"if they asked to choose; they prefer DOACs". (*Phys.4).

According to some interviewed HCPs, patients sometimes miss their scheduled clinic appointments, which can result in incomplete data on their OAC use.

> *" Regular INR monitoring and keeping appointments are crucial for treatment outcomes but some patients may capture unnoticed periods of nonadherence "*. (Phys. 5)

5.9.3.2. Variations in adherence to OACs between hospitalised and discharged patients

The interviewees were asked about the differences in adherence to OACs between hospitalised and discharged patients. The participants acknowledged that there were differences in adherence levels between these two groups. They explained that patients tend to be more compliant with their medication regimen while they are hospitalised, as they have access to more support for taking their medications and modifying their behaviour.

> ‟*Not all patients are adherent, they are adherent while admitted, but not sure when they are discharged*; that's *because the staff in the hospital care for medications while patients in the hospital*‟. (Nurse 2).

> ″*Discharged patients take tablet at home; I assume they take their tablets regularly*‟. (Nurse 1).

5.9.4. Theme 4: Impediments for adherence among OACs users

The theme of this section explored the obstacles that impede patients' adherence to OACs, including how non-adherent patients are identified and the underlying reasons for their non-adherence.

5.9.4.1. Viewpoints of HCPs on identification of non-adherent patients

The topic of non-adherence among OACs users was discussed with HCPs, including their understanding of the concept of non-adherence among their patients. The interviewees clarified that they consider patients who skip doses or do not take their OACs as prescribed as non-adherent.

> ″*non-adherent patient does* n*ot mean just patients who are missing doses, it can also include those who are taking their OACs incorrectly*″. (Phys. 7).

The interviewed HCPs explained that patients who take incorrect doses, miss doses, take medications at the wrong time, or do not follow the recommended counselling, are considered

non-adherent. They also mentioned that patients who overdose on their medication can also be classified as non-adherent.

> *"taking too many tablets can be considered as non-adherence as well as taking few tablets".* (Pharm.1)

> *"not take tablets at the recommended time or not taking tablets as counselled by a doctor or a pharmacist is non-adherence".* Pharm 2.

> *"taking the incorrect number of tablets, whether it is over or under will affect adherence".* (pharm. 1).

According to the participants, they regularly evaluate patients' adherence to oral anticoagulants (OACs) and take necessary measures to enhance it.

> *" I immediately inform my patients about importance of adherence to improve treatment outcomes".* (Phys. 5).

Regarding differences in non-adherence between patients using warfarin and DOACs, healthcare professionals (HCPs) stated that they have observed a higher incidence of non-adherence among warfarin users compared to those using DOACs

> *". Warfarin users tend to show non-adherence more than DOACs users".* (Phys. 1)

> *"DOACs users are more adherent than warfarin users".* (Phys. 6)

HCPs were asked to explain the reason behind the higher rate of non-adherence among warfarin users compared to DOACs users. They clarified that the complexity of warfarin dosing for some patients was the main reason for this increase.

> *" Doses of warfarin are complex compared to DOACs; patients make mistakes sometimes".* (Phys. 3).

"Patients need to take several tablets to makeup the dose, sometimes make errors". (Pharm. 1)

HCPs who were interviewed stated that non-adherence was prevalent among patients who were taking OACs. However, they expressed uncertainty about the level of non-adherence in Saudi Arabia and acknowledged the lack of reliable data on the extent of non-adherence.

"Some patients are non-adherent because they do not want to take the tablets". (Pharm. 2)

"Some patients do not take the tablets because there are barriers". (Pharm. 1)

"We do not know the exact situation with non-adherence". (Phys. 7)

"At the moment we do not have statistics about non-adherence problem". (Phys. 4).

5.9.4.2. Perception of HCPs on reasons for non-adherence among OACs' users

The interviewed HCPs highlighted several factors that were considered as indicators for non-adherence in patients taking OACs. These included insufficient knowledge about the condition and how to manage it, as well as adverse events and side effects associated with the medication. The use of multiple medications, or polypharmacy, was also identified as a possible contributor to non-adherence. Moreover, forgetfulness was recognised as a common problem that leads to non-adherence among OAC users. These results suggest that addressing these factors may be crucial in enhancing adherence to OAC therapy.

"Some patients know little information about their conditions and about importance of adherence". (Pharm. 2)

"Some patients who suffer side effects or adverse events become reluctant to take their medications". (Phys. 7)

"Patients who are taking too many tablets may be confused about their OACs". (Pharm.1)

"Some patients forget to take their tablets, especially elderly patients". (Pharm. tech. 2).

5.9.5. Theme 5: Viewpoints of interviewed HCPs on supporting adherence of patients who are taking OACs

In this theme, the topic of supporting patients on OACs was explored, including counselling for warfarin and DOACs users, the use of compliance aids, and the role of social care.

5.9.5.1. Counselling of OACs' users

Many participants brought up the importance of counselling patients on how to take OACs as prescribed. They also expressed provision of counselling when starting patients on OACs.

"I explain to my patients how to take OACs so they can get the maximum benefit". (Phys. 8).

"I counsel my patients when I prescribe OACs". (Pharm. 2)

When asked about their counselling practices for patients taking OACs, interviewees noted that counselling methods differed depending on the type of medication prescribed. Specifically, they confirmed that counselling practices varied between DOACs and warfarin patients. Warfarin use was noted to require more extensive counselling due to its complex nature, whereas DOACs were considered simpler to manage and required less counselling.

"Counselling about warfarin is different to DOACs". (Phys. 8)

"warfarin and DOACs are different groups of OACs, we counsel patients according to the drugs that is being used". Pharmacy technician (Pharm. tech. 1)

" there *are different protocols for counselling patients on DOACs and warfarin".* (Pharm. 2*)*

Interviewees revealed that patient's education unit is available to answer queries from patients regarding OACs.

> *"Our patients can contact us about issues with their OACs, there is a help line designated for this purpose".*(pharm tech. 2)

5.9.5.2. Counselling for patients who are taking warfarin

According to the HCPs interviewed, they provide guidance to patients taking warfarin regarding the administration of the drug, as well as information about potential food and drug interactions and how to minimise the risk of adverse effects such as bleeding.

> *"Use of warfarin carry some risk of bleeding, I try to reduce this risk by counselling my patients about this point".* (Phys. 1)
>
> *"I tell my patients about the interaction between green vegetables and warfarin and about over the counter medications".* (Phys. 5)
>
> *"I tell my patients when to take the warfarin dose, we also advise them to reduce their green vegetables intake, and also, we advise to speak to pharmacists in their communities when buying over the counter medications".* (Phys. 3)

The HCPs mentioned that they provide guidance to warfarin patients regarding the significance of undergoing regular INR checks and emphasised the need to keep appointments for these checks.

> *"I tell my patients to come regularly to check their INR".* (Phys.4)
>
> *"I explain to my patients they must come for INR check because it tells how they are doing with their warfarin".* (Phys. 1)
>
> *"One of the points that I stress to warfarin users is regular INR check, without INR check patients may suffer adverse event".* (Phys. 7)
>
> *"I inform patients on warfarin that it is necessary to come to hospital to get the INR checked, this is necessary for successful treatment".* (Phys. 6)

HCPs reported that they instruct warfarin patients to reach out to the hospital in case they experience adverse events, such as bleeding.

> *" I encourage my patients to contact the hospital and inform us about any adverse event so we can address the issue "*. (Pharm. 2)
>
> *"I tell my patients to contact the warfarin clinic if they have problem"*. (Pharm. 3)
>
> *"I encourage my patients to contact the clinic if they suffer bleeding"*. (Pharm. 1)

Some of the HCPs noted that language can be a hindrance when providing counselling to warfarin users.

> *" As you know patients here talk different languages, sometimes it's a problem".* (Phys. 5)

When asked about how they deal with such problem they reported that interpretation services available in the hospital.

> *" W*e *contact interpretation service to provide an interpreter"*. (Phys. 1)

5.9.5.3. Counselling for DOACs patients

The HCPs who were interviewed agreed that DOACs had fewer side effects compared to warfarin, and that they did not require monitoring. As a result, there was a consensus among the HCPs that patients preferred taking DOACs due to these characteristics.

> *" DOACs are not like warfarin, they have fewer side effects"*. (Phys. 5)
>
> *" when we look at DOACs and warfarin we find they do not need monitoring of coagulation status as in warfarin".* (Phys. 8).

Interviewed HCPS expressed that they inform patients how to take DOACs (daily doses) and taking the doses on specified times.

> *" when counselling my patients about DOACs I tell them about dosing and frequency".* (Phys. 6)

According to the HCPs who were interviewed, they assess patients' renal function status and risk of internal bleeding before prescribing DOACs.

> *" DOACs are associated with risk of internal bleeding and therefore I check risk factors such as history of peptic ulceration and use of NSAIDs".* (Phys. 3)
>
> *"side effects of DOACs are low, therefore counselling about this group is not like counselling about warfarin".* (Phys. 5)
>
> *"counselling about DOACs is not as exhaustive as in warfarin, I advise my patients how many tablets they need to take and how many times a day".* (Phys. 1)

5.9.5.4. Availability of adherence aids for OACs users

During the interviews, the HCPs were questioned about the availability of adherence aids in the market. They reported that there are some multi-compartment systems that are currently available.

> *"Multicompartment systems compliance aids are widely available".* (Pharm tech. 1)
>
> *"People are used to compliance aids that they fill it with tablets".* (Pharm. 3)

Interviewed HCPs were asked about groups of patients that they recommend adherence aid for? They clarified polypharmacy patients as the main group.

> *"I recommend compliance aids to improve adherence for patients who are taking multiple medications and for elderly patients because they are forgetful".* (Phys.3)
>
> *"When I recommend adherence aids, I consider the patient rather than the medication".* (Phys. 8)

When asked about community awareness of adherence aids, HCPs mentioned that patients often have the option to choose such devices themselves. They noted that some patients use compliance aids even without being recommended to do so by healthcare professionals.

"Some of my patients prefer to use compliance aids, they bought it from community pharmacies, they think it help with remembering when to take the tablets". (Phys. 3)

5.9.5.5. Social care input in facilitating adherence to OACs

The HCPs who were interviewed for the study stated that there is no involvement of social care providers in assisting patients with taking their OAC medications. They explained that care workers do not have any role in addressing medication-related issues.

The HCPs interviewed as part of the study emphasised that there is a notable absence of involvement from social care providers when it comes to assisting patients with their OAC medications. They clarified that care workers, although available to aid patients in various aspects of their daily lives, do not play any active role in addressing medication-related concerns or offering support in the medication-taking process.

"There are carers for the patients; but they are not working in medication area; they do not support medication taking". (Phys. 3)

This assertion underscores that, despite the presence of social care input for patients in Saudi Arabia, their responsibilities do not extend to assisting patients with their medication regimens, particularly concerning OACs.

5.9.6. Theme 6: Insight of pharmacists and pharmacy technicians in issues related to adherence to OACs

In this thematic area, the role of pharmacists and pharmacy technicians was explored. Several topics were discussed, including training programmes designed to improve pharmacists' and pharmacy technicians' abilities to counsel patients and promote adherence to medication regimens. Additionally, the role of pharmacists and pharmacy technicians in monitoring of warfarin users and the provision of support to patients with polypharmacy concerns were also

discussed. The use of validated scales as a routine practice in pharmacies, as well as the availability of pharmaceutical services for OACs users in community pharmacies and the sales of OTC products for OACs users, were also explored.

5.9.6.1. Accreditation of pharmacists and pharmacy technicians for conducting advanced pharmaceutical services

Professional development of pharmacists was discussed with pharmacists and pharmacy technicians. Interviewees were asked if they receive approved training on review of medication and counselling of patients. Interviewees highlighted that currently formally accredited programmes for reviewing of medications and for medicines reconciliations are not available.

> *"We do not have accreditation system for pharmacists and pharmacy technicians".* (Pharm. 2)

> *" The continuous education centre organises training courses and workshops for doctors and nurses and pharmacy staff about medications problems".* (pharm. 1)

The interviewees were asked if they receive specialised training to evaluate medication adherence. They stated that such training is not included in their professional development program.

> *"No special training to assess adherence is provided, but I look up materials from the internet".* (Pharm 2)

5.9.6.2. Perceptions of pharmacists and pharmacy technicians in monitoring warfarin users

During the interviews, pharmacists and pharmacy technicians were asked about their role in monitoring patients taking warfarin and optimising INR. They were also asked if hospital pharmacists are involved in coagulation clinics. The respondents confirmed that in almost all

hospitals, INR is only checked by physicians and that pharmacists and pharmacy technicians do not have a role in this aspect of patient care.

> *"INR is only checked by physicians; pharmacists are not trained to do that".* (Pharm 2)

> *"Pharmacists can check INR; but they are not allowed, physicians do it".* (Pharm 3)

Some of the interviewees noted that certain hospitals have begun to provide training to pharmacists on checking INR levels. However, they mentioned that this practice is currently limited and may be subject to expansion in the future.

> *"I am aware of some pharmacists who are checking INR in other hospitals; it is a new trial".* (Pharm.1).

> *"Some of my colleague pharmacists in other hospitals have started checking INR, it is spreading slowly".* (Pharm. 3)

5.9.6.3. Input of pharmacists and pharmacy technicians in supporting polypharmacy patients

The pharmacists and pharmacy technicians who were interviewed were asked about the availability of Monitored Dose Systems (MDS) for patients with polypharmacy. According to the interviewees, MDS trays are not widely available in Saudi Arabia, and both hospital and community pharmacists are unable to prepare them for patients to use.

> *" MDS are not available, we only dispense OACs and up to patients to use compliance aids".* (pharm. 1).

> *"We dispense OACs, but we do not prepare MDS".* (Pharm. Tech. 1).

> *"It is personal choice to use compliance aids, we supply OACs to patients".* (Pharm tech. 2)

5.9.6.4. Use of validated scales in routine pharmacy practice

During the interviews, hospital pharmacists and pharmacy technicians were asked about the use of validated scales to assess adherence, knowledge, and awareness among OAC users. They indicated that they do not use these tools in their routine practice. Instead, they reported having conversations with patients about OACs and encouraging them to adhere to their medication.

> *"We do not do formally assess adherence; it is evaluated through questioning patients about the problems that facing them with the medications".* (Pharm. 1).

> *" If needed we check how patients use OACs, but we do not use tools to assess adherence".* (Pharm 2)

The pharmacists and pharmacy technicians who were interviewed reported that they refer patients to their doctors if there is a need to change their medication-taking behavior. They explained that all interventions related to medications are performed by physicians.

> *"I send patients to doctor to perform interventions, when they discuss it with the doctor they listen to their advice".* (Pharm. 3)

> *"For the safety of patients, I send them to doctors because they may have another opinion".* (Pharm. Tech. 2)

> *"It is better to see the doctor, it is much safer".* (Pharm. Tech. 1)

5.9.6.5. Barriers to patients' education by pharmacists and pharmacy technicians

The interviewed pharmacists and pharmacy technicians were asked about obstacles that may hinder their attempts to enhance patients' education regarding OACs. The interviewees identified patients' beliefs about the qualifications of pharmacists and time limitations as the primary factors.

> *"Many patients think pharmacists can only dispense medications; they do not know they can advise about OACs".* (Pharm 2)

"*Patients prefer to speak to doctors about problems with tablets*". Pharm. 3

"*The general impression of patients about pharmacists they supply tablets, they think physicians who should they speak to*". (Pharm. 1)

"*Sometime pressure of work is high; we struggle to find enough time to spend with patients*". (Pharm. Tech. 1)

"*When the pharmacy is short staffed, the load of the work increases, we have to do a lot of things in short time*". (Pharm. Tech. 2).

5.9.6.6. Availability of pharmaceutical services for OACs users in community pharmacies

When discussing the communication between hospital and community pharmacists regarding monitoring patients on warfarin and exchanging information about patients' coagulation status, interviewees mentioned that community pharmacies do not play a role in monitoring warfarin. They explained that community pharmacists are not involved in this aspect of patient care.

"*At the moment, warfarin is a hospital medication; community pharmacists are not involved in management of its users*". (Pharm 3)

"*Patients who are taking warfarin are treated by hospitals, they go there for issues related with their warfarin*". (pharm. 1)

Pharmacists and pharmacy technicians were asked about the support provided to OACs users in adhering to their OACs in the community if patients do not have access to a hospital pharmacy. The respondents indicated that community pharmacists can provide guidance to patients on dosing instructions and advise them on possible side effects. Additionally, community pharmacists can answer patients' questions when needed.

"*If patients asked pharmacists about DOACs they will answer their queries, they use their skills as pharmacists*". (pharm. 1).

"In the end they are pharmacists; they know how to advise patients about DOACs despite it is not available in community pharmacies". (Pharm. 3)

5.9.6.7. Sales of OTC medicines to OACs users in community pharmacies

In the study, the topic of purchasing OTC medications by patients using OACs was discussed with pharmacists and pharmacy technicians. The interviewees explained that community pharmacies do not have access to patients' medical records and do not maintain records of the dispensed items

Community pharmacies do not have access to medical records of patients". (pharm. 1).

"Community pharmacies do not keep records for dispensed medications". (Pharm. 3).

They also added that warfarin users do not carry booklets nor warning cards that identify them as warfarin users and inform about the anticoagulation status of the patients. Nevertheless, patients are encouraged to inform community pharmacists that they are taking warfarin before buying OTC.

"We advise warfarin users to tell community pharmacists about their warfarin". (Pharm.3)

In addition, interviewed pharmacists and pharmacy technicians raised their concerns about buying OTC on behalf of OACs users, and in cases of language barriers between patients and pharmacists in the community.

" community pharmacists sell OTC to all patients, if the patient informs them about OAC then they will check if the requested item is suitable to be sold". (Pharm.2)

"When selling OTC to OACs users without checking interactions, this may increase the risk of adverse events". (pharm. 1).

"Sometimes there might be a language barrier between patients and pharmacists, if OACs users carry a warning card or a booklet this will help to overcome such problem". (Pharm. tech 1)

5.10. Similarities and disparities among interviewed HCPs

Different points of views were expressed by the interviewed HCPs during conversations. There were inter and intra professionals' variations among the interviewees. Interviewed physicians highlighted variable views on the level of adherence to OACs among patients. Some physicians underlined high levels of adherence to OACs among patients while others expressed that significant numbers of patients are non-adherent to OACs.

"Most of my patients are adherent to OACs in my experience"(Phys. 8)

Some HCPs raised concerns about adherence of some patients who are taking warfarin.

"There are some of my warfarin patients who are not adherent, but they are few." (phys.3)

"some of *my warfarin patients are not adherent as they should be their INR is never within the range ".* (Phys. 2)

Physicians agreed that prescribing of OACs including warfarin and DOACs is well established in Saudi Arabia. They confirmed the importance of prescribing the right OAC for patients' conditions and circumstances.

"prescribing of warfarin is well established, launching of DOACs has increased treatment options for patients". (Phys. 7)

"I have to confirm prescribing of warfarin or DOACs outweigh the benefit, each group of drugs has its pros and cons". (Phys. 6)

However, only one physician expressed that other factors such as economic status of patients may be involved in the decision to prescribe OACs.

> *"Cost of OACs by itself is not a barrier in Saudi Arabia, it is provided free of charge to the patients, I consider other factors like ease of access to service, socio-economic situation before prescribing".* (Phys.4)

Interviewed physicians also agreed that warfarin has more barriers to prescribe compared to DOACs. They expressed many risk factors such as risk of bleeding, and risk of food and drug interactions are correlated with prescribing warfarin.

> *"Use of warfarin carry some risk of bleeding, I try to reduce this risk by counselling my patients about this point".* (Phys. 2)
>
> *"I tell my patients about the interaction between green vegetables and warfarin and about over the counter medications".*

Interviewed physicians agreed about use of INR as a predictor of adherence to warfarin, some physicians expressed that they use INR as a sole indicator for adherence of warfarin users.

> *"If the INR is within the range; most likely the patient is adherent"*(Phys. 1)

Some physicians showed a different point of view as they added other factors such as regular follow up in the coagulation clinic can be taken collectively as indicator for adherence.

> *"I tell my patients to come regularly to check their INR".* (Phys. 7)
>
> *"I explain to my patients they must come for INR check because it tells how they are doing with their warfarin".* (Phys. 5)

Pharmacists and pharmacy technicians expressed views which were focused on pharmaceutical aspects of the adherence to OACs such as dispensing of OACS, and counselling of patients. Interviewed pharmacists and pharmacy technicians agreed on the importance of counselling patients about their OACs, they added that such intervention leads to improvement of adherence. However, they disagreed about how often they check adherence of OACs' patients.

"*counselling is important for successful treatment*". (Pharm. 2)

"*patients receive detailed information about how to use OACs*". (Pharm. 1)

"there *are different protocols for counselling patients on DOACs and warfarin; but it doesn't determine frequency of counselling*". (Pharm 3)

Pharmacists and pharmacy technicians confirmed they were second line when it comes to identifying non-adherent patients as physicians are the first contact.

"*Doctors are the first contact point; they send patients to us if there is a problem with adherence*"(Pharm. 1)

Hospital pharmacists confirmed that the majority of hospital pharmacists are not involved in INR checks for warfarin patients.

"*INR is only checked by physicians; pharmacists are not trained to do that*". (Pharm. 2)

"*Pharmacists are not trained to check INR; but they are not allowed, physicians do it*" (Pharm. 3)

Interviewed pharmacists and pharmacy technicians also expressed variable views on the impact of socio-economic status on adherence to OACs.

"*Low socio-economic background and un-educated patients are less concerned about their adherence*". (Pharm. 2)

"*socio-economic status of the patients has no relation to adherence*". (Pharm. 3)

There was consensus among all interviewed HCPs about importance of adherence to OACs, with widespread agreement on the significant impact of patients' education on adherence to OACs.

In contrast, pharmacists and physicians expressed different opinions about predictors of adherence to OACs. While physicians highlighted INR as a predictor for adherence to warfarin,

pharmacists indicated additional measures such as patients' behaviour when taking tablets, beliefs about medications, and perception of patients about the condition.

Also, switching patients between DOACs, due to issues with the supply of these DOACs, was not considered as a barrier to adherence by physicians. In contrast, pharmacists expressed that this might cause a degree of confusion to some patients, consequently they may take these drugs incorrectly, with resultant non-adherence to DOACs.

5.11. Incorporation of outcomes of HCPs interviews and findings of cross-sectional study

This research used explanatory mixed methods approach to achieve its objectives. Integrating findings from the quantitative and qualitative data provided a comprehensive understanding of factors affecting adherence to OACs. This included the following aspects:

5.11.1. Overall Adherence

Quantitative data showed that the overall adherence rate is 29.8%, with higher adherence for warfarin (34%) compared to DOACs (22%). Participants in the qualitative study reported that adherence to OACs improves when patients perceive the seriousness of their condition, suggesting that patient education and awareness about their conditions can play a crucial role in improving adherence to these medications.

5.11.2. Patient Profiles

Quantitatively, 47.8% of patients were prescribed warfarin, and 46.2% were diagnosed with AF. Interviewed HCPs stated that the prescribing of warfarin is well established in the study area but adding DOACs to their local formulary have increased options for patients. This indicates that the type of prescribed medication can influence adherence.

5.11.3. Effect of age and education on adherence to OACs

The quantitative results of this study illustrated that age and level of education have a significant association with adherence to OACs in the study area, with lower adherence among older and less educated patients. This aligns with findings of the HCPs interviews which suggested that adherence to OACs improves with increased patient perception of the seriousness of their condition, which could be linked to education levels.

5.11.4. Duration of OAC Use

The obtained data from quantitative study showed that longer duration of OAC use is associated with better adherence to OACs, indicating that adherence tends to improve over time. Qualitatively, hospitalised patients tend to be more adherent due to higher support levels, which might also indicate a longer duration of treatment.

5.11.5. Correlation between sex, comorbidities, and adherence to OACs

Results from the cross-sectional study showed that sex and the number of comorbidities do not significantly impact adherence to OACs in the study area. Interviewed HCPs believe that adherence is more prevalent among DOACs' users compared to warfarin users, suggesting that factors like patient education and support may be more critical than demographic factors.

5.11.6. Awareness about reasons for prescribing OACs

The obtained data from patients who participated in the cross-sectional study showed that most patients were aware of the reasons for prescribing OACs. However, interviewed HCPs reported a significant portion of patients is not aware of their INR target, which is essential for warfarin therapy. This highlights the need for better patient education.

5.11.7. Reasons for Missing Doses

Patients who participated in the quantitative study stated reasons for missing doses of OACs include forgetfulness, side effects, and food/drug interactions. Interviewed HCPs specified factors contributing to non-adherence to OACs as insufficient knowledge, side effects, and

forgetfulness. This reinforces the importance of patient s' education and support in addressing these issues.

In summary, the incorporation of quantitative and qualitative data underscores the complex nature of adherence to OACs in the study area. It highlights the importance of patients' education, healthcare provider involvement, selection of appropriate OAC and the need for better coordination between healthcare sectors to improve adherence rates among OAC users.

5.12. Discussion

This study represents a significant advancement in our understanding of adherence to OACs specifically in the context of Eastern Saudi Arabia. It investigated various critical aspects of OACs' management, including prescribing practices, patient adherence, and the mechanisms available for promoting adherence, yielding novel insights into this crucial clinical challenge. Despite the potential of pharmacists in the region to deliver top-tier pharmaceutical services, the research findings have revealed a significant limitation concerning their role in enhancing OAC adherence. This limitation arises from the absence of organised training programs designed to equip pharmacists with the necessary skills to provide advanced pharmaceutical services, like conducting comprehensive medicines use reviews. Furthermore, the study's outcomes indicated that pharmacists in eastern Saudi Arabia are not currently involved in managing warfarin clinics, a common practice in other countries within the region. Such practices have gained a positive reputation due to their substantial positive impact on improving patients' experiences with OACs (Elewa et al., 2018). This study highlights the unexploited potential of pharmacists in the region, whose roles have predominantly been limited to dispensing medications. Therefore, it underscores the missed opportunities for influencing their expertise and skills to enhance adherence to OACs, thus indicating room for improvement. The study suggests that by expanding the scope of pharmacists' responsibilities beyond mere dispensing and providing them with advanced training, their capabilities can be fully utilized to improve patient outcomes in the context of OAC adherence.

While interviewed HCPs in Eastern Saudi Arabia recognised the significance of patients' counselling and on the use of OACs, there were genuine concerns about the effectiveness of these efforts in boosting adherence rates in the study area. These doubts result from the limited availability of such services, primarily offered by physicians, which restricts access for OACs' users. Similar research conducted in the Middle East stressed the potential for substantial improvements in adherence to OACs through counselling and the expansion of patient education (Alajami et al., 2021). Furthermore, HCPs indicated that they do not routinely incorporate using scales to measure adherence to OACs into their clinical procedures. This research questions the conventional approach of not incorporating adherence measurement tools and underscores the necessity for their structured inclusion in clinical care. The utilisation of such scales has demonstrated effectiveness in identifying the causes of non-adherence and follow up of persistence of adherence to OACs (Basu et al., 2019).

Moreover, communication tools like the warfarin yellow books, designed to facilitate communication between OACs' users and HCPs across different sectors, are not being used in the study area. This lack of communication tools can negatively impact the OACs' users care provided by HCPs, including community pharmacists and dentists. Consequently, the processes involving patient education about OACs and communication between patients and the various groups of HCPs responsible for their care are minimised. This outcome can partially contribute to explaining of the results of low adherence rates to OACs in the study area. When combined with other findings from the cross-sectional study, such as the low level of education among participants and the high prevalence of polypharmacy, addressing issues like training pharmacists and improving communication between different sectors of HCPs can significantly enhance adherence to OACs.

Participants of this study reported distinct disparities in adherence levels among hospitalised and community patients' surface, hinting at the influence of the care environment on patient compliance. This discovery underscores the potential benefits of support for patients to take medications as prescribed. Moreover, the findings of this study revealed that community support for

OACs' users is undermined by limited availability of devices such as multiple compartments and lack of multi dose units (MDS) in addition to lack of trained care workers who can support patients with taking medications. Studies have shown that use of MDS can improve adherence to medications particularly in complex regimens (Polnsky and Henry, 2016).

Moreover, the research highlighted the necessity for additional investigations aimed at uncovering non-adherence issues in the study area, such as determining the precise prevalence of non-adherence, understanding the factors that contribute to non-adherence, and classifying the various types of non-adherence. Identifying these issues related to non-adherence to OACs in the region will enable the development and implementation of targeted interventions to address this problem (Farinha, Jones, Lip, 2022). Moreover, the study reinforces the issue of non-adherence to OACs in Eastern Saudi Arabia, a concern compounded by the lack of comprehensive data on its extent and underlying factors in the region. The findings of this study highlighted reasons for non-adherence such as forgetfulness, inadequate condition awareness, and polypharmacy, reaffirming the obtained results from our cross-sectional study, in which, patients highlighted forgetfulness as a reason for non-adherence. The HCPs' called for further research underscores the urgency of better understanding the details of non-adherence to OACs to develop effective strategies for improving patient outcomes.

Because of these findings, the processes involving patients' education about OACs and communication between patients and the various groups of HCPs responsible for their care are minimised.

In conclusion, the findings highlighted by interviewed HCPs in this study can contribute to explaining the low adherence rates to OACs in the study area. Furthermore, these outcomes when combined with the results from the cross-sectional study, such as the low level of education among participants and the high prevalence of polypharmacy, emphasise the pressing need for addressing issues like training pharmacists and improving communication between patients and different sectors of HCPs to enhance the prevalence of adherence to OACs, as well as using adherence scales in routine practice.

CHAPTER SIX

OVERALL DISCUSSION

This DPharm thesis investigated the use of OACs in Eastern Saudi Arabia, by examine three main areas: the adherence of patients to taking OACs in Eastern Saudi Arabia, the experience of patients with taking OACs medications in the area, and HCPs' views on patients' adherence to OACs, barriers to adherence to these drugs, and supporting patients with taking OACs .

This thesis conducted a comprehensive review of existing literature to investigate the adherence to OACs in patients with AF in the Middle East. The results showed that the level of adherence to OACs in the region was low. The review also found that there is a connection between patient-related factors, such as their knowledge and education, and their adherence to OACs. However, the outcomes related to patient factors were inconsistent across the region. Additionally, there is limited research on how the health systems and patient-physician relationships can impact adherence to OACs. The findings of the selected studies were influenced using small cross-sectional studies and self-reporting tools, which provided an incomplete understanding of the non-clinical factors related to adherence to OACs in the region.

The second study in this thesis was cross-sectional research conducted in Eastern Saudi Arabia, which aimed to measure the adherence of patients taking OACs using the Hill-Bone self-reported scale, a validated tool for measuring medication adherence. The study collected data on patient demographics, such as age, gender, education, and comorbidities, as well as the reasons for prescribing OACs and the conditions under which the medication was prescribed. The results revealed that the adherence to OACs was low in the research area, with only 29.8% of the participants being adherent to their medication. Additionally, the study found that warfarin was more commonly prescribed than DOACs in the area, and OACs were indicated for various medical conditions, including valve disease, atrial fibrillation, deep vein thrombosis, pulmonary embolism, and stroke. The study also identified several factors, including age, sex, duration of OAC use, missed doses, reported reasons for non-adherence,

and knowledge about the INR target, as predictors for adherence to OACs in the area. The study's findings shed light on the low adherence levels in the region and suggest that there is a need for further research to identify and address the barriers to medication adherence in this population.

The third study used qualitative methods and interviews with HCPs to provide their detailed views and experience on prescribing and adherence to OACs in Eastern Saudi Arabia. The study also identified areas for improving patients' adherence, investigated the role of pharmacists in supporting patients' adherence to OACs, and evaluated the contribution of social care to support patients' adherence to OACs. According to the findings of this study, patients requiring OACs have a wide range of options available represented by VKA and DOACs. The interviewed HCPs highlighted the importance of selecting the most suitable OAC based on patient-specific factors, such as age and other co-morbidities. HCPs also underlined the need for counselling to ensure maximum adherence, which is crucial for successful treatment outcomes. The study also revealed that non-adherence to OACs is a prevalent issue in Eastern Saudi Arabia, and several factors contribute to it, including forgetfulness, poor knowledge about conditions, and polypharmacy. The participating HCPs suggested that more research is needed to determine the specific factors that contribute to non-adherence to OACs and to develop effective strategies to improve adherence. Improving the education and training of pharmacists in Eastern Saudi Arabia and introducing advanced pharmaceutical services could positively impact patient care by increasing their knowledge and confidence in their practice and improving overall care processes.

6.1. Systematic review of data on adherence to OACs in the Middle East

The systematic review revealed a low level of adherence to OACs in the Middle East and identified factors associated with taking OACs as prescribed. Adherence to OACs is variable between the countries of the region and remains in the low side. The research showed that

direct methods of assessing drug adherence have not been used to measure adherence to OACs in the Middle East. Instead, self-report methods for assessing adherence to OACs in the region are the primary means of assessing patients' adherence to OACs from the studies investigated.

6.1.1. Systematic review of data on patients' related factors affecting adherence to OACs' in the Middle East

Published data from the Middle East also showed mixed results on factors influencing adherence to OACs. Several patients' related factors were identified. A factor can influence adherence in one part, but the same factor could have no effect on adherence to OACs in another country in the region. For example, knowledge of OACs, was associated with adherence to warfarin in parts of the western Saudi Arabia (Elbur et al., 2015), but it was not a predisposing factor in patients taking warfarin in other countries of the region such as Sudan (Eltayeb et al., 2017). The results of our systematic review of patients' related factors in the Middle East highlighted that there is no consensus on adherence to OACs in the Middle East or on patients' related factors that can affect adherence to these drugs. This may be due to large regional differences in patients' attitudes towards medications and the level of health services provided in each country.

Overall, adherence to OACs in the Middle East is at a low level, but the reasons for this low level varied from country to country in the region. Furthermore, the differences in the association of adherence to OACs with patients' related factors and the variations reported across studies reflects disparities in the Middle East's healthcare systems. It is important to consider the differences in the socioeconomic status of populations living in the countries of the region and the cultural differences that are reflected in the attitudes of people in the region towards medication adherence, especially when using OACs.

Research has shown that low adherence to OACs is a widespread problem worldwide. It is not limited to developing countries but is also found in developed countries and in the Western

world. Salmasi et al., (2020) systematically reviewed data about adherence to OACs in Western countries, such as the United States, United Kingdom, Sweden, and Spain. The authors reported that approximately 30% of AF patients taking OAC were not adherent to these drugs. In addition, the author documented why participants in these countries adhered to OACs. These included patient-related factors such as old age, disease related factors such as a history of increased risk of stroke, and chronic conditions (eg, hypertension, diabetes, or stroke), drug related factors such as cardiovascular drug use, experience as an experienced OACs' user, complexity of daily dosing regimen (Salmasi et al., 2020).

Other researchers have reported similar results regarding adherence to OACs. For example, Castellucci et al., (2015) reported that 43% of DOAC users and 44% of warfarin users showed poor adherence to OACs' therapy. Similarly, Davis et al., 2005 found that 50% of patients taking OAC had inadequate adherence to the regimen. The results of this study are consistent with those of previous studies.

In the Middle East, there are various studies identifying the association between OACs' adherence and contributor factors, and some studies have reported a positive association between OACs adherence and patient related factors such as medication knowledge (Ababneh et. al., 2016; Mayet, 2015). One study documented that patient knowledge of OAC was negatively associated with taking warfarin as directed (Eltayeb et al., 2017). From the systematic review in this thesis the overall reasons for adherence and non-adherence reported were similar in developed and developing countries.

6.2. Assessment of adherence to OACs in Eastern Saudi Arabia

In this thesis, the results obtained from assessing adherence to OACs in Eastern Saudi Arabia showed a low adherence level to these medications (29.8%). These results are consistent with the findings of our systematic review of adherence to OACs in the Middle East. Furthermore,

our adherence rates of OACs agree with results from other parts of Saudi Arabia. For example results of Al-Omair et al., (2015) in Central Saudi Arabia reported that only 20.4 % of participants had high adherence, while 53.1% showed medium adherence, and 26.6% had low adherence. Moreover, Mayet et al., (2015) reported 53.6% of the participants in their study in Riyadh area had low adherence rate. Both studies used Morisky Medication Adherence Scale (MMAS-8) for measuring adherence. Eastern Saudi Arabia is no exception to other parts of the country where adherence to OACs is documented to be as low as our findings reported 29.8% overall adherence to OACs in Eastern Saudi Arabia.

6.3. Study of patients' related factors and their impact on adherence to OACs in Eastern Saudi Arabia

6.3.1. Impact of age on adherence to OACs in Eastern Saudi Arabia

The results of this research showed less adherence to OACs among older participants in Eastern Saudi Arabia. The result is consistent with Emren et al, (2018) who found a similar result in Turkey. The authors justified their findings by effect of advance age in reducing cognitive abilities to remember taking medications, and impact of polypharmacy.

In contrast, our results do not match Obamiro et al. (2018) findings in Australia who evaluated the proportion of OACs' users with inadequate adherence to these medications using the Morisky Medication Adherence Scale (MMAS-8), only 54.9% of participants of their study reported excellent adherence to OACs. In addition, the author documented that participants over the age of 65 were more likely to show higher adherence to OACs compared to younger participants. The authors explained this finding by the higher level of knowledge about OACs among patients > 65. Furthermore, Jin et al., 2008 in Singapore in their qualitative review about factors influence adherence to OACs documented that (better) adherence to OACs among elderly population could be attributed to presence of multiple comorbidities, thereby making older patients more concerned about their health, leading to better medication taking behaviour.

6.3.2. Adherence to OACs, general literacy, and health literacy in Eastern Saudi Arabia

Health literacy is defined as "the capacity to acquire, interpret and understand basic health information" (Simmonds, 1974). In this study, the general literacy level of participating patients was low, as about 63% of female participants were uneducated or elementary school educated. Similarly, about 25% of male participants had illiteracy or primary school education. Studies showed that people with low levels of general literacy have low levels of health literacy, poor preventive care, poor management of chronic illness, and are more likely to be hospitalised more than once than patients with high literacy rates (DeWalt et al., 2004). In addition, patients with low health literacy have been reported to have less confidence in access to health resources and tend to gain confidence in benefiting from the health system (DeWalt et al., 2004).

Fang et al., (2006) reported that low health literacy is a barrier to knowledge about adherence to warfarin. However, the authors highlighted that there was no significant association between adherence to warfarin and low health literacy among their study participants.

In Saudi Arabia, Almubarak et al., (2019) reported that about half of Saudi Arabia's population has low health literacy. In addition, the authors state that poor education is one of the risk factors for poor health literacy in Saudi Arabia. In addition, the results of our study show that literacy levels are positively correlated with adherence to OACs in Eastern Saudi Arabia.

These findings underscore the need for further research to assess the relationship between health literacy, patients' behaviour, and adherence to OACs in Eastern Saudi Arabia.

6.4. Adherence to OACs and indications for prescribing these medications

OACs are used for multiple conditions such as AF and VTE. Indications for taking OACs in Eastern Saudi Arabia included chronic diseases such as valvular heart disease, atrial fibrillation, and stroke. Studies on adherence to medications in chronic conditions have shown

that patients who are aware of the chronicity of their condition are expected to be more adherent. In their study, Chen et al., (2011) investigated the relationship between illness perception and adherence to medication and self-management recommendations among hypertensive patients in Taiwan. The study aimed to test a theoretical model based on the Common-Sense Model, which proposes that patient beliefs and perceptions about their illness affect their health behaviours. The results confirmed the proposed model, indicating that patients' illness perceptions were positively associated with medication adherence and self-management behaviours. The study highlights the significance of illness perceptions in promoting adherence and suggests that enhancing patients' illness perceptions could lead to improved health behaviours. In Eastern Saudi Arabia, our results showed that patients who were taking warfarin for valvular heart disease showed more adherence to the drug than patients who were taking DOACs for VTE and AF. Our results follow the suggested model by Chen et al., (2011) as there was a significant association between the indications for using OACs and adherence to these drugs. However, it was not clear if this higher adherence can be attributed to knowledge about warfarin or awareness about the condition.

6.5. Reasons for non-adherence to OACs in Eastern Saudi Arabia

The perception of illness and beliefs about therapy are widely considered as determinants of adherence to medications (Kucukarslan, 2012). Kennedy et al., (2017) reported that understanding of patients' beliefs concerning their therapy can be useful in resolving suboptimal adherence because health beliefs that are based on incomplete or inaccurate information can have a negative consequence on patients' attitudes towards adherence to medications.

The participants in our study were asked if they believe that reasons for non-adherence to OACs such as side effects can be a barrier to their adherence OACs, the majority of the participating patients in our study reported that they would keep taking OACs despite these barriers. This

outcome suggests that intentional non-adherence may be a less likely contributing factor in the low adherence to OACs that was reported in Eastern Saudi Arabia among the study population.

Our study could not ascertain the confounding factors to low adherence to OACs in Eastern Saudi Arabia. It could be due to unintentional influences or intentional reasons. In addition, further research is needed to examine the patient's views on taking OACs, as it helps to tailor the necessary interventions to the patient's needs (Peltzer, 2004; Kennedy et al., 2017).

6.6. Increasing adherence to DOACs in Eastern Saudi Arabia is a necessity

Despite the higher adherence to VKA in our study compared to DOACs (34% and 22%, respectively), this finding should reinforce the need to improve adherence to OACs, especially DOACs. Non-adherence to OAC therapy can have adverse effects on Patients' health outcomes. Furthermore, some of the potential consequences of poor adherence to OACs include an increased risk of stroke and bleeding, poor disease management, higher healthcare costs, and reduced quality of life (Jortveit, et al., 2019). Moreover, patients who do not follow their OAC prescription may experience symptoms, complications, and more frequent healthcare application (Shore et al., 2014). It is crucial HCPs to collaborate with patients to ensure they comprehend the importance of adherence to OAC therapy and provide them with support to follow their prescribed treatment plan (Manzoor et al., 2020). Additionally, a recent study by Ho et al. (2020) who reviewed local policies for prescribing of OACs in English primary care reported that adherence to DOACs is increasing while recommendations for VKA is decreasing. This suggests that DOACs are becoming the preferred choice of OACs, and as their use becomes more established and adhered to, the incidence of treatment failure due to non-adherence is expected to decrease. In summary, the study highlights the increasing popularity of DOACs and their potential to improve adherence and treatment outcomes.

6.7.Outcomes of interviews with HCPs in Eastern Saudi Arabia

A semi-structured approach was used to collect qualitative data for this thesis. In addition, we used a thematic analysis approach to analyse the collected data. The interviewed HCPs confirmed the importance of adhering to OACs for successful treatment. This finding of our study agrees with the results of Yao et al., (2016) who, in their retrospective cohort analysis, stressed the importance of adherence to warfarin particularly among patients with CHA2DS2-VASc score ≥2, whereas the benefits of anticoagulation may not outweigh the harms in patients with CHA2DS2-VASc score 0 or 1.moreover Yang et al., (2022) reported that adherent use of DOACs could be associated with the lower risk of ischemic stroke and MI, when compared with non-adherent use.

The result of our exploratory study also highlighted the low adherence to OACs in Eastern Saudi Arabia, which agree with the findings of our quantitative study as 29.8% adherence rate to OACs was documented.

To improve adherence to OAC therapy, various measures can be taken in Eastern Saudi Arabia. These measures can include simplifying the medication regimen to enhance the treatment plan's feasibility for patients. Additionally, technology-based interventions such as reminders, mobile applications, and telemedicine can be employed to improve medication adherence (Wiecek et al., 2020). Furthermore, improving patient education about the importance of adhering to OAC therapy can help increase adherence rates (Matalqah et al., 2013). In addition, encouraging patients to be active participants in their treatment plan, including involving them in decision-making and goal setting, can help improve adherence (Mackey et al., 2012).

Moreover, addressing patient concerns and side effects associated with OAC therapy can help patients better understand the benefits of adhering to their treatment plan (Feldman et al., 2017). Collaboration between healthcare providers can also improve adherence to OAC therapy,

including regular communication between primary care physicians and specialists. By implementing these measures, healthcare providers can enhance adherence to OAC therapy, leading to better health outcomes for users of OACs (Lowres et al., 2015).

6.7.1. Strengthening the role of hospital pharmacists in Eastern Saudi Arabia

The results of the interviews with HCP showed that the role of pharmacists in Eastern Saudi Arabia was primarily limited to the dispensing of OACs. It also became clear that there are currently no regular reviews or assessments of medication adherence by pharmacists. In addition, the pharmacists surveyed identified low patient awareness of the pharmacist's ability to provide intervention and time constraints as a major barrier to efforts to increase patient knowledge of OACs and improve adherence to OACs.

The study conducted by Al-Jedai et al. (2016) aimed to provide an overview of the pharmacy practice in Saudi Arabia. The study revealed that a significant number of community pharmacists in Saudi Arabia were not Saudi nationals, and their degrees were mainly from other countries in the Middle East and the Far East. The majority of these pharmacists had BPharm degrees and had not received much practice-based learning during their training. This raised concerns about the equivalence of their education to the local pharmacy curricula.

One notable finding was that Saudi pharmacists tended to avoid working in community settings due to relatively lower pay and job satisfaction. Additionally, community pharmacies in Saudi Arabia did not maintain patient records, and there was a lack of electronic documentation, making it challenging to relay information back to primary care providers.

On the other hand, hospital staff pharmacists in Saudi Arabia had more defined roles, which included medication verification and dispensing, management of medication storage and supplies, provision of drug information to other healthcare providers, and training of residents and students. Some hospital pharmacists also worked in particular areas, such as preparing

sterile medications, chemotherapy, and parenteral nutrition. Another significant responsibility of pharmacists in Saudi Arabia was the identification and reporting of adverse drug events or pharmacovigilance. Overall, the study shed light on several issues affecting pharmacy practice in Saudi Arabia, including the need for more robust training programs, electronic documentation, and better pay and job satisfaction for community pharmacists. It also highlighted the critical roles that hospital pharmacists played in delivering patient care and ensuring medication safety.

In our exploratory study, we conducted interviews with pharmacists and pharmacy technicians to gather insights into the role of community pharmacies in monitoring patients taking warfarin and DOACs. The findings of our study showed that community pharmacies in general are not involved in monitoring warfarin patients. However, they can still provide valuable advice and support to both warfarin and DOAC users as needed. The interviews conducted with pharmacists and pharmacy technicians revealed that community pharmacies did not have a formal system in place for monitoring warfarin patients. Instead, most warfarin patients were typically monitored by a hospital or clinic. Despite this, pharmacists and pharmacy technicians were still able to provide advice and support to patients who had questions about their warfarin or DOAC medications. Pharmacists and pharmacy technicians were able to offer advice on the proper use of medications, potential side effects, and drug interactions. They were also able to recommend over-the-counter medications that were safe to take with warfarin or DOACs. Furthermore, pharmacists and pharmacy technicians were able to help patients manage their medication regimens by providing guidance on how to properly take their medications, and how to avoid missing doses.

Overall, our study highlighted the limited role that community pharmacies currently play in monitoring warfarin patients, but also showed that they can still provide valuable support and advice to these patients as well as those taking DOACs. This suggests the potential for

community pharmacies to expand their role in the management of anticoagulant therapy and underscores the importance of continued education and training for pharmacists and pharmacy technicians in this area.

Studies have shown that increasing adherence to warfarin through patients' education interventions by pharmacists improves adherence to the medication (Li et al., 2018). Moreover, training pharmacists to advise patients and provide information on the correct use of OACs to improve the patients' understanding of the need for OACs and reducing awareness of side effects of these medications could improve adherence (Matalqah, 2019).

Therefore, the provision of counselling and patients' education by pharmacists is expected to have a positive impact on improving adherence to OACs in Eastern Saudi Arabia. These obligations (adherence monitoring, patients' counselling, and education) are currently limited to physicians in the region.

The New Medicines Services (NMS) in the England includes following up patients immediately after initiation of the services to monitor adherence and resolve barriers to taking medications as prescribed. Published data showed that NMS increased adherence to medication in the England by 10.2–70.7%, compared with 60.5% adherence reported before introduction of the service (Elliott et al., 2016). Introducing a similar community pharmacy service in Eastern Saudi Arabia would have the potential to improve adherence to OACs and could include interventions provided by community pharmacists in Eastern Saudi Arabia to help educate patients about their medications and usage. Such service requires incentivising the community pharmacists in Saudi Arabia, which is not currently available.

6.7.2. Communications between physicians, patients, and other HCPs in Eastern Saudi Arabia

Studies have shown that communication with physicians is actively associated with medication use (Davis, 1968; Francis et al., 1969). In addition, communication is an important part of

medical care. In addition, studies have shown that patient adherence is linked with how patients communicate with their physicians, and that physicians can improve adherence if they are trained to be better communicators. (Zolnierek and DiMatteo, 2009).

Effective treatment physician-patient relationships are essential to inform patients about their medication intake and to provide support for medications adherence (Roter and Hall, 1992). In addition, communication contributes to the patient's understanding of their conditions and the benefits and risks of the recommended treatment (Osterberg and Blaschke, 2005).

In the United Kingdom, warfarin users are provided with a communication tool known as the "yellow book" to display essential information, such as INR and warfarin dosage. This booklet serves as a means of communication between the patient and healthcare providers, facilitating continuity of care. The yellow book could potentially improve communication between warfarin users and healthcare providers, including community pharmacists, dentists, and other physicians in Eastern Saudi Arabia.

The yellow book is a useful tool that allows patients to easily track and record their warfarin treatment progress. It enables patients to document their INR results, warfarin dosage, and other relevant information that can help healthcare providers monitor their condition effectively. The booklet can also be used to communicate essential information about the patient's condition to other healthcare providers, including community pharmacists, dentists, and other physicians, who may be involved in their care. The potential benefits of the yellow book in improving communication between warfarin users and healthcare providers in Eastern Saudi Arabia are significant. By facilitating communication between patients and healthcare providers, the yellow book could help to improve patient outcomes and reduce the risk of adverse events. Moreover, it could also promote patient empowerment and engagement in their healthcare, as it allows them to have a more active role in monitoring their condition.

Overall, the yellow book is a useful tool that could potentially improve communication and collaboration between warfarin users and healthcare providers, including community pharmacists, dentists, and other physicians, in Eastern Saudi Arabia. It could promote patient engagement and empowerment, improve continuity of care, and help to reduce the risk of adverse events. Further research is needed to assess the feasibility and effectiveness of implementing the yellow book in the Saudi Arabian healthcare system.

6.7.3. Social care and needs of adherence to OACs in Eastern Saudi Arabia

Interviews with HCPs in this thesis showed that current social welfare in Eastern Saudi Arabia does not include assisting patients with taking medicines. Social care is available for patients who are taking OACs; however, support with taking medications is beyond their scope of social workers' practice. Moreover, Almudidi et al, (2022) reported that the Social Determinants of Health (SDH) are not well incorporated within the provision of health care in Saudi health care systems. The authors suggested that educating HCPs about social care needs of patients will have a positive impact on supporting patients.

Social workers involved in providing healthcare services to patients to bridge the gap between patients' cultural behaviour, which may limit their ability to take medicines, and the advice of medical professionals, especially regarding taking prescribed medicines. Social workers can often spend more face-to-face time with their patients.

As a result, they can provide patients with more information and support regarding their medications intake. Published reports underline that health outcomes are associated with social support and drug use (Garay-Sevilla et al., 2011).

In addition, previous studies have shown that social support is associated with medication adherence in patients with a variety of conditions, including heart failure, HIV disease, and the first episode of psychiatric illness (Cheng et al., 2015; Maeda et al., 2013).

Adherence to OACs in Eastern Saudi Arabia can be improved through contributions of social care, such as promoting medication intake and alleviating barriers reported by patients such as polypharmacy.

6.7.4. Integration of the results from quantitative and qualitative data

The obtained data from cross-sectional study indicates a low overall adherence rate of 29.8% among OACs' users, signalling a significant issue in patients' adherence. The qualitative insights from HCPs interviews further illuminate the problem, revealing that adherence measurement scales are not routinely utilised in routine practice. This absence of regular measurement tools suggests a potential gap in the system's ability to monitor and support patients' adherence effectively. Addressing this issue could involve the implementation of standardised adherence assessment tools within clinical practice to better identify and support patients struggling with adherence, ultimately improving patient outcomes (Nguyen et al., 2016). Moreover, qualitative insights from hospital pharmacists indicate a significant lack of their involvement in key aspects of OACs care, including INR checks for warfarin patients and counselling on the users' of DOACs and warfarin. The correlation between qualitative statements and quantitative outcomes underscores the potential impact of pharmacist involvement on patient adherence. Therefore, it is necessary that hospitals consider enhancing the role of pharmacists in OACs management to improve patients' outcomes and adherence to OACs (Jones et al., 2020).

In addition, quantitative findings indicated a high level of patients' satisfaction with OACs, with 93% of patients expressing contentment with OACs as a treatment choice. Qualitative insights from interviewees substantiate these findings, highlighting that HCPs actively engage in discussions with patients about their treatment options, resulting in a high concordance between HCPs recommendations and patient preferences. This synergy between patient satisfaction and HCPs-patient communication highlights the effectiveness of shared decision-

making in treatment selection, ultimately enhancing patient outcomes and the overall quality of care in managing conditions that require OACs (Zolnierek and Dimatteo, 2009).

Furthermore, outcomes of the HCPs interviews suggest that limiting access to OACs exclusively to hospitals reduces the services available to OACs' users in community pharmacies. This limitation in access may have implications for the convenience and availability of these medications for patients outside hospital settings.

Furthermore, 29% of patients also reported side effects as barriers to adherence. These findings suggest that while patients are generally comfortable with OACs treatment, side effects can pose challenges to adherence. Therefore, it's essential to strike a balance between accessibility, patient satisfaction, and addressing side effects when designing OAC distribution and management strategies to ensure the best possible care and adherence for patients (Prakash, 2010; Cabrera-Barona et al., 2017).

6.8.Research strengths and limitations

6.8.1. Strengths

The strengths of this study include novelty in assessing adherence to OACs in the study area. This is because it is the first survey in Eastern Saudi Arabia. This study used a self-assessment method to examine adherence to OACs. The HB scale was first used to assess adherence to OACs in Eastern Saudi Arabia.

Mixed methods used in this research is a valuable strength in the study, as it enabled us to examine adherence to OACs in Eastern Saudi Arabia from varied perspectives. Mixed methods research involves the integration of both qualitative and quantitative data collection and analysis methods, allowing for a more comprehensive understanding of a phenomenon.

In our study, the use of mixed methods allowed us to gather data on adherence to OACs through both quantitative measures, such as adherence scores, and qualitative measures, such as HCPs

interviews. By incorporating both types of data, gained a deeper understanding of the reasons behind adherence behaviours and the impact of various factors on adherence.

Additionally, mixed methods research allowed us to examine adherence from multiple perspectives, including the perspectives of patients, and HCPs. This provides a more holistic view of the issue and allows for the identification of factors that may be overlooked when examining adherence from only one perspective.

Furthermore, mixed methods research is well-suited for studying complex, multifaceted phenomena, such as adherence to OACs, as it allows for the integration of both quantitative and qualitative data, which can provide a more comprehensive and nuanced understanding of the phenomenon. Overall, the use of mixed methods research in the study enabled us to examine adherence to OACs in Eastern Saudi Arabia from multiple perspectives, providing a more comprehensive understanding of the issue. This approach is a significant strength of our research, as it allows for a more complete understanding of medication adherence behaviours and the factors that influence them.

6.8.2. Limitations

Our quantitative study which measured adherence to OACs was limited by using a self-reported adherence measure (HB scale). Measuring adherence to OACs using multiple self-reporting scales or by methods other than self-reporting scales can help determine the intervention needed to improve adherence to OACs. This study was also limited by the cross-sectional nature of the study design, which can expose the study population to selection bias. In addition, to these limitations, the small sample size expected for sampling and the fact that the survey was conducted at a single centre in Eastern Saudi Arabia undermines the generalisation of results to the entire population of Saudi Arabia. However, given the resources available for this study, this approach was the best available method.

The qualitative study in this research was limited by selection bias associated with the identification and recruitment process of participants. The HCPs who participated in the study were chosen based on their willingness and ability to participate, which may limit the generalisability of the findings to the wider population. As a result, interviewees may have had biased opinions about the current role and integration of pharmacists, and there is a potential for self-reporting bias, social desirability bias, recall bias, and researcher bias in the collection, analysis, and interpretation of the qualitative data. To mitigate this, the study included participants with varied experience and working status from different geographic locations in Eastern Saudi Arabia. However, the study did not consider the perceptions of other key stakeholders, such as hospital staff. Therefore, future research may need to include a qualitative study with different clinical and non-clinical practice teams, such as practitioners and other non-medical staff, to explore these barriers further. Additionally, the use of a questionnaire distributed by the researcher could have introduced recruitment/response bias. However, the participant information sheet attached to the questionnaire reassured participants that the study aimed to assess the service provided, rather than to evaluate the practice of individual HCPs.

6.9. Recommendations for practice

The results of this thesis showed that the role of reviewing patients' dosing, monitoring adherence to OACs, and advising patients on the correct use of OACs is focused on physicians. Giving pharmacists the roles of reviewing drug use and assessing adherence to OACs can be of great benefit to OACs users. In addition, it makes it easier to identify and eliminate obstacles to the proper use of OACs.

Training non-physician members of the interdisciplinary teams of care in the hospital to assess the patients' adherence to OACs can improve the ability of non-physicians to provide advice on the correct use of OACs and other drugs as well as strengthens recommendations for the clinical practices. An interdisciplinary approach by training non-physician HCPs, especially

pharmacists, running warfarin clinics, monitoring adherence to OACs, and advising patients on drugs' usage reduces the burden on physicians and other patient care providers and could improve care for patients in the region.

Another recommendation for this thesis is to facilitate communication between different HCPs that care for patients in a variety of situations, including primary care and dental care. Communication materials such as the yellow book mentioned above benefit patients by showing their coagulation status so that patients can be given the medical care they need.

6.10. Future research

The results of this thesis identified some areas that needed further investigation. Rigorous cohort studies that assess interventions to increase adherence to OACs are of great value in increasing patients' adherence to OACs in Eastern Saudi Arabia. Identifying the root cause of non-adherence to OACs facilitates the design of patient-centred interventions to improve adherence to OACs. Such cohort studies to measure adherence to OACs using methods other than self-assessment, or multiple self-assessment methods, are of great value.

In addition, assessing the impact of pharmacist-operated warfarin clinics on improving care provided to OACs' users will increase pharmacist contributions to providing medical services to patients. Studies conducted in Saudi Arabia and Qatar, a neighbouring country of Saudi Arabia, evaluated the impact on adherence to VKA when pharmacists run clinics. The authors of these publications reported that such clinics are medical equivalent to clinics run by physicians (Dib et al., 2014; Elewa et al., 2018).

Our results show that adherence to OACs is higher among the younger age populations. We also showed that younger patients have more general literacy skills compared to older participants. Some researchers reported that adherence to OACs was increased in older patients (> 65 years) than in younger patients (Obamiro et al., 2018). It is not clear whether patient age

and literacy rates contribute to adherence to OACs in Eastern Saudi Arabia Eastern Saudi Arabia as the results showed increased adherence to OACs among patients under the age of 65 years. Further research is needed to highlight the reasons for the low rates of adherence to OACs among the population aged 65 and over in Eastern Saudi Arabia.

This thesis investigated adherence to OACs in Eastern Saudi Arabia. Indications for prescribing OACs to participants included mechanical valvular disease, atrial fibrillation, and VTE. Currently, DOACs are licensed only for AF and VTE (NICE NG196, 2021; NICE NG158, 2020). Moreover, VKA anticoagulant warfarin remains the only option for patients with mechanical valvular disease. Our results show that we have reported a higher adherence to warfarin than DOACs. Investigation of the underlying reasons and assessment of patient-related factors such as knowledge of the disease and patient perception of treatment are needed to explain these differences in adherence.

DOACs have been approved for patients with atrial fibrillation who need to take it for life-long for stroke prevention (NICE NG196, 2021). It is also approved for the treatment and for prevention of recurrence in VTE patients. The recommended duration of use is 3 months; it can be extended based on the patients' post-evaluation medical decision (NICE NG158, 2020). By assessing adherence to DOACs based on the conditions under which DOAC is prescribed, it is possible to identify factors that affects long and short terms adherence to OACs. It can also clarify the variations in medication taking behaviour and patients' attitudes towards long and short terms prescribed OACs and assess whether treatment duration affects adherence to OACs in Eastern Saudi Arabia (temporary vs permanent use).

Future studies may also include assessing the impact of services that pharmacists provide to patients with cardiovascular disease using a combination of quantitative and qualitative data collection techniques such as questionnaires followed by patients' focus groups. Such methods helps to explore the patient's perspective and experience in relation to the patient-facing role

offered by other HCPs. These focus groups can include both long-term medical condition counselling and discussions about reasons for dosing non-adherence.

The results of this thesis, which monitored adherence to OACs in Eastern Saudi Arabia, show that patients using OACs are also taking medications for other cardiovascular diseases such as hypertension. The patients' polypharmacy contributes to classify the patients' adherence status. Further studies on adherence with other chronic disease treatments (eg, anti-diabetes and antihypertensive drugs) may identify the effect of polypharmacy on adherence to OACs in Eastern Saudi Arabia. It also helps to understand drug use behaviours in Eastern Saudi Arabia by identifying disparities in adherence to OACs and other medications.

Future studies may also include RCTs that assess the impact of pharmacists conducting a Medicine Use Review (MUR) to benefit all medications' users, including OACs. Such studies can involve formally trained pharmacists to acquire the skills and knowledge needed to validate the use of medications. It may also aim to evaluate the benefits of implementing MUR. Such RCT can be extended to Saudi Arabia.

6.11. Conclusion

The overall aim of this DPharm thesis was to measure adherence to OACs in Eastern Saudi Arabia, identify factors which contributed to this phenomenon, explore views of HCPs on adherence to OACs, and recognise factors associated with prescribing of OACs. The evidence presented in this research showed that adherence to OACs in the study area is low. Some patients' related factors such as age of patients, literacy, and polypharmacy status can be used as predictors of adherence to OACs. The obtained data also showed that adherence to warfarin is higher compared to adherence to DOACs. This can be explained by the longstanding use of warfarin compared to DOACs in Eastern Saudi Arabia.

The outcomes of interviews with HCPs in Eastern Saudi Arabia agreed with findings of measuring adherence in terms of the low adherence to OACs in Eastern Saudi Arabia. Moreover, the outcomes of the interviews with HCPs revealed that hospital pharmacists are not widely involved in providing direct care to patient such as assessing adherence to OACs and reviewing patients' medications use. The role of pharmacists can be expanded to allow hospital pharmacists to assess adherence to OACs, and review use of medications on regular basis.

In Eastern Saudi Arabia, the implementation of a coagulation clinic operated by a pharmacist has already commenced. However, providing hospital pharmacists with structured training could enhance their effectiveness in improving adherence to oral anticoagulants (OACs).

Nevertheless, now, hospital pharmacists face challenges related to the work environment and available support. Communication between hospital pharmacists and other HCPs needs to be improved by clearly understanding and acknowledging the role of hospital pharmacists, which should be re-considered to exploit knowledge, expertise, and clinical skills of pharmacists to improve adherence to medications, especially OACs.

The interviewed HCPs also revealed that communication between HCPs could be further improved for the benefit of patients to maximise the benefits of OACs and reduce the risk of unwanted events by sharing information about use of OACs among different health sectors (primary and secondary care). All HCPs need to work closely to ensure the optimal care for the benefit of OACs' users. These factors are important for improving adherence to OACs in Eastern Saudi Arabia. All of these findings reveal the scope of adherence to OACs in Eastern Saudi Arabia and provide evidence of policy development and implementation aimed at increasing adherence to OACs and reducing the risks associated with OACs misuse. It also raises awareness of the potential for unleashing the potential role that hospital pharmacists can play.

References

Ababneh, M., Al-Azzam,S., Alzoubi.,K., and Rababa'h,A. 2016. Adherence in outpatients taking warfarin and its effect on anticoagulation control in Jordan. Int J Clin Pharm 38:816–821

Abdul Jabbar, M., & Al-Shammari, S. A. (1993). Compliance in Saudi epileptic patients: Determinants of compliance in Saudi epileptic patients. Annals of Saudi medicine, 13(1), 60–63. https://doi.org/10.5144/0256-4947.1993.60

Afzal, S., Zaidi, S., Merchant, H. A., Babar, Z. U., & Hasan, S. S. (2021). Prescribing trends of oral anticoagulants in England over the last decade: a focus on new and old drugs and adverse events reporting. Journal of thrombosis and thrombolysis, 52(2), 646–653. https://doi.org/10.1007/s11239-021-02416-4

Ageno, W., Gallus, A. S., Wittkowsky, A., Crowther, M., Hylek, E. M., & Palareti, G. (2012). Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141(2 Suppl), e44S–e88S. https://doi.org/10.1378/chest.11-2292

Aitken, M., & Gorokhovich, L. (2012). Advancing the responsible use of medicines: applying levers for change. Available at SSRN 2222541.

Al Sowielem, L.S. & El Zubier, A.G. (1998). Compliance and knowledge of hypertensive patients attending PHC centres in AL-Khobar, Saudi Arabia. EMHJ - Eastern Mediterranean Health Journal, 4 (2), 301-307, 1998 https://apps.who.int/iris/handle/10665/118129

Alajami, H. N., Alshammari, S. A., Al-Dossari, D. S., Alajmi, A. N., Alsaikhan, A. S., Alessa, M. S., Alessa, H. S., Khalaf Alhothaly, S., Alnami, M. I., Atey, T. M., Alnajrani, R. H., & Ali, S. (2021). Knowledge of Anticoagulation Among Saudi Patients With Atrial Fibrillation: A Cross-Sectional Study. Cureus, 13(11), e19237. https://doi.org/10.7759/cureus.19237

Alalwan, M. A., Al-Ohaid, F., Alhajjaj, H. M., Al Hazeem, A., AlJulaih, G. H., Al-Khedher, R., Alshehri, A., & Jatoi, N. A. (2021). Stroke Prevention Therapy and Prevalence of Risk Factors Among Patients With Atrial Fibrillation at King Fahad University Hospital in Al Khobar: A Retrospective, Single-Center Study. Cureus, 13(1), e12493. https://doi.org/10.7759/cureus.12493

Al-Faris, E. A., Abdulghani, H. M., Mahdi, A. H., Salih, M. A., & Al-Kordi, A. G. (2002). Compliance with appointments and medications in a pediatric neurology clinic at a University Hospital in Riyadh, Saudi Arabia. Saudi medical journal, 23(8), 969–974.

Algabbani, F. M., & Algabbani, A. M. (2020). Treatment adherence among patients with hypertension: findings from a cross-sectional study. Clinical hypertension, 26, 18. https://doi.org/10.1186/s40885-020-00151-1

Alhazzani, A. A., Mahfouz, A. A., Abolyazid, A. Y., Awadalla, N. J., Aftab, R., Faraheen, A., & Khalil, S. N. (2018). Study of Stroke Incidence in the Aseer Region, Southwestern Saudi Arabia. International journal of environmental research and public health, 15(2), 215. https://doi.org/10.3390/ijerph15020215

Al-Jedai A, Qaisi S, Al-Meman A. Pharmacy Practice and the Health Care System in Saudi Arabia. Can J Hosp Pharm. 2016 May-Jun;69(3):231-7. doi: 10.4212/cjhp.v69i3.1561. Epub 2016 Jun 30. PMID: 27403003; PMCID: PMC4924944.

Almegren M. (2017). Reversal of direct oral anticoagulants. Vascular health and risk management, 13, 287–292. https://doi.org/10.2147/VHRM.S138890

Al-Meman,A., and Almutairi,N.2014. Safety of Dabigatran in Patients with Non-valvular Atrial Fibrillation: A Short-Term Registry. J. of Pharm. and Pharmac. 2: 565-569

Almubark, R., Basyouni, M., Alghanem, A., Althumairi, N., Alkhamis, D., Alharbi, L. S., Alammari, N., Algabbani, A., Alnofal, F., Alqahtani, A., & BinDhim, N. (2019). Health literacy in Saudi Arabia: Implications for public health and healthcare access. Pharmacology research & perspectives, 7(4), e00514. https://doi.org/10.1002/prp2.514

Almujadidi, B., Adams, A., Alquaiz, A. 2022. Exploring social determinants of health in a Saudi Arabian primary health care setting: the need for a multidisciplinary approach. *Int J Equity Health* **21,** 24. https://doi.org/10.1186/s12939-022-01627-2

Al-Omair, S. F., Musallam, N. A., Al-Deghaither, N. Y., Al-Sadoun, N. A., & Bayoumy, N. M. (2016). Compliance with and awareness about long-term oral anticoagulant therapy among Saudi patients in a University Hospital, Riyadh, Saudi Arabia. Journal of Applied Hematology, 7(1), 10.

Alotayfi, M., Alsohaimi, S., AL-Qadi, B., Kamil, S., Aththi, A., Alhazmi, G., Qasem, H., Bugis, A. (2018). Poor Compliance to Anti-Hypertensive Drugs in Saudi Arabia. The Egyptian Journal of Hospital Medicine, 73(5), 6696-6701. doi: 10.21608/ejhm.2018.16015

Alqarni, A. M., Alrahbeni, T., Qarni, A. A., & Qarni, H. (2018). Adherence to diabetes medication among diabetic patients in the Bisha governorate of Saudi Arabia - a cross-sectional survey. Patient preference and adherence, 13, 63–71. https://doi.org/10.2147/PPA.S176355

Al-Rajeh, S. A. A. D., Awada, A., Niazi, G., & Larbi, E. (1993). Stroke in a Saudi Arabian National Guard community. Analysis of 500 consecutive cases from a population-based hospital. Stroke, 24(11), 1635-1639.

Al-Saikhan F. I. (2020). Genetic risk assessment towards warfarin application: Saudi Arabia study with a potential to predict and prevent side effects. Saudi journal of biological sciences, 27(1), 456–459. https://doi.org/10.1016/j.sjbs.2019.11.007

Al-Saffar, N, Deshmukh, A, Carter, P, Adib, S. (2005). Effect of information leaflets and counselling on antidepressant adherence: open randomised controlled trial in a psychiatric hospital in Kuwait. Int J Pharm Pract. 13:123-131. http://doi:10.1211/0022357056181

Alshammari, A. and Alhantoushi,M. 2018 .Assessment of Family Physician's Knowledge, Attitude and Barriers to the use of Oral Anticoagulation Therapy among Atrial Fibrillation Patients in Riyadh City. JMSCR 06:07 347-358

Al Sowielem, L.S. & El Zubier, A.G. (1998). Compliance and knowledge of hypertensive patients attending PHC centres in AL-Khobar, Saudi Arabia. EMHJ - Eastern Mediterranean Health Journal, 4 (2), 301-307, 1998 https://apps.who.int/iris/handle/10665/118129

Althubaiti A. (2016). Information bias in health research: definition, pitfalls, and adjustment methods. Journal of multidisciplinary healthcare, 9, 211–217. https://doi.org/10.2147/JMDH.S104807

Anghel, L. A., Farcas, A. M., & Oprean, R. N. (2019). An overview of the common methods used to measure treatment adherence. Medicine and pharmacy reports, 92(2), 117-122.

Austin P. C. (2011). An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. Multivariate behavioral research, 46(3), 399–424. https://doi.org/10.1080/00273171.2011.568786

Alyousif,S. and Alsaileek,A. 2016. Quality of anticoagulation control among patients with atrial fibrillation: An experience of a tertiary care center in Saudi Arabia. J. of the Saud. Heart. Assoc.: 28: 4: 239-243

Alzahrani, T., Nguyen, T., Ryan, A., Dwairy, A., McCaffrey, J., Yunus, R., Forgione, J., Krepp, J., Nagy, C., Mazhari, R., & Reiner, J. (2019). Cardiovascular Disease Risk Factors and Myocardial Infarction in the

Transgender Population. Circulation. Cardiovascular quality and outcomes, 12(4), e005597. https://doi.org/10.1161/CIRCOUTCOMES.119.005597

Amin, A., Houmsse, A., Ishola, A., Tyler, J., & Houmsse, M. (2016). The current approach of atrial fibrillation management. Avicenna journal of medicine, 6(1), 8–16. https://doi.org/10.4103/2231-0770.173580

Anouassi, Z., Atallah, B., Alsoud, L. O., El Nekidy, W., Al Mahmeed, W., AlJaabari, M., & Almuti, K. (2021). Appropriateness of the Direct Oral Anticoagulants Dosing in the Middle East Gulf Region. Journal of cardiovascular pharmacology, 77(2), 182–188.

Appleby,J.Hemmings,N. Maguire,D. and Wellings.2019. Public satisfaction with the NHS and social care in 2019: Results and trends from the British Social Attitudes survey.

Atkinson, P., Coffey, A., Delamont, S., Lofland, J., & Lofland, L. (Eds.). (2001). Handbook of ethnography. Sage.

Baetz, B. E., & Spinler, S. A. (2008). Dabigatran etexilate: an oral direct thrombin inhibitor for prophylaxis and treatment of thromboembolic diseases. *Pharmacotherapy*, *28*(11), 1354–1373. https://doi.org/10.1592/phco.28.11.1354

Bahit, M. C., Lopes, R. D., Wojdyla, D. M., Held, C., Hanna, M., Vinereanu, D., Hylek, E. M., Verheugt, F., Goto, S., Alexander, J. H., Wallentin, L., & Granger, C. B. (2017). Non-major bleeding with apixaban versus warfarin in patients with atrial fibrillation. Heart (British Cardiac Society), 103(8), 623–628. https://doi.org/10.1136/heartjnl-2016-309901

Baker D. W. (2006). The meaning and the measure of health literacy. Journal of general internal medicine, 21(8), 878–883. https://doi.org/10.1111/j.1525-1497.2006.00540.x

Balamurugan, A., Ohsfeldt, R., Hughes, T., & Phillips, M. (2006). Diabetes self-management education program for Medicaid recipients: a continuous quality improvement process. The Diabetes educator, 32(6), 893–900. https://doi.org/10.1177/0145721706294787

Balkhi B, Al-Rasheedi M, Elbur AI, Alghamadi A.2018. Association between satisfaction with and adherence to warfarin therapy on the control of international normalized ratio: A hospital-based study in Saudi Arabia. Saudi Pharm J.26(1):145-149.

Bangalore S, Kamalakkannan G, Parkar S, Messerli FH.(2007). Fixed-dose combinations improve medication compliance: a meta-analysis. Am J Med.;120(8):713–719.

Barbour R. S. (2000). The role of qualitative research in broadening the 'evidence base' for clinical practice. Journal of evaluation in clinical practice, 6(2), 155–163. https://doi.org/10.1046/j.1365-2753.2000.00213.x

Barner J.(2010). Medication Adherence: Focus on Secondary Database Analysis. ISPOR Student Forum

Bassili, A., Zaki, A., El Sawy, I.H., Bedwani, R. & Tognoni, G. (1998). Current health care of childhood bronchial asthma in Alexandria, Egypt. EMHJ - Eastern Mediterranean Health Journal, 4 (3), 575-584, 1998 https://apps.who.int/iris/handle/10665/118507

Bertoletti, L., Le Gal, G., Aujesky, D., Roy, P. M., Sanchez, O., Verschuren, F., Bounameaux, H., Perrier, A., & Righini, M. (2011). Prognostic value of the Geneva prediction rule in patients in whom pulmonary embolism is ruled out. Journal of internal medicine, 269(4), 433–440. https://doi.org/10.1111/j.1365-2796.2010.02328.x

Björck S, Palaszewski B, Friberg L, Bergfeldt L. Atrial fibrillation, stroke risk, and warfarin therapy

Blaschke, T. F., Osterberg, L., Vrijens, B., & Urquhart, J. (2012). Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annual review of pharmacology and toxicology, 52, 275–301. https://doi.org/10.1146/annurev-pharmtox-011711-113247

Boriani, G., Vitolo, M., Lane, D. A., Potpara, T. S., & Lip, G. Y. (2021). Beyond the 2020 guidelines on atrial fibrillation of the European society of cardiology. European journal of internal medicine, 86, 1–11. https://doi.org/10.1016/j.ejim.2021.01.006

Borbasi, S., & Jackson, D. (2012). Qualitative research: the whole picture. Elsevier.

Bowling, A. (2014). Research methods in health: investigating health and health services. McGraw-hill education (UK).

Brass, L. M., Krumholz, H. M., Scinto, J. M., & Radford, M. (1997). Warfarin use among patients with atrial fibrillation. Stroke, 28(12), 2382–2389. https://doi.org/10.1161/01.str.28.12.2382

Braun, V., & Clarke, V. (2006). Using thematic analysis in psychology. Qualitative research in psychology, 3(2), 77-101.

Brown, M. T., & Bussell, J. K. (2011). Medication adherence: WHO cares?. Mayo Clinic proceedings, 86(4), 304–314. https://doi.org/10.4065/mcp.2010.0575

Bryman, A., Becker, S., & Sempik, J. (2008). Quality criteria for quantitative, qualitative and mixed methods research: A view from social policy. International journal of social research methodology, 11(4), 261-276.

Bull, F. C., Al-Ansari, S. S., Biddle, S., Borodulin, K., Buman, M. P., Cardon, G., Carty, C., Chaput, J. P., Chastin, S., Chou, R., Dempsey, P. C., DiPietro, L., Ekelund, U., Firth, J., Friedenreich, C. M., Garcia, L., Gichu, M., Jago, R., Katzmarzyk, P. T., Lambert, E., … Willumsen, J. F. (2020). World Health Organization 2020 guidelines on physical activity and sedentary behaviour. British journal of sports medicine, 54(24), 1451–1462. https://doi.org/10.1136/bjsports-2020-102955

Burdett, P., & Lip, G. Y. H. 2022. Atrial fibrillation in the UK: predicting costs of an emerging epidemic recognizing and forecasting the cost drivers of atrial fibrillation-related costs. *European heart journal. Quality of care & clinical outcomes*, *8*(2), 187–194. https://doi.org/10.1093/ehjqcco/qcaa093

Burn,J. and Pirmohamed,M.2018. Direct oral anticoagulants versus warfarin: is new always better than the old?.2018.Open Heart. ;5:e000712. doi:10.1136/openhrt-2017-000712

Burns, N., & Grove, S. K. (2010). Understanding nursing research-eBook: Building an evidence-based practice. Elsevier Health Sciences.

Burt, V. L., Cutler, J. A., Higgins, M., Horan, M. J., Labarthe, D., Whelton, P., Brown, C., & Roccella, E. J. (1995). Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. Hypertension (Dallas, Tex. : 1979), 26(1), 60–69. https://doi.org/10.1161/01.hyp.26.1.60

Bushman, B. J., & Huesmann, L. R. (2001). Effects of televised violence on aggression. In D. G. Singer, & J. L. Singer (Eds.) Handbook of children and the media (pp. 223-254). Thousand Oaks, CA: Sage Publications.

European Heart Rhythm Association, European Association for Cardio-Thoracic Surgery, Camm, A. J., Kirchhof, P., Lip, G. Y., Schotten, U., Savelieva, I., Ernst, S., Van Gelder, I. C., Al-Attar, N., Hindricks, G., Prendergast, B., Heidbuchel, H., Alfieri, O., Angelini, A., Atar, D., Colonna, P., De Caterina, R., De Sutter, J., Goette, A., … Rutten, F. H. (2010). Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). European heart journal, 31(19), 2369–2429. https://doi.org/10.1093/eurheartj/ehq278

Carlson, M. D., & Morrison, R. S. (2009). Study design, precision, and validity in observational studies. Journal of palliative medicine, 12(1), 77–82. https://doi.org/10.1089/jpm.2008.9690

Castelluci, L. A., Shaw, J., van der Salm, K., Erkens, P., Le Gal, G., Petrcich, W., & Carrier, M. (2015). Self-reported adherence to anticoagulation and its determinants using the Morisky medication adherence scale. Thrombosis research, 136(4), 727-731.

Cavanagh, K., Strauss, C., Cicconi, F., Griffiths, N., Wyper, A., & Jones, F. (2013). A randomised controlled trial of a brief online mindfulness-based intervention. Behaviour research and therapy, 51(9), 573–578. https://doi.org/10.1016/j.brat.2013.06.003

Chan, A. H. Y., Horne, R., Hankins, M., & Chisari, C. (2020). The Medication Adherence Report Scale: A measurement tool for eliciting patients' reports of nonadherence. *British journal of clinical pharmacology*, *86*(7), 1281–1288. https://doi.org/10.1111/bcp.14193

Chao, T. F., Lip, G., Liu, C. J., Lin, Y. J., Chang, S. L., Lo, L. W., Hu, Y. F., Tuan, T. C., Liao, J. N., Chung, F. P., Chen, T. J., & Chen, S. A. (2018). Relationship of Aging and Incident Comorbidities to Stroke Risk in Patients With Atrial Fibrillation. Journal of the American College of Cardiology, 71(2), 122–132. https://doi.org/10.1016/j.jacc.2017.10.085

Chien, K. L., Su, T. C., Hsu, H. C., Chang, W. T., Chen, P. C., Chen, M. F., & Lee, Y. T. (2010). Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese. International journal of cardiology, 139(2), 173–180. https://doi.org/10.1016/j.ijcard.2008.10.045

Chen, S. L., Tsai, J. C., & Chou, K. R. (2011). Illness perceptions and adherence to therapeutic regimens among patients with hypertension: a structural modeling approach. International journal of nursing studies, 48(2), 235–245. https://doi.org/10.1016/j.ijnurstu.2010.07.005

Cheng K, Ingram N, Keenan J. (2015). Evidence of poor adherence to secondary prevention after acute coronary syndromes: possible remedies through the application of new technologies. Open Heart ;2:e000166. doi:10.1136/openhrt-2014-000166

Choumane, N.S., Malaeb, D.N., Malaeb, B. (2018). A multicenter, prospective study evaluating the impact of the clinical pharmacist-physician counselling on warfarin therapy management in Lebanon. BMC Health Serv Res 18, 80. https://doi.org/10.1186/s12913-018-2874-7

Chugh, S. S., Havmoeller, R., Narayanan, K., Singh, D., Rienstra, M., Benjamin, E. J., Gillum, R. F., Kim, Y. H., McAnulty, J. H., Jr, Zheng, Z. J., Forouzanfar, M. H., Naghavi, M., Mensah, G. A., Ezzati, M., & Murray, C. J. (2014). Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation, 129(8), 837–847. https://doi.org/10.1161/CIRCULATIONAHA.113.005119

Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001; 23(8):1296–1310.

Cleland J. A. (2017). The qualitative orientation in medical education research. Korean journal of medical education, 29(2), 61–71. https://doi.org/10.3946/kjme.2017.53

Clifford S, Barber N, Horne R. Understanding different beliefs heldby adherers, unintentional nonadherers, and intentional nonadherers:application of the Necessity-Concerns Framework. J Psychosom Res.2008;64(1):41–46

Cohen, J. L., Mann, D. M., Wisnivesky, J. P., Home, R., Leventhal, H., Musumeci-Szabó, T. J., & Halm, E. A. (2009). Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. *Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology*, *103*(4), 325–331. https://doi.org/10.1016/s1081-1206(10)60532-7

Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–1151.

Connolly, S. J., Ezekowitz, M. D., Yusuf, S., Eikelboom, J., Oldgren, J., Parekh, A., Pogue, J., Reilly, P. A., Themeles, E., Varrone, J., Wang, S., Alings, M., Xavier, D., Zhu, J., Diaz, R., Lewis, B. S., Darius, H., Diener, H. C., Joyner, C. D., Wallentin, L., … RE-LY Steering Committee and Investigators (2009). Dabigatran versus warfarin in patients with atrial fibrillation. The New England journal of medicine, 361(12), 1139–1151. https://doi.org/10.1056/NEJMoa0905561

Cramer, J. A., Roy, A., Burrell, A., Fairchild, C. J., Fuldeore, M. J., Ollendorf, D. A., & Wong, P. K. (2008). Medication compliance and persistence: terminology and definitions. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research, 11(1), 44–47. https://doi.org/10.1111/j.1524-4733.2007.00213.x

Cramer, J. A., Scheyer, R. D., & Mattson, R. H. (1990). Compliance declines between clinic visits. Archives of internal medicine, 150(7), 1509–1510.

Creswell, J. W. (2013). Qualitative Inquiry & Research Design: Choosing among Five Approaches (3rd ed.). Thousand Oaks, CA: SAGE.

Creswell. J.W. and Creswell, J.D. (2017) Research Design: Qualitative, Quantitative, and Mixed Methods Approaches. 4th Edition, Sage, Newbury Park.

Crotty, M. J. (1998). The foundations of social research: Meaning and perspective in the research process. The foundations of social research, 1-256.

Curry, L. A., Nembhard, I. M., & Bradley, E. H. (2009). Qualitative and mixed methods provide unique contributions to outcomes research. Circulation, 119(10), 1442-1452.

Davis, M. S. (1968). Variations in patients' compliance with doctors' advice: an empirical analysis of patterns o communication. American Journal of Public Health and the Nations Health, 58(2), 274-288.

Davari, M., Khorasani, E., & Tigabu, B. M. (2018). Factors Influencing Prescribing Decisions of Physicians: A Review. Ethiopian journal of health sciences, 28(6), 795–804. https://doi.org/10.4314/ejhs.v28i6.15

Davis, N. J., Billett, H. H., Cohen, H. W., & Arnsten, J. H. (2005). Impact of adherence, knowledge, and quality of life on anticoagulation control. The Annals of pharmacotherapy, 39(4), 632–636. https://doi.org/10.1345/aph.1E464

De Geest, S., & Sabaté, E. (2003). Adherence to long-term therapies: evidence for action. European journal of cardiovascular nursing, 2(4), 323. https://doi.org/10.1016/S1474-5151(03)00091-4

Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W.2012.Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature . *Circulation*; **126:** 2381‑91.

Dewalt, D. A., Berkman, N. D., Sheridan, S., Lohr, K. N., & Pignone, M. P. (2004). Literacy and health outcomes: a systematic review of the literature. Journal of general internal medicine, 19(12), 1228–1239. https://doi.org/10.1111/j.1525-1497.2004.40153.x

Dib, J. G., Mohammed, K., Momattin, H. I., & Alshehri, A. M. (2014). Implementation of pharmacist-managed anticoagulation clinic in a saudi arabian health center. Hospital pharmacy, 49(3), 260–268. https://doi.org/10.1310/hpj4903-260

DiCicco-Bloom, B., & Crabtree, B. F. (2006). The qualitative research interview. Medical education, 40(4), 314-321.

DiMatteo, M. R., Haskard, K. B., & Williams, S. L. (2007). Health beliefs, disease severity, and patient adherence: a meta-analysis. Medical care, 45(6), 521–528. https://doi.org/10.1097/MLR.0b013e318032937e

Dornyei, Z. (2007). Research Methods in Applied Linguistics. Oxford: Oxford University Press. e325–e332.

Dotta-Celio, J., Alatri, A., Locatelli, I., Salvi, M., Bugnon, O., Schneider, M. P., & Mazzolai, L. (2019). Patient adherence to rivaroxaban in deep vein thrombosis, a cohort study in Switzerland: quantitative results. International journal of clinical pharmacy, 41(6), 1625–1633. https://doi.org/10.1007/s11096-019-00928-x

Ekong, G., & Kavookjian, J. (2016). Motivational interviewing and outcomes in adults with type 2 diabetes: A systematic review. Patient education and counseling, 99(6), 944–952. https://doi.org/10.1016/j.pec.2015.11.022

Elbur,A., Albarraq, A., Maugrabi, M., and Alharthi, S.2015.Knowledge of, Satisfaction with and Adherence to Oral Anticoagulant Drugs among Patients in King Fasial Hospital; Taif, Kingdom Saudi Arabia. Int. J. Pharm. Sci. Rev. Res., 31:1: 274-280

Elewa, H., El-Makaty,H., and Ali, Z.2018. Appropriateness of Dabigatran and Rivaroxaban Prescribing in Qatar: A 5-Year Experience. J. of Cardio. Pharmac. and Therap. , 23:2: 155-161.

Elewa,H., AbdelSamad,O., Elmubark,A.E.,Al-Taweel,H.,Mohamed,A.,Kheir,N., Ibrahim,M., and Awaisu,A.2016a. The first pharmacist-managed anticoagulation clinic under a collaborative practice agreement in Qatar: clinical and patient-oriented outcomes. J. of Clin. Pharm. and Therap., 41: 403–408

Elewa,H., Alhaddad,A., Al-Rawi1,S., Nounou,A., Mahmoud,H., and Singh,R.2017. Trends in oral anticoagulant use in Qatar: a 5-year experience. J Thromb Thrombolysis 43:411–416

Elewa,H., Jalali,F., Khudair,N., Hassaballah,N., Abdelsamad,O., Mohammed,S.2016. Evaluation of pharmacist-based compared to doctor-based anticoagulation management in Qatar. J. of Eval. in Clin. Pract. 22: 433–438

Elliott, R. A., Boyd, M. J., Salema, N. E., Davies, J., Barber, N., Mehta, R. L., Tanajewski, L., Waring, J., Latif, A., Gkountouras, G., Avery, A. J., Chuter, A., & Craig, C. (2016). Supporting adherence for people starting a new medication for a long-term condition through community pharmacies: a pragmatic randomised controlled trial of the New Medicine Service. BMJ quality & safety, 25(10), 747–758. https://doi.org/10.1136/bmjqs-2015-004400

Elliott, R. A., Tanajewski, L., Gkountouras, G., Avery, A. J., Barber, N., Mehta, R., ... & Waring, J. (2017). Cost effectiveness of support for people starting a new medication for a long-term condition through community pharmacies: an economic evaluation of the new medicine service (NmS) compared with normal practice. Pharmacoeconomics, 35(12), 1237-1255.

El-Shazly, M., Abdel-Fattah, M., Zaki, A., Bedwani, R., Assad, S., Tognoni, G., & Nicolucci, A. (2000). Health care for diabetic patients in developing countries: a case from Egypt. Public health, 114(4), 276-281.

Eltayeb TYM, Mohamed MS, Elbur AI, Elsayed ASA.2016. Satisfaction with and adherence to warfarin treatment: a cross-sectional study among Sudanese patients. J Saudi Heart Assoc. 29(3):169–175

Elzubier, A. G., Husain, A. A., Suleiman, I. A., & Hamid, Z. A. (2000). Drug compliance among hypertensive patients in Kassala, Eastern Sudan. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit, 6(1), 100–105.

Emren,S., Oktay S, Bilgin, M., Beton,O., Aslan,A., Dinc¸ L., Asarcikli, Hakan, C¸ Bekar,L., Bolat,I.,Yayla, Barıs¸ C¸ elebi, Onur Dalgic¸, and Og˘uzhan C¸ elik.2018. Drug Adherence in Patients With Nonvalvular Atrial Fibrillation Taking Non-Vitamin K Antagonist Oral Anticoagulants in Turkey: NOAC-TR. Clin. and Applied Thrombosis/Hemostasis , 24:3: 525-531

Eriksson, B. I., Quinlan, D. J., & Weitz, J. I. (2009). Comparative pharmacodynamics and pharmacokinetics of oral direct thrombin and factor xa inhibitors in development. *Clinical pharmacokinetics*, *48*(1), 1–22. https://doi.org/10.2165/0003088-200948010-00001

Eriksson, Bengt & Quinlan, Daniel & Eikelboom, John. (2011). Novel Oral Factor Xa and Thrombin Inhibitors in the Management of Thromboembolism. Annual review of medicine. 62. 41-57. 10.1146/annurev-med-062209-095159.

Essam, A. E., Sharif, G., & Al-Hameed, F. (2011). Venous thromboembolism-related mortality and morbidity in King Fahd General Hospital, Jeddah, Kingdom of Saudi Arabia. Annals of thoracic medicine, 6(4), 193–198. https://doi.org/10.4103/1817-1737.84772

Ezekowitz, J. A., Kaul, P., Bakal, J. A., Armstrong, P. W., Welsh, R. C., & McAlister, F. A. (2009). Declining in-hospital mortality and increasing heart failure incidence in elderly patients with first myocardial infarction. *Journal of the American College of Cardiology*, *53*(1), 13–20. https://doi.org/10.1016/j.jacc.2008.08.067

Fahey, M., Abdulmajeed, A., & Sabra, K. (2006). Measurement of adherence to anti-hypertensive medication as perceived by doctors and patients. Qatar Medical Journal, 2006(1), 16.

Fang, M. C., Machtinger, E. L., Wang, F., & Schillinger, D. (2006). Health literacy and anticoagulation-related outcomes among patients taking warfarin. Journal of general internal medicine, 21(8), 841-846.

Farinha, J. M., Jones, I. D., & Lip, G. Y. H. (2022). Optimizing adherence and persistence to non-vitamin K antagonist oral anticoagulant therapy in atrial fibrillation. European heart journal supplements : journal of the European Society of Cardiology, 24(Suppl A), A42–A55. https://doi.org/10.1093/eurheartj/suab152

Farmer K. C. (1999). Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice. Clinical therapeutics, 21(6), 1074–1073. https://doi.org/10.1016/S0149-2918(99)80026-5

Feldman, S. R., Vrijens, B., Gieler, U., Piaserico, S., Puig, L., & van de Kerkhof, P. (2017). Treatment Adherence Intervention Studies in Dermatology and Guidance on How to Support Adherence. American journal of clinical dermatology, 18(2), 253–271. https://doi.org/10.1007/s40257-017-0253-5

Fido AA, Husseini AM. (1998). Noncompliance with treatment among psychiatric patients in Kuwait. Medical Principles and Practice, 7:28–32.

Foley, G., & Timonen, V. (2015). Using Grounded Theory Method to Capture and Analyze Health Care Experiences. Health services research, 50(4), 1195–1210. https://doi.org/10.1111/1475-6773.12275

Foley, G., & Timonen, V. (2015). Using Grounded Theory Method to Capture and Analyze Health Care Experiences. Health services research, 50(4), 1195–1210. https://doi.org/10.1111/1475-6773.12275

for clinical and health psychology (pp. 56-68). London: Sage.

Foster, J. M., Usherwood, T., Smith, L., Sawyer, S. M., Xuan, W., Rand, C. S., & Reddel, H. K. (2014). Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. The Journal of allergy and clinical immunology, 134(6), 1260–1268.e3. https://doi.org/10.1016/j.jaci.2014.05.041

Francis, V., Korsch, B. M., & Morris, M. J. (1969). Gaps in doctor-patient communication: Patients' response to medical advice. New England Journal of Medicine, 280(10), 535-540.

Frankel DS, Piette JD, Jessup M, Craig K, Pickering F, Goldberg LR.2006. Validation of prognostic models among patients with advanced heart failure. *J Card Fail.* 2006;12:430-438.

Gage, B. F., Waterman, A. D., Shannon, W., Boechler, M., Rich, M. W., & Radford, M. J. (2001). Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. Jama, 285(22), 2864-2870.

Garay-Sevilla, M. E., Porras, J. S., & Malacara, J. M. (2011). Coping strategies and adherence to treatment in patients with type 2 diabetes mellitus. *Revista de investigación clínica*, *63*(2), 155-161.

García-Pallarés, J., Sánchez-Medina, L., Carrasco, L., Díaz, A., & Izquierdo, M. (2009). Endurance and neuromuscular changes in world-class level kayakers during a periodized training cycle. European journal of applied physiology, 106(4), 629–638. https://doi.org/10.1007/s00421-009-1061-2

Garfield, S., Clifford, S., Eliasson, L., Barber, N., & Willson, A. (2011). Suitability of measures of self-reported medication adherence for routine clinical use: a systematic review. BMC medical research methodology, 11, 149. https://doi.org/10.1186/1471-2288-11-149

Gatti, M. E., Jacobson, K. L., Gazmararian, J. A., Schmotzer, B., & Kripalani, S. (2009). Relationships between beliefs about medications and adherence. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists, 66(7), 657–664. https://doi.org/10.2146/ajhp080064

Gaziano,T.2005. Cardiovascular Disease in the Developing World and Its Cost-Effective Management. Circulation. 112:3547–3553

Gazmararian, J. A., Williams, M. V., Peel, J., & Baker, D. W. (2003). Health literacy and knowledge of chronic disease. Patient education and counseling, 51(3), 267–275. https://doi.org/10.1016/s0738-3991(02)00239-2

GBD 2019 Stroke Collaborators (2021). Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. Neurology, 20(10), 795–820. https://doi.org/10.1016/S1474-4422(21)00252-0

Ghandehari K. (2011). Barriers of thrombolysis therapy in developing countries. Stroke research and treatment, 2011, 686797. https://doi.org/10.4061/2011/686797

Giugliano RP, Ruff CT, Braunwald E.2014. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. ;369:2093

Giugliano, R. P., Ruff, C. T., Braunwald, E., Murphy, S. A., Wiviott, S. D., Halperin, J. L., Waldo, A. L., Ezekowitz, M. D., Weitz, J. I., Špinar, J., Ruzyllo, W., Ruda, M., Koretsune, Y., Betcher, J., Shi, M., Grip, L. T., Patel, S. P., Patel, I., Hanyok, J. J., Mercuri, M., … ENGAGE AF-TIMI 48 Investigators (2013). Edoxaban versus warfarin in patients with atrial fibrillation. The New England journal of medicine, 369(22), 2093–2104. https://doi.org/10.1056/NEJMoa1310907

Glund, S., Stangier, J., Schmohl, M., Gansser, D., Norris, S., van Ryn, J., Lang, B., Ramael, S., Moschetti, V., Gruenenfelder, F., Reilly, P., & Kreuzer, J. (2015). Safety, tolerability, and efficacy of idarucizumab for the reversal of the anticoagulant effect of dabigatran in healthy male volunteers: a randomised, placebo-controlled, double-blind phase 1 trial. Lancet (London, England), 386(9994), 680–690. https://doi.org/10.1016/S0140-6736(15)60732-2

Gohil, R., Peck, G., & Sharma, P. (2009). The genetics of venous thromboembolism. A meta-analysis involving approximately 120,000 cases and 180,000 controls. Thrombosis and haemostasis, 102(2), 360–370. https://doi.org/10.1160/TH09-01-0013

Goldhaber S. Z. (1997). Pulmonary embolism thrombolysis: broadening the paradigm for its administration. Circulation, 96(3), 716–718. https://doi.org/10.1161/01.cir.96.3.716

Gómez-Outes, A., Lagunar-Ruíz, J., Terleira-Fernández, A. I., Calvo-Rojas, G., Suárez-Gea, M. L., & Vargas-Castrillón, E. (2016). Causes of Death in Anticoagulated Patients With Atrial Fibrillation. Journal of the American College of Cardiology, 68(23), 2508–2521. https://doi.org/10.1016/j.jacc.2016.09.944

Gordon, K., Smith, F., & Dhillon, S. (2007). Effective chronic disease management: patients' perspectives on medication-related problems. Patient education and counseling, 65(3), 407–415. https://doi.org/10.1016/j.pec.2006.09.012

Gorst-Rasmussen A, Skjøth F, Larsen TB, Rasmussen LH, Lip GY, Lane DA.2015. Dabigatran adherence in atrial fibrillation patients during the first year after diagnosis: a nationwide cohort study. J Thromb Haemost.;13:495–504.

Granger CB, Alexander JH, McMurray JJ .2011. Apixaban versus warfarin in patients with atrial fibrillation. New Engl J Med. 365:981–992

Guba, E. (1981). Criteria for Assessing the Trustworthiness of Naturalistic Inquiries. Educational Technology Research and Development, 29 (2), 75-91.

Guba, E. G., & Lincoln, Y. S. (2005). Paradigmatic Controversies, Contradictions, and Emerging Confluences. In N. K. Denzin & Y. S. Lincoln (Eds.), The Sage handbook of qualitative research (pp. 191–215). Sage Publications Ltd

Gulbay, B. E., Doğan, R., Yildiz, Ö. A., Gürkan, Ö. U., Acican, T., Saryal, S., ... & Köse, K. (2006). Patients adherence to treatment and knowledge about chronic obstructive pulmonary disease. COPD, 1(6.51), 0-005.

Hall, R. (2013). Mixed methods: In search of a paradigm. Conducting research in a changing and challenging world, 71-78.

Hamer,S. & Collinson, G. (2014). Achieving Evidence-Based Practice: A Handbook for Practitioners. Elsevier Health Sciences. P.236

Hart, R. G., Pearce, L. A., & Aguilar, M. I. (2007). Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Annals of internal medicine, 146(12), 857–867. https://doi.org/10.7326/0003-4819-146-12-200706190-00007

Harvey, Y. Luxford, L. Moxham, T. Park, B. Parker, K. Reid-Searl and D. Stanley (Eds.), Kozier and Erb's Fundamentals of Nursing (2nd ed., Vol. 1). Frenchs Forest, Sydney: Pearson Australia.

Hashmi, S. K., Afridi, M. B., Abbas, K., Sajwani, R. A., Saleheen, D., Frossard, P. M., Ishaq, M., Ambreen, A., & Ahmad, U. (2007). Factors associated with adherence to anti-hypertensive treatment in Pakistan. PloS one, 2(3), e280. https://doi.org/10.1371/journal.pone.0000280

Haynes, R. B., Gibson, E., Hackett, B., Sackett, D., Taylor, D. W., Roberts, R., & Johnson, A. (1976). Improvement of medication compliance in uncontrolled hypertension. The Lancet, 307(7972), 1265-1268.

Heidbuchel H, Verhamme P, Alings M.2015 . Updated European heart rhythm association practical guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace;17:1467–507.

Heidenreich PA, Trogdon JG, Khavjou OA.2011. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 123:933–944.

Hess, L. M., Raebel, M. A., Conner, D. A., & Malone, D. C. (2006). Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. The Annals of pharmacotherapy, 40(7-8), 1280–1288. https://doi.org/10.1345/aph.1H018

Hindricks, G., Potpara,T., Nikolaos Dagres.2021. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation. *European Heart Journal*, Volume 42, Issue 5, 1 February 2021, Pages 373–498, https://doi.org/10.1093/eurheartj/ehaa612

Hirsh, J. (1992). Substandard monitoring of warfarin in North America: time for change. Archives of internal medicine, 152(2), 257-258.

Hirsh, J. (1995). Optimal intensity and monitoring warfarin. The American journal of cardiology, 75(6), 39B-42B.

Hirsh, J., Warkentin, T. E., Shaughnessy, S. G., Anand, S. S., Halperin, J. L., Raschke, R., Granger, C., Ohman, E. M., & Dalen, J. E. (2001). Heparin and low-molecular-weight heparin: mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest, 119(1 Suppl), 64S–94S. https://doi.org/10.1378/chest.119.1_suppl.64s

Ho, K. H., van Hove, M., & Leng, G. (2020). Trends in anticoagulant prescribing: a review of local policies in English primary care. BMC health services research, 20(1), 279. https://doi.org/10.1186/s12913-020-5058-1

Ho, P. M., Bryson, C. L., & Rumsfeld, J. S. (2009). Medication adherence: its importance in cardiovascular outcomes. Circulation, 119(23), 3028–3035. https://doi.org/10.1161/CIRCULATIONAHA.108.768986

Holloway, I., & Brown, L. (2012). Essentials of a Qualitative Doctorate (1st ed.). Routledge. https://doi.org/10.4324/9781315429458

Horne R. (2006). Compliance, adherence, and concordance: implications for asthma treatment. Chest, 130(1 Suppl), 65S–72S. https://doi.org/10.1378/chest.130.1_suppl.65S

Horne, R., & Weinman, J. (1999). Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. Journal of psychosomatic research, 47(6), 555–567. https://doi.org/10.1016/s0022-3999(99)00057-4

Horne, R., & Weinman, J. (2002). Self-regulation and self-management in asthma: exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. Psychology & Health, 17(1), 17–32. https://doi.org/10.1080/08870440290001502

Huston, P., & Rowan, M. (1998). Qualitative studies. Their role in medical research. Canadian family physician Medecin de famille canadien, 44, 2453–2458.

Jimmy, B., & Jose, J. (2011). Patient medication adherence: measures in daily practice. Oman medical journal, 26(3), 155–159. https://doi.org/10.5001/omj.2011.38

Jin, J., Sklar, G. E., Min Sen Oh, V., & Chuen Li, S. (2008). Factors affecting therapeutic compliance: A review from the patient's perspective. Therapeutics and clinical risk management, 4(1), 269–286. https://doi.org/10.2147/tcrm.s1458

Joffe, H., & Yardley, L. (2004). Content and thematic analysis. Research methods

Johnson, J. A., Gong, L., Whirl-Carrillo, M., Gage, B. F., Scott, S. A., Stein, C. M., Anderson, J. L., Kimmel, S. E., Lee, M. T., Pirmohamed, M., Wadelius, M., Klein, T. E., Altman, R. B., & Clinical Pharmacogenetics Implementation Consortium (2011). Clinical Pharmacogenetics Implementation Consortium Guidelines for CYP2C9 and VKORC1 genotypes and warfarin dosing. Clinical pharmacology and therapeutics, 90(4), 625–629. https://doi.org/10.1038/clpt.2011.185

Jortveit, J., Pripp, A.H., Langørgen, J., & Halvorsen, S. (2019). Poor adherence to guideline recommendations among patients with atrial fibrillation and acute myocardial infarction. European Journal of Preventive Cardiology, 26, 1373 - 1382.

Kamel, N. M., Badawy, Y. A., el-Zeiny, N. A., & Merdan, I. A. (1999). Sociodemographic determinants of management behaviour of diabetic patients. Part I. Behaviour of patients in relation to management of their disease. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit, 5(5), 967–973.

Kardas, P., Lewek, P., & Matyjaszczyk, M. (2013). Determinants of patient adherence: a review of systematic reviews. Frontiers in pharmacology, 4, 91. https://doi.org/10.3389/fphar.2013.00091

Kennedy, B. M., Rehman, M., Johnson, W. D., Magee, M. B., Leonard, R., & Katzmarzyk, P. T. (2017). Healthcare Providers versus Patients' Understanding of Health Beliefs and Values. Patient experience journal, 4(3), 29–37.

Khalil, S. A., & Elzubier, A. G. (1997). Drug compliance among hypertensive patients in Tabuk, Saudi Arabia. Journal of hypertension, 15(5), 561–565. https://doi.org/10.1097/00004872-199715050-00013

Khan, A. R., Lateef, Z. N. A. A., Al Aithan, M. A., Bu-Khamseen, M. A., Al Ibrahim, I., & Khan, S. A. (2012). Factors contributing to non-compliance among diabetics attending primary health centers in the Al Hasa district of Saudi Arabia. Journal of Family and Community Medicine, 19(1), 26.

Khattab, M. S., Aboifotouh, M. A., Khan, M. Y., Humaidi, M. A., & al-Kaldi, Y. M. (1999). Compliance and control of diabetes in a family practice setting, Saudi Arabia. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit, 5(4), 755–765.

Khayyat, S. M., Khayyat, S. M., Hyat Alhazmi, R. S., Mohamed, M. M., & Abdul Hadi, M. (2017). Predictors of Medication Adherence and Blood Pressure Control among Saudi Hypertensive Patients Attending Primary Care Clinics: A Cross-Sectional Study. PloS one, 12(1), e0171255. https://doi.org/10.1371/journal.pone.0171255

Kotecha, D., Bunting, K. V., Gill, S. K., Mehta, S., Stanbury, M., Jones, J. C., Haynes, S., Calvert, M. J., Deeks, J. J., Steeds, R. P., Strauss, V. Y., Rahimi, K., Camm, A. J., Griffith, M., Lip, G., Townend, J. N., Kirchhof, P., & Rate Control Therapy Evaluation in Permanent Atrial Fibrillation (RATE-AF) Team (2020). Effect of Digoxin vs Bisoprolol for Heart Rate Control in Atrial Fibrillation on Patient-Reported Quality of Life: The RATE-AF Randomized Clinical Trial. JAMA, 324(24), 2497–2508. https://doi.org/10.1001/jama.2020.23138

Krijthe, B. P., Kunst, A., Benjamin, E. J., Lip, G. Y., Franco, O. H., Hofman, A., Witteman, J. C., Stricker, B. H., & Heeringa, J. (2013). Projections on the number of individuals with atrial fibrillation in the European Union, from 2000 to 2060. European heart journal, 34(35), 2746–2751. https://doi.org/10.1093/eurheartj/eht280

Kripalani, S., LeFevre, F., Phillips, C. O., Williams, M. V., Basaviah, P., & Baker, D. W. (2007). Deficits in communication and information transfer between hospital-based and primary care physicians: implications for patient safety and continuity of care. JAMA, 297(8), 831–841. https://doi.org/10.1001/jama.297.8.831

Kruger, P. C., Eikelboom, J. W., Douketis, J. D., & Hankey, G. J. (2019). Deep vein thrombosis: update on diagnosis and management. Medical Journal of Australia, 210(11), 516-524.

Kucher, N., Koo, S., Quiroz, R., Cooper, J. M., Paterno, M. D., Soukonnikov, B., & Goldhaber, S. Z. (2005). Electronic alerts to prevent venous thromboembolism among hospitalized patients. The New England journal of medicine, 352(10), 969–977. https://doi.org/10.1056/NEJMoa041533

Kucukarslan S. N. (2012). A review of published studies of patients' illness perceptions and medication adherence: lessons learned and future directions. Research in social & administrative pharmacy : RSAP, 8(5), 371–382. https://doi.org/10.1016/j.sapharm.2011.09.002

Kuntz, J. L., Safford, M. M., Singh, J. A., Phansalkar, S., Slight, S. P., Her, Q. L., Lapointe, N. A., Mathews, R., O'Brien, E., Brinkman, W. B., Hommel, K., Farmer, K. C., Klinger, E., Maniam, N., Sobko, H. J., Bailey, S. C., Cho, I., Rumptz, M. H., Vandermeer, M. L., & Hornbrook, M. C. (2014). Patient-centered interventions to

improve medication management and adherence: a qualitative review of research findings. Patient education and counseling, 97(3), 310–326. https://doi.org/10.1016/j.pec.2014.08.021

Lambert, E. V., Steyn, K., Stender, S., Everage, N., Fourie, J. M., & Hill, M. (2006). Cross-cultural validation of the hill-bone compliance to high blood pressure therapy scale in a South African, primary healthcare setting. Ethnicity & disease, 16(1), 286–291.

Lambert, H., & McKevitt, C. (2002). Anthropology in health research: from qualitative methods to multidisciplinarity. BMJ (Clinical research ed.), 325(7357), 210–213. https://doi.org/10.1136/bmj.325.7357.210

Lane, D. A., & Lip, G. Y. (2012). Use of the CHA(2)DS(2)-VASc and HAS-BLED scores to aid decision making for thromboprophylaxis in nonvalvular atrial fibrillation. Circulation, 126(7), 860–865. https://doi.org/10.1161/CIRCULATIONAHA.111.060061

Laupacis, A., Albers, G., Dalen, J., Dunn, M., Feinberg, W., & Jacobson, A. (1995). Antithrombotic therapy in atrial fibrillation. Chest, 108(4 Suppl), 352S–359S. https://doi.org/10.1378/chest.108.4_supplement.352s

Lavsa, S. M., Holzworth, A., & Ansani, N. T. (2011). Selection of a validated scale for measuring medication adherence. Journal of the American Pharmacists Association : JAPhA, 51(1), 90–94. https://doi.org/10.1331/JAPhA.2011.09154

Lehane E, McCarthy G.2007. Intentional and unintentional medication non-adherence: a comprehensive framework for clinical research and practice? A discussion paper. Int J Nurs Stud.44(8):1468–1477.

Lehane, E., & McCarthy, G. (2009). Medication non-adherence--exploring the conceptual mire. International journal of nursing practice, 15(1), 25–31. https://doi.org/10.1111/j.1440-172X.2008.01722.x

Li, R., Curtain, C., Bereznicki, L. et al. (2018). Community pharmacists' knowledge and perspectives of reporting adverse drug reactions in Australia: a cross-sectional survey. Int J Clin Pharm 40, 878–889. https://doi.org/10.1007/s11096-018-0700-2

Lincoln, Y. S., Lynham, S. A., & Guba, E. G. (2011). Paradigmatic controversies, contradictions, and emerging confluences, revisited. The Sage handbook of qualitative research, 4(2), 97-128.

Linn AJ, van Weert JC, Smit EG, Schouten BC, Van Bodegraven A, Van Dijk L.2012. Words that make pills easier to swallow: a communication typology to address practical and perceptual barriers to medication intake behavior. Patient Prefer Adherence. 6:871–885.

Lip, G. Y., & Lim, H. S. (2007). Atrial fibrillation and stroke prevention. The Lancet. Neurology, 6(11), 981–993. https://doi.org/10.1016/S1474-4422(07)70264-8

Lip, G. Y., Beevers, M., & Beevers, G. (1994). The failure of malignant hypertension to decline: a survey of 24 years' experience in a multiracial population in England. Journal of hypertension, 12(11), 1297-1305.

Lip, G. Y., Larsen, T. B., Skjøth, F., & Rasmussen, L. H. (2012). Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. Journal of the American College of Cardiology, 60(8), 738-746.

Lip, G., Coca, A., Kahan, T., Boriani, G., Manolis, A. S., Olsen, M. H., Oto, A., Potpara, T. S., Steffel, J., Marín, F., de Oliveira Figueiredo, M. J., de Simone, G., Tzou, W. S., Chiang, C. E., Williams, B., Reviewers:, Dan, G. A., Gorenek, B., Fauchier, L., Savelieva, I., … Field, M. (2017). Hypertension and cardiac arrhythmias: a consensus document from the European Heart Rhythm Association (EHRA) and ESC Council on Hypertension, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE). Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and

cardiac cellular electrophysiology of the European Society of Cardiology, 19(6), 891–911. https://doi.org/10.1093/europace/eux091

Lip, GY.2013. Stroke and bleeding risk assessment in atrial fibrillation: when, how, and why? Eur Heart J. 34(14):1041-1049.

LoBiondo-Wood, G., & Haber, J. (2013). 'LEARNINGAOUTCOMES. Nursing Research: Methods and Critical Appraisal for Evidence-Based Practice, 199.

Lowres N, Giskes K, Hespe C, Freedman B. Reducing Stroke Risk in Atrial Fibrillation: Adherence to Guidelines Has Improved, but Patient Persistence with Anticoagulant Therapy Remains Suboptimal. Korean Circ J. 2019 Oct;49(10):883-907. doi: 10.4070/kcj.2019.0234. PMID: 31535493; PMCID: PMC6753021.

Lowry KP, Dudley TK, Oddone EZ, Bosworth HB. 2005.Intentional and unintentional nonadherence to antihypertensive medication. Ann Pharmacother. 39(7–8):1198–1203.

Mack, N. (2005). Qualitative research methods: A data collector's field guide.

Mackey K, Parchman ML, Leykum LK, Lanham HJ, Noël PH, Zeber JE. Impact of the Chronic Care Model on medication adherence when patients perceive cost as a barrier. Prim Care Diabetes. 2012 Jul;6(2):137-42. doi: 10.1016/j.pcd.2011.12.004. Epub 2012 Jan 20. PMID: 22264426; PMCID: PMC3558316.

Maeda, U., Shen, B. J., Schwarz, E. R., Farrell, K. A., & Mallon, S. (2013). Self-efficacy mediates the associations of social support and depression with treatment adherence in heart failure patients. International journal of behavioral medicine, 20(1), 88-96.

Malik, A. H., Yandrapalli, S., Aronow, W. S., Panza, J. A., & Cooper, H. A. (2019). Meta-Analysis of Direct-Acting Oral Anticoagulants Compared With Warfarin in Patients >75 Years of Age. The American journal of cardiology, 123(12), 2051–2057. https://doi.org/10.1016/j.amjcard.2019.02.060

Manzoor, B. S., Lee, T. A., Sharp, L. K., Walton, S. M., Galanter, W. L., & Nutescu, E. A. (2017). Real-World Adherence and Persistence with Direct Oral Anticoagulants in Adults with Atrial Fibrillation. Pharmacotherapy, 37(10), 1221–1230. https://doi.org/10.1002/phar.1989

Morillo, C. A., Banerjee, A., Perel, P., Wood, D., & Jouven, X. (2017). Atrial fibrillation: the current epidemic. Journal of geriatric cardiology : JGC, 14(3), 195–203. https://doi.org/10.11909/j.issn.1671-5411.2017.03.011

Markides, V., & Schilling, R. J. (2003). Atrial fibrillation: classification, pathophysiology, mechanisms and drug treatment. Heart (British Cardiac Society), 89(8), 939–943. https://doi.org/10.1136/heart.89.8.939

Martínez ,C., Lanas,F., Radaideh ,G., Kharabsheh,S., Lambelet , M., Viaud,M., Ziadeh,N., Turpie,A.2018. XANTUS-EL: A real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation in Eastern Europe, Middle East, Africa and Latin America. The Egyptian Heart Journal 70:4 :307-313

Masadeh, Mousa. (2012). Linking Philosophy, Methodology, and Methods: Toward Mixed Model Design in the Hospitality Industry. European Journal of Social Sciences. 28.

Matalqah, L., Radaideh, K. M., Sulaiman, S. A. S., Hassali, M. A., & Abdul Kader, M. A. S. (2013). Relationship between patients' warfarin knowledge and anticoagulation control: results of a validated tool in Malaysia. J Pharm Biomed Sci, 30(30), 967-974.

Mathers CD, Fat DM, Inoue M, Rao C, Lopez AD. 2005. Counting the dead and what they died from: an assessment of the global status of cause of death data. Bull World Health Organ. ;83(3):171-7.

Mavrakanas, T. A., Samer, C. F., Nessim, S. J., Frisch, G., & Lipman, M. L. (2017). Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients. Journal of the American Society of Nephrology : JASN, 28(7), 2241–2248. https://doi.org/10.1681/ASN.2016090980

Mayet, A. Y. (2016). Patient adherence to warfarin therapy and its impact on anticoagulation control. Saudi pharmaceutical journal, 24(1), 29-34.

Mayet, AY, Alsaqer AI, Alhammad AM, Al-Omar HA.2018.Rivaroxaban prescribing in a Saudi tertiary care teaching hospital.Saudi Pharm J. 2018 Sep;26(6):775-779

McCullough, K. B., Formea, C. M., Berg, K. D., Burzynski, J. A., Cunningham, J. L., Ou, N. N., ... & Nicholson, W. T. (2011). Assessment of the pharmacogenomics educational needs of pharmacists. American journal of pharmaceutical education, 75(3).

McGrath, C., Palmgren, P. J., & Liljedahl, M. (2019). Twelve tips for conducting qualitative research interviews. Medical teacher, 41(9), 1002-1006.

McHorney, C. A., Ashton, V., Laliberté, F., Germain, G., Wynant, W., Crivera, C., Schein, J. R., Lefebvre, P., & Peterson, E. D. (2017). Adherence to Rivaroxaban Compared with Other Oral Anticoagulant Agents Among Patients with Nonvalvular Atrial Fibrillation. Journal of managed care & specialty pharmacy, 23(9), 980–988. https://doi.org/10.18553/jmcp.2017.23.9.980

McManus, D. D., Rienstra, M., & Benjamin, E. J. (2012). An update on the prognosis of patients with atrial fibrillation. Circulation, 126(10), e143–e146. http://doi:10.1161/CIRCULATIONAHA.112.129759

McManus, D. D., Saczynski, J. S., Ward, J. A., Jaggi, K., Bourrell, P., Darling, C., & Goldberg, R. J. (2012). The Relationship Between Atrial Fibrillation and Chronic Kidney Disease : Epidemiologic and Pathophysiologic Considerations for a Dual Epidemic. Journal of atrial fibrillation, 5(1), 442. https://doi.org/10.4022/jafib.442

Mearns ES, White CM, Kohn CG, et al. 2014.Quality of vitamin K antagonist control and outcomes in atrial fibrillation patients: a meta-analysis and meta-regression. *Thromb J.*24:12–14.

Meyer, G., Vicaut, E., Danays, T., Agnelli, G., Becattini, C., Beyer-Westendorf, J., Bluhmki, E., Bouvaist, H., Brenner, B., Couturaud, F., Dellas, C., Empen, K., Franca, A., Galiè, N., Geibel, A., Goldhaber, S. Z., Jimenez, D., Kozak, M., Kupatt, C., Kucher, N., … PEITHO Investigators (2014). Fibrinolysis for patients with intermediate-risk pulmonary embolism. The New England journal of medicine, 370(15), 1402–1411. https://doi.org/10.1056/NEJMoa1302097

Miller, N. H., Hill, M., Kottke, T., & Ockene, I. S. (1997). The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. Circulation, 95(4), 1085–1090. https://doi.org/10.1161/01.cir.95.4.1085

Miller, W. R. and Rollnick, S. (1991) Motivational interviewing: Preparing people to change addictive behavior. New York: Guilford Press, ISBN 0–89862–566–1

Miyasaka, Y., Barnes, M. E., Gersh, B. J., Cha, S. S., Bailey, K. R., Abhayaratna, W. P., Seward, J. B., & Tsang, T. S. (2006). Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. Circulation, 114(2), 119–125. https://doi.org/10.1161/CIRCULATIONAHA.105.595140

Modi, A. C., Ingerski, L. M., Rausch, J. R., Glauser, T. A., & Drotar, D. (2012). White coat adherence over the first year of therapy in pediatric epilepsy. The Journal of pediatrics, 161(4), 695–9.e1. https://doi.org/10.1016/j.jpeds.2012.03.059

Moral, R. R., Torres, L. A., Ortega, L. P., Larumbe, M. C., Villalobos, A. R., García, J. A., Rejano, J. M., & Collaborative Group ATEM-AP Study (2015). Effectiveness of motivational interviewing to improve therapeutic

adherence in patients over 65 years old with chronic diseases: A cluster randomized clinical trial in primary care. Patient education and counseling, 98(8), 977–983. https://doi.org/10.1016/j.pec.2015.03.008

Morisky, D. E., Ang, A., Krousel-Wood, M., & Ward, H. J. (2008). Predictive validity of a medication adherence measure in an outpatient setting. Journal of clinical hypertension (Greenwich, Conn.), 10(5), 348–354. https://doi.org/10.1111/j.1751-7176.2008.07572.x

Morisky, D. E., Green, L. W., & Levine, D. M. (1986). Concurrent and predictive validity of a self-reported measure of medication adherence. Medical care, 24(1), 67–74. https://doi.org/10.1097/00005650-198601000-00007

Morris LS, Schulz RM. Medication compliance: the patient's perspective.1993. Clin Ther 15:593– 606

Moser, A., & Korstjens, I. (2018). Series: Practical guidance to qualitative research. Part 3: Sampling, data collection and analysis. The European journal of general practice, 24(1), 9–18. https://doi.org/10.1080/13814788.2017.1375091

Moxham, L. 2012. Nurse Education, Research and Evidence-Based Practice. In A. Berman, S. J. Snyder, T. Levett-Jones, M. Hales, N.

Murray, C. J., Abbafati, C., Abbas, K. M., Abbasi, M., Abbasi-Kangevari, M., Abd-Allah, F., ... & Nagaraja, S. B. (2020). Five insights from the global burden of disease study 2019. The Lancet, 396(10258), 1135-1159.

Naderi, S. H., Bestwick, J. P., & Wald, D. S. (2012). Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. The American journal of medicine, 125(9), 882–7.e1. https://doi.org/10.1016/j.amjmed.2011.12.013

Naringrekar, H., MD,Charles,J., and. Rodgers. 2019. It's Not All Deep Vein Thrombosis: Sonography of the Painful Lower Extremity With Multimodality Correlation. J.Ult. Med.38:4:1075-1089

National Institute for Health and Care Excellence. 2021. Atrial fibrillation: diagnosis and management. NICE guideline [NG196].

Naringrekar, H., Sun, J., Ko, C., & Rodgers, S. K. (2019). It's not all deep vein thrombosis: Sonography of the painful lower extremity with multimodality correlation. Journal of Ultrasound in Medicine, 38(4), 1075-1089.

Ncama, B. P., McInerney, P. A., Bhengu, B. R., Corless, I. B., Wantland, D. J., Nicholas, P. K., ... & Davis, S. M. (2008). Social support and medication adherence in HIV disease in KwaZulu-Natal, South Africa. International journal of nursing studies, 45(12), 1757-1763.

Nguyen, T. M., La Caze, A., & Cottrell, N. (2014). What are validated self-report adherence scales really measuring?: a systematic review. British journal of clinical pharmacology, 77(3), 427–445. https://doi.org/10.1111/bcp.12194

Obamiro, K. O., Chalmers, L., Lee, K., Bereznicki, B. J., & Bereznicki, L. (2018). Anticoagulation knowledge in patients with atrial fibrillation: An Australian survey. International journal of clinical practice, 72(3), e13072. https://doi.org/10.1111/ijcp.13072

Obamiro, K. O., Chalmers, L., Lee, K., Bereznicki, B. J., & Bereznicki, L. (2018). Anticoagulation knowledge in patients with atrial fibrillation: An Australian survey. International journal of clinical practice, 72(3), e13072. https://doi.org/10.1111/ijcp.13072

O'Brien, E. C., Simon, D. N., Thomas, L. E., Hylek, E. M., Gersh, B. J., Ansell, J. E., Kowey, P. R., Mahaffey, K. W., Chang, P., Fonarow, G. C., Pencina, M. J., Piccini, J. P., & Peterson, E. D. (2015). The ORBIT bleeding

score: a simple bedside score to assess bleeding risk in atrial fibrillation. European heart journal, 36(46), 3258–3264. https://doi.org/10.1093/eurheartj/ehv476

Oldgren, J., Alings, M., Darius, H., Diener, H. C., Eikelboom, J., Ezekowitz, M. D., Kamensky, G., Reilly, P. A., Yang, S., Yusuf, S., Wallentin, L., Connolly, S. J., & RE-LY Investigators (2011). Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the CHADS2 score: a subgroup analysis of the RE-LY trial. Annals of internal medicine, 155(10), 660–W204. https://doi.org/10.7326/0003-4819-155-10-201111150-00004

Olesen, J. B., Lip, G. Y., Hansen, M. L., Hansen, P. R., Tolstrup, J. S., Lindhardsen, J., Selmer, C., Ahlehoff, O., Olsen, A. M., Gislason, G. H., & Torp-Pedersen, C. (2011). Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ (Clinical research ed.), 342, d124. https://doi.org/10.1136/bmj.d124

Orlandi, M., Dover, D. C., Sandhu, R. K., Hawkins, N. M., Kaul, P., & McAlister, F. A. (2022). The Introduction of Direct Oral Anticoagulants Has Not Resolved Treatment Gaps for Frail Patients With Nonvalvular Atrial Fibrillation. The Canadian journal of cardiology, 38(1), 77–84. https://doi.org/10.1016/j.cjca.2021.09.021

Osterberg, L., & Blaschke, T. (2005). Adherence to medication. The New England journal of medicine, 353(5), 487–497. https://doi.org/10.1056/NEJMra050100

Palacio, A., Garay, D., Langer, B., Taylor, J., Wood, B. A., & Tamariz, L. (2016). Motivational Interviewing Improves Medication Adherence: a Systematic Review and Meta-analysis. Journal of general internal medicine, 31(8), 929–940. https://doi.org/10.1007/s11606-016-3685-3

Pannucci, C. J., & Wilkins, E. G. (2010). Identifying and avoiding bias in research. Plastic and reconstructive surgery, 126(2), 619–625. https://doi.org/10.1097/PRS.0b013e3181de24bc

Parker, K., & Thachil, J. (2018). The use of direct oral anticoagulants in chronic kidney disease. British journal of haematology, 183(2), 170–184. https://doi.org/10.1111/bjh.15564

Patel MR, Mahaffey KW, Garg.2013. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–891. revisited: a population-based study. Stroke.; 44(11):3103-3108.

Patton, M. Q. (2002). Qualitative research & evaluation methods. sage.

Peltzer, K. (2004). Health beliefs and prescription medication compliance among diagnosed hypertension clinic attenders in a rural South African Hospital. Curationis, 27(3), 15-23.

Peters, S., & Woodward, M. (2019). Established and novel risk factors for atrial fibrillation in women compared with men. Heart (British Cardiac Society), 105(3), 226–234. https://doi.org/10.1136/heartjnl-2018-313630

Pring, R. (2000). The 'false dualism'of educational research. Journal of Philosophy of Education, 34(2), 247-260.

Polit, D.F. and Beck, C.T. (2017) Nursing Research: Generating and Assessing Evidence for Nursing Practice. 10th Edition, Wolters Kluwer Health, Philadelphia, 784 p. https://doi.org/10.1016/j.iccn.2015.01.005

Polit, D.F. and Hungler, B.P. 2013. Essentials of Nursing Research: Methods, Appraisal, and Utilization (8th Edition ed.). Philadelphia: Wolters Kluwer/Lippincott Williams and Wilkins

Pollack, A., Kontorovich, A. R., Fuster, V., & Dec, G. W. (2015). Viral myocarditis--diagnosis, treatment options, and current controversies. Nature reviews. Cardiology, 12(11), 670–680. https://doi.org/10.1038/nrcardio.2015.108

Pope, C., & Mays, N. (1995). Qualitative research: reaching the parts other methods cannot reach: an introduction to qualitative methods in health and health services research. bmj, 311(6996), 42-45.

Pring, R. (2000). The 'false dualism'of educational research. Journal of Philosophy of Education, 34(2), 247-260.

Raskob, G. E., Angchaisuksiri, P., Blanco, A. N., Buller, H., Gallus, A., Hunt, B. J., Hylek, E. M., Kakkar, A., Konstantinides, S. V., McCumber, M., Ozaki, Y., Wendelboe, A., Weitz, J. I., & ISTH Steering Committee for World Thrombosis Day (2014). Thrombosis: a major contributor to global disease burden. Arteriosclerosis, thrombosis, and vascular biology, 34(11), 2363–2371. https://doi.org/10.1161/ATVBAHA.114.304488

Risser, J., Jacobson, T. A., & Kripalani, S. 2007. Development and psychometric evaluation of the Self-efficacy for Appropriate Medication Use Scale (SEAMS) in low-literacy patients with chronic disease. Journal of nursing measurement, 15(3), 203–219. https://doi.org/10.1891/106137407783095757

Roaeid, R. B., & Kablan, A. A. (2007). Profile of diabetes health care at Benghazi Diabetes Centre, Libyan Arab Jamahiriya. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit, 13(1), 168–176.

Robson, C., & McCartan, K. (2016). Real World Research. Wiley

Rodwin, B. A., Salami, J. A., Spatz, E. S., Valero-Elizondo, J., Virani, S. S., Blankstein, R., Blaha, M. J., Nasir, K., & Desai, N. R. (2019). Variation in the Use of Warfarin and Direct Oral Anticoagulants in Atrial Fibrillation and Associated Cost Implications. The American journal of medicine, 132(1), 61–70.e1. https://doi.org/10.1016/j.amjmed.2018.09.026

Roebuck, M. C., Liberman, J. N., Gemmill-Toyama, M., & Brennan, T. A. (2011). Medication adherence leads to lower health care use and costs despite increased drug spending. Health affairs (Project Hope), 30(1), 91–99. https://doi.org/10.1377/hlthaff.2009.1087

Roumie, C. L., Elasy, T. A., Greevy, R., Griffin, M. R., Liu, X., Stone, W. J., Wallston, K. A., Dittus, R. S., Alvarez, V., Cobb, J., & Speroff, T. (2006). Improving blood pressure control through provider education, provider alerts, and patient education: a cluster randomized trial. Annals of internal medicine, 145(3), 165–175. https://doi.org/10.7326/0003-4819-145-3-200608010-00004

Roter, D. L., & Hall, J. A. (1992). Doctors talking with patients/patients talking with doctors: Improving communication in medical visits. Auburn House/Greenwood Publishing Group.

Rubak, S., Sandbaek, A., Lauritzen, T., & Christensen, B. (2005). Motivational interviewing: a systematic review and meta-analysis. The British journal of general practice : the journal of the Royal College of General Practitioners, 55(513), 305–312.

Sabaté, E.2003. Adherence to long-term therapies. World Health Organization: Establishing the domains of non-adherence used to categorize research interventions to improve adherence. P.1-209

Salam,A., AlBinali,H., Al-Mulla, MB,A., Singh,R., and JAl Suwaidi, J.2012. Secular Trends, Treatments, and Outcomes of Middle Eastern Arab and South Asian Patients Hospitalized With Atrial Fibrillation: Insights From a 20-Year Registry in Qatar (1991-2010). Angiology 64: 7:498-504

Salmasi, S., Loewen, P. S., Tandun, R., Andrade, J. G., & De Vera, M. A. (2020). Adherence to oral anticoagulants among patients with atrial fibrillation: a systematic review and meta-analysis of observational studies. BMJ open, 10(4), e034778.

Santos, J., António, N., Rocha, M., & Fortuna, A. (2020). Impact of direct oral anticoagulant off-label doses on clinical outcomes of atrial fibrillation patients: A systematic review. British journal of clinical pharmacology, 86(3), 533–547. https://doi.org/10.1111/bcp.14127

Seifi, S., Khatony, A., Moradi, G. et al. 2018. Accuracy of pulse oximetry in detection of oxygen saturation in patients admitted to the intensive care unit of heart surgery: comparison of finger, toe, forehead and earlobe probes. BMC Nurs 17, 15. https://doi.org/10.1186/s12912-018-0283-1

Schillinger, D., Piette, J., Grumbach, K., Wang, F., Wilson, C., Daher, C., Leong-Grotz, K., Castro, C., & Bindman, A. B. (2003). Closing the loop: physician communication with diabetic patients who have low health literacy. Archives of internal medicine, 163(1), 83–90. https://doi.org/10.1001/archinte.163.1.83

Schmaier, A. A., Ambesh, P., & Campia, U. 2018. Venous thromboembolism and cancer. *Current cardiology reports*, *20*, 1-10.

Schulman, B. Shortt, M. Robinson, M. and Eikelboom, M. 2013. Adherence to anticoagulation treatment with dabigatran in a real world setting, Thromb. Haemost. 11

Schulman S. (2014). New oral anticoagulant agents - general features and outcomes in subsets of patients. Thrombosis and haemostasis, 111(4), 575–582. https://doi.org/10.1160/TH13-09-0803

Shankari, G., Ng, S. C., Goh, S. Y., Woon, F. P., Doshi, K., Wong, P. S., Fan, Q., Tan, I. F., Narasimhalu, K., & De Silva, D. A. (2020). Modifiable Factors Associated with Non-Adherence to Secondary Ischaemic Stroke Prevention Strategies. Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association, 29(12), 105395. https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105395

Shehab,A., Elnour,A., Adel Sadik, A., Abu Mandil, M., AlShamsi, A, Al Suwaidi, A., Bhagavathula, S., Erkekoglu, P., Hamad, F., Nuaimi, S.2015. Clinical utility of dabigatran in Central United Arab Emirates. Saudi Med J 2015; 36 :11:179-189

Shikiar R, Halpern M, McGann M, Seidlin M.1999. Patient satisfaction with treatment of otitis externa: development of an instrument and its relations to clinical outcomes. Clin Ther ;21:1091–104.

Shilbayeh SAR, Alyahya SA, Alshammari NH, Almutairi WA, Shaheen E.2018. Treatment Satisfaction Questionnaire for Medication: Validation of the Translated Arabic Version among Patients Undergoing Warfarin Therapy in Saudi Arabia.Value Health Reg Issues. 2018 Sep;16:14-21.

Shilbayeh,S., Almutairi,W., Alyahya,S., Alshammari,N. Shaheen,E., Adam,A.2018a. Validation of knowledge and adherence assessment tools among patients on warfarin therapy in a Saudi hospital anticoagulant clinic. International J. of Clin. Pharm. 40:56–66

Shiovitz-Ezra, S., Leitsch, S., Graber, J., & Karraker, A. (2009). Quality of life and psychological health indicators in the national social life, health, and aging project. Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 64(suppl_1), i30-i37.

Shore S, Carey EP, Turakhia MP, Jackevicius CA, Cunningham F, Pilote L, Bradley SM, Maddox TM, Grunwald GK, Baron AE. 2014. Adherence to dabigatran therapy and longitudinal patient outcomes: insights from the veterans health administration. Am Heart J. ;167:810–817. 5.

Siddoway L. A. (2003). Amiodarone: guidelines for use and monitoring. American family physician, 68(11), 2189–2196.

Siddoway L. A. (2003). Amiodarone: guidelines for use and monitoring. American family physician, 68(11), 2189–2196.

Silveira, P. C., Ip, I. K., Goldhaber, S. Z., Piazza, G., Benson, C. B., & Khorasani, R. (2015). Performance of Wells Score for Deep Vein Thrombosis in the Inpatient Setting. JAMA internal medicine, 175(7), 1112–1117. https://doi.org/10.1001/jamainternmed.2015.1687

Smith, F. (2002). Research Methods in Pharmacy Practice, Pharmaceutical Press.

Simmonds, S. (1974). Health Education Monographs, Volume: 2 issue: 1_suppl, page(s): 1-10 Issue published: March 1,

Sinnott, C., Mc Hugh, S., Browne, J., & Bradley, C. (2013). GPs' perspectives on the management of patients with multimorbidity: systematic review and synthesis of qualitative research. BMJ open, 3(9), e003610. https://doi.org/10.1136/bmjopen-2013-003610

Sokol, M. C., McGuigan, K. A., Verbrugge, R. R., & Epstein, R. S. (2005). Impact of medication adherence on hospitalization risk and healthcare cost. Medical care, 43(6), 521–530. https://doi.org/10.1097/01.mlr.0000163641.86870.af

Spinewine, A., Schmader, K. E., Barber, N., Hughes, C., Lapane, K. L., Swine, C., & Hanlon, J. T. (2007). Appropriate prescribing in elderly people: how well can it be measured and optimised?. The Lancet, 370(9582), 173-184.

Spyropoulos, A. C., & Douketis, J. D. (2012). How I treat anticoagulated patients undergoing an elective procedure or surgery. *Blood*, *120*(15), 2954–2962. https://doi.org/10.1182/blood-2012-06-415943

Starks, H., & Trinidad, S. B. (2007). Choose your method: a comparison of phenomenology, discourse analysis, and grounded theory. Qualitative health research, 17(10), 1372–1380. https://doi.org/10.1177/1049732307307031

Steiner, J. F., & Earnest, M. A. (2000). The language of medication-taking. Annals of internal medicine, 132(11), 926–930. https://doi.org/10.7326/0003-4819-132-11-200006060-00026

Stirratt, M. J., Dunbar-Jacob, J., Crane, H. M., Simoni, J. M., Czajkowski, S., Hilliard, M. E., Aikens, J. E., Hunter, C. M., Velligan, D. I., Huntley, K., Ogedegbe, G., Rand, C. S., Schron, E., & Nilsen, W. J. (2015). Self-report measures of medication adherence behavior: recommendations on optimal use. Translational behavioral medicine, 5(4), 470–482. https://doi.org/10.1007/s13142-015-0315-2

Straka, R. J., Fish, J. T., Benson, S. R., & Suh, J. T. (1997). Patient self-reporting of compliance does not correspond with electronic monitoring: an evaluation using isosorbide dinitrate as a model drug. Pharmacotherapy, 17(1), 126–132.

Svarstad, B. L., Chewning, B. A., Sleath, B. L., & Claesson, C. (1999). The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. Patient education and counseling, 37(2), 113–124. https://doi.org/10.1016/s0738-3991(98)00107-4

Swanson, R. A., & Chermack, T. J. (2013). Theory building in applied disciplines. Berrett-Koehler Publishers.p122

Tan, x., Patel, i., Chang,J.(2014). Review of the four item Morisky Medication Adherence Scale (MMAS-4) and eight item Morisky Medication Adherence Scale (MMAS-8),Innovations in Pharmcy, 5:3 , 1-8

Tang EO, Lai CS, Lee KK, Wong RS, Cheng G, Chan TY.2003. Relationship between patients' warfarin knowledge and anticoagulation control. *Ann Pharmacother*, 37, 34-39.

Tommelein, E., Mehuys, E., Van Hees, T., Adriaens, E., Van Bortel, L., Christiaens, T., Van Tongelen, I., Remon, J. P., Boussery, K., & Brusselle, G. (2014). Effectiveness of pharmaceutical care for patients with chronic obstructive pulmonary disease (PHARMACOP): a randomized controlled trial. British journal of clinical pharmacology, 77(5), 756–766. https://doi.org/10.1111/bcp.12242

Tsai, S.C. Erickson, J. Yang, A.S. Harada, B.K. Solow, H.C. Lew, 2013. Adherence, persistence and switching patterns of dabigatran etexilate, Am. J. Manag. Care 19

van de Steeg, N., Sielk, M., Pentzek, M., Bakx, C., & Altiner, A. (2009). Drug-adherence questionnaires not valid for patients taking blood-pressure-lowering drugs in a primary health care setting. Journal of evaluation in clinical practice, 15(3), 468–472. https://doi.org/10.1111/j.1365-2753.2008.01038.x

van Dulmen S, van Bijnen E. What makes them (not) talk about proper medication use with their patients? An analysis of the determinants of GP communication using reflective practice. Int J Pers Cent Med. 2011;1: 27–34.

Velligan, D. I., Wang, M., Diamond, P., Glahn, D. C., Castillo, D., Bendle, S., Lam, Y. W., Ereshefsky, L., & Miller, A. L. (2007). Relationships among subjective and objective measures of adherence to oral antipsychotic medications. Psychiatric services (Washington, D.C.), 58(9), 1187–1192. https://doi.org/10.1176/ps.2007.58.9.1187

Velligan, D. I., Wang, M., Diamond, P., Glahn, D. C., Castillo, D., Bendle, S., Lam, Y. W., Ereshefsky, L., & Miller, A. L. (2007). Relationships among subjective and objective measures of adherence to oral antipsychotic medications. Psychiatric services (Washington, D.C.), 58(9), 1187–1192. https://doi.org/10.1176/ps.2007.58.9.1187

Vermeire, E., Hearnshaw, H., Van Royen, P., & Denekens, J. (2001). Patient adherence to treatment: three decades of research. A comprehensive review. Journal of clinical pharmacy and therapeutics, 26(5), 331–342. https://doi.org/10.1046/j.1365-2710.2001.00363.x

Vermond, R. A., Geelhoed, B., Verweij, N., Tieleman, R. G., Van der Harst, P., Hillege, H. L., Van Gilst, W. H., Van Gelder, I. C., & Rienstra, M. (2015). Incidence of Atrial Fibrillation and Relationship With Cardiovascular Events, Heart Failure, and Mortality: A Community-Based Study From the Netherlands. Journal of the American College of Cardiology, 66(9), 1000–1007. https://doi.org/10.1016/j.jacc.2015.06.1314

Vinogradova, Y., Coupland, C., Hill, T., & Hippisley-Cox, J. (2018). Risks and benefits of direct oral anticoagulants versus warfarin in a real world setting: cohort study in primary care. *BMJ (Clinical research ed.)*, *362*, k2505. https://doi.org/10.1136/bmj.k2505

Vik, S. A., Maxwell, C. J., & Hogan, D. B. (2004). Measurement, correlates, and health outcomes of medication adherence among seniors. The Annals of pharmacotherapy, 38(2), 303–312. https://doi.org/10.1345/aph.1D252

von Wagner, C., Semmler, C., Good, A., & Wardle, J. (2009). Health literacy and self-efficacy for participating in colorectal cancer screening: The role of information processing. Patient education and counseling, 75(3), 352–357. https://doi.org/10.1016/j.pec.2009.03.015

Wang X, Wu Z (2007) Factors associated with adherence to antiretroviral therapy among HIV/AIDS patients in rural China. AIDS 21: S149–S155.

Weaver M, Markson PD, Frederick MD, Berger M. Issues in the management of treatment satisfaction. Am J Manag Care 1997;3:579–94.

Weaver M, Patrick DL, Markson LE, Martin D, Frederic I,Berger M. Issues in the measurement of satisfaction with treatment. Am J Manag Care 1997;3:579–94.

White, L. and Millar, R.B. (2014). Quantitative Approaches. In V. Wright-St Clair, D. Reid, S. Shaw and J. Ramsbotham (Eds.), Evidencebased Health Practice. South Melbourne: Oxford University Press.

Wiecek E, Torres-Robles A, Cutler R, Benrimoj S, Garcia-Cardenas V.2020. Impact of a Multicomponent Digital Therapeutic Mobile App on Medication Adherence in Patients with Chronic Conditions: Retrospective Analysis J Med Internet Res ;22(8): e17834. DOI: 10.2196/17834

Wong, G. 2014. Research Questions. In V. Wright-St Clair, D. Reid, S. Shaw and J. Ramsbotham (Eds.), Evidence-based Health Practice. South Melbourne: Oxford University Press.

World Health Organization. (2003). Adherence to long-term therapies: evidence for action / [edited by Eduardo Sabaté]. World Health Organization .P.1-209

Wroe A. L. (2002). Intentional and unintentional nonadherence: a study of decision making. Journal of behavioral medicine, 25(4), 355–372. https://doi.org/10.1023/a:1015866415552

Yang SY, Kang DW, Nam JH, Choi EK, Lee EK, Shin JY, Kwon SH. Adherence is an optimal factor for maximizing the effective and safe use of oral anticoagulants in patients with atrial fibrillation. Sci Rep. 2022 Mar 1;12(1):3413. doi: 10.1038/s41598-022-07316-y. PMID: 35233055; PMCID: PMC8888574.

Yao, X., Abraham, N. S., Alexander, G. C., Crown, W., Montori, V. M., Sangaralingham, L. R., Gersh, B. J., Shah, N. D., & Noseworthy, P. A. (2016). Effect of Adherence to Oral Anticoagulants on Risk of Stroke and Major Bleeding Among Patients With Atrial Fibrillation. Journal of the American Heart Association, 5(2), e003074. https://doi.org/10.1161/JAHA.115.003074

Youssef, R. M., & Moubarak, I. I. (2002). Patterns and determinants of treatment compliance among hypertensive patients. Eastern Mediterranean health journal = La revue de sante de la Mediterranee orientale = al-Majallah al-sihhiyah li-sharq al-mutawassit, 8(4-5), 579–592.

Zhang, J., Cai, J., Liu, S., & Zhang, X. (2018). Value of Dual-energy Lung Perfusion Imaging Using a Dual-source CT System for the Pulmonary Embolism. Open life sciences, 13, 107–111. https://doi.org/10.1515/biol-2018-0015

Zolnierek KB, Dimatteo MR.(2009). Physician communication 2. and patient adherence to treatment: a meta-analysis. Med Care.;47(8):826–34

Zubaid, M., Saad,S., Ridha,M., Nair,K.Rashed,W., Alhamdan,R., Alenezi,F., Maghami,M., and Sadek,A.2013. Quality of Anticoagulation with Warfarin Across Kuwait. Hellenic J Cardiol ; 54: 102-106

Zubaid,M., Rashed,W., Alsheikh-Ali, A., Al-Zakwani, I., AlMahmeed, W., Shehab,A., Sulaiman, K., Al Qudaimi, A., Asaad,N., and Amin,H. 2015. Management and 1-Year Outcomes of Patients With Atrial Fibrillation in the Middle East: Gulf Survey of Atrial Fibrillation Events. Angiology , 66:5: 464-471.

Appendix I

Ethical Approvals of University of Birmingham, and

Ethics Committee in the site of the study (Prince Sultan Cardiac Centre PSCC), Saudi Arabia

Ethical Approval (University of Birmingham)

From: Samantha Waldron (Research Support Group)
Sent: 25 June 2019 09:05
To: Abdel Medani (DPharm (MSc entry) PT); Zahraa Jalal (Pharmacy and Therapeutics)
Subject: Application for Ethical Review ERN_19-0689

Dear Dr. Medani & Dr. Jalal,

Re: "Measuring Adherence and assessing Patients' beliefs about their Oral Anticoagulants in AlHassa Area"
Application for Ethical Review ERN_19-0689

Thank you for your application for ethical review for the above project, which was reviewed by the Science, Technology, Engineering and Mathematics Ethical Review Committee.

On behalf of the Committee, I confirm that this study now has full ethical approval.

I would like to remind you that any substantive changes to the nature of the study as described in the Application for Ethical Review, and/or any adverse events occurring during the study should be promptly brought to the Committee's attention by the Principal Investigator and may necessitate further ethical review.

Please also ensure that the relevant requirements within the University's Code of Practice for Research and the information and guidance provided on the University's ethics webpages (available at https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Links-and-Resources.aspx) are adhered to and referred to in any future applications for ethical review. It is now a requirement on the revised application form (https://intranet.birmingham.ac.uk/finance/accounting/Research-Support-Group/Research-Ethics/Ethical-Review-Forms.aspx) to confirm that this guidance has been consulted and is understood, and that it has been taken into account when completing your application for ethical review.

Please be aware that whilst Health and Safety (H&S) issues may be considered during the ethical review process, you are still required to follow the University's guidance on H&S and to ensure that H&S risk assessments have been carried out as appropriate. For further information about this, please contact your School H&S representative or the University's H&S Unit at healthandsafety@contacts.bham.ac.uk<mailto:healthandsafety@contacts.bham.ac.uk>.

Kind regards,

Ms Sam Waldron
Deputy Research Ethics Officer
Research Support Group
C Block Dome (room 132)
Aston Webb Building
University of Birmingham
Edgbaston B15 2TT
Tel: 0121 414 8101
Email: s.m.waldron@bham.ac.uk<mailto:s.m.waldron@bham.ac.uk>

Web: https://intranet.birmingham.ac.uk/finance/RSS/Research-Support-Group/Research-Ethics/Research-Integrity-at-the-University-of-Birmingham.aspx

Ethical Approval (site of the study)

IRB Registration Number with KACST, KSA: H-05-HS-080
Date: **17/03/2019**
IRB Meeting No: 011
Project Type: Internal [✓] External [ ]
Category of approval: Full [✓] Conditional [ ] Rejected [ ]

Dear: Dr. AbdelRaahman Medani

I'm please to inform you that your study titled: **Evaluation of Adherence to Oral Anti-Coagulants among patients in Alhassa area**

Was reviewed at IRB meeting No.(11) held on **13/03/2019** and was approved according to Good Clinical Practice Guidelines. The list of documents reviewed and members present are attached.

Pleased be informed that in conducting this study, your principal investigator are required to abide by the rules and regulations of the government of Saudi Arabia, the PSSCH/IRB policies and procedures, and the IHC Good Clinical Practice Guidelines.

Further, you're required to submit progress report before **13/09/2019**; it can be reviewed by IRB before lapse of approval.

The approval of this proposal will be automatically suspended on **14/09/2019** pending the acceptance of the progress report. You also need to notify the IRB as soon as possible in the case of

1. Any amendments to the project
2. Termination of the study
3. Any serious unexpected adverse events (within two working days)
4. Any event or new information that may affect the benefit /risk ratio the proposal.

Please observe the following:

1. Personal identifying data should only be collected when necessary for the research ;
2. The data collected should only be used for the proposal;
3. Data should be stored securely so that a few authorized users are permitted access to the database ;
4. Secondary disclosure of personal identifiable data is not allowed.
5. Copy of consent form should be kept in Research Subject's Medical Record and the consent process should be documented in medical record;
6. A copy of the pharmacy clearance must be kept in the medical records.

If you have any further questions feel free to contact IRB coordinator at (+966) 13-573000-Ext 4048

Email: hasa-psh-researchbio@moh.gov.sa

Sincerely yours;

Date: **17/03/2019**

Dr. Abdullah Al Abdulgader MD,DCH(I),DCH(Edinb),MRCP(UK),ABP,FRCP(UK)
Senior Consultant Congenital Cardiologist, Invasive Electrophysiologist
Chairman of IRB, Prince Sultan Cardiac Center- AlHassa,
31982, AlHassa, Saudi Arabia
Tel: +966) 13-573000-Ext 4327

Appendix II

Prospero Registration, JBI Critical Appraisal Checklists for Cross-Sectional and Cohort Studies, and Table of Data Extraction

Citation

Abdel Rahman Medani, Anthony Cox, Zahraa Jalal. Adherence to oral anticoagulants for treatment of atrial fibrillation in the Middle East: a systematic review. PROSPERO 2019 CRD42019124610 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019124610

Review question

To assess the atrial fibrillation patients' adherence to oral anticoagulants in the Middle East.

Searches

Published articles in peered reviewed journals were searched systematically. The purpose of this organized search was to obtain published research articles about oral anticoagulants and adherence of patients with AF. The search also looked at how the adherence was measured. Several databases were used in the search including PubMed, PubMed Central UK, Embase, ScienceDirect, and Google Scholars. The period of time which was covered with the searched was from 01/01/2009 to 31/12/2018. Selection of these dates is justified by the first authorisation of Dabigatran, which was the first NOAC to be used.

Types of study to be included [1 change]

Publications in the journals which included articles that studied adherence to oral anticoagulants in AF population. The designs of the selected studies are: analytical cross-sectional, descriptive cross-sectional, retrospective cohort studies, and prospective cohort studies.

Condition or domain being studied

Atrial fibrillation AF is the major type of arrhythmia that affects the human heart. It affects about 1% of the world population. The disease is a risk factor for stroke which can be a disabling condition and can cause death. The numbers of individuals affected by the condition is increasing around the world. By 2050 the total number of patients who suffer (AF) is expected to be about 16 million in the United States alone. These figures are candidate for further escalation in the forthcoming future.

Participants/population [1 change]

The study population in selected studies is patients who are diagnosed with atrial fibrillation (AF) and who are prescribed oral anticoagulants for prevention of stroke. The selected publications also include published data about adult patients, residents in the Middle East, receiving their treatment in the Middle East, and publications are English language. Data from registries from other parts of the world which included patients from the Middle East were not included. Also publications about other type of anticoagulants (e.g. parental), and publications not in English are excluded.

Intervention(s), exposure(s) [1 change]

The interventions of the selected studies are: assessing adherence of patients to prescribed oral anticoagulants, identifying reasons for non-adherence to oral anticoagulants, testing knowledge about oral anticoagulants, and assessing perception about oral anticoagulants.

Comparator(s)/control

Not applicable.

Main outcome(s) [2 changes]

Adherence to prescribed oral anticoagulants will be most important. Factors associated with adherence such levels of knowledge, and patients' beliefs about their oral anticoagulants will be investigated.

Measures of effect

JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies

Reviewer_____Date_____

Author _____Year_____Record Number _____

	Yes	No	Unclear	Not applicable
1. Were the criteria for inclusion in the sample clearly defined?	□	□	□	□
2. Were the study subjects and the setting described in detail?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were objective, standard criteria used for measurement of the condition?	□	□	□	□
5. Were confounding factors identified?	□	□	□	□
6. Were strategies to deal with confounding factors stated?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was appropriate statistical analysis used?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments (Including reason for exclusion)

_____

_____

_____

JBI CRITICAL APPRAISAL CHECKLIST FOR COHORT STUDIES

Reviewer_____

Date_____

Author_____Year_____ Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the two groups similar and recruited from the same population?	□	□	□	□
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?	□	□	□	□
3. Was the exposure measured in a valid and reliable way?	□	□	□	□
4. Were confounding factors identified?	□	□	□	□
5. Were strategies to deal with confounding factors stated?	□	□	□	□
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	□	□	□	□
7. Were the outcomes measured in a valid and reliable way?	□	□	□	□
8. Was the follow up time reported and sufficient to be long enough for outcomes to occur?	□	□	□	□
9. Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	□	□	□	□
10. Were strategies to address incomplete follow up utilized?	□	□	□	□
11. Was appropriate statistical analysis used?	□	□	□	□

Overall appraisal: Include □ Exclude □ Seek further info □

Comments (Including reason for exclusion)

Data Extraction for Systematic Review

No	Title of the study	Anticoagulant(s) studied	Tools	Outcome	Country
1	Eltayeb *et al.*,2016	warfarin	Morisky 8-item Scale & Anti-Clot Treatment Scale ACTS	- Adherence rate to warfarin - Level of satisfaction of patients with warfarin as anticoagulant - Association between adherence to warfarin and level of satisfaction with warfarin	Sudan
2	Balkhi *et al.*, 2017	Warfarin	Medication Adherence Questionnaire (MAQ) &	- Adherence rate to warfarin - Level of satisfaction with warfarin as anticoagulant - Factors that may influence adherence to warfarin - Association between adherence to warfarin and level of satisfaction with warfarin	Saudi Arabia

			Anti-Clot Treatment Scale ACTS		
3	Mayet *et al*., 2018	Rivaroxaban	Electronic medical records (EMRs) & the hospital's health information system (HIS) to evaluate the prescriptions	- Use of rivaroxaban and its prescribing patterns - indications for which rivaroxaban was recommended - compared licensed indications with reasons for prescribing rivaroxaban for patients	Saudi Arabia
4	Elbur *et al.*,2015	Warfarin	Designed questionnaire, Anti-Clot Treatment Scale	- Level of adherence to warfarin - Level of patients' satisfaction with warfarin - Association between level of adherence to warfarin and level of satisfaction with warfarin was assessed.	Saudi Arabia

			ACTS, 4-item Morisky scale		
5	Alshammari and Alhantoushi, 2018	Warfarin	Designed questionnaire	- Family physicians' knowledge about use of anticoagulants by patients varies between physicians. - Barriers to knowledge about anticoagulants were defined as lack of follow-up system and lab investigations. - Educational programs for physicians are necessary to provide follow-up system and facilitate performing to overcome barriers.	Saudi Arabia
6	Zubaid *et al*.,2013	Warfarin	Time in therapeutic range (TTR) was measured using	- Level of adherence to warfarin. - Further investigations are needed for the effect knowledge about warfarin on adherence.	Kuwait

			proportion of INR readings in therapeutic range and Rosendaal method		
7	Al-Meman & Almutairi, 2014	Dabigatran	PMR	- Experience of adverse events to dabigatran including cases of minor bleeding and stroke. - The most common adverse events to dabigatran reported by patients. - Treatment with dabigatran was considered as safe, however, high risk patients need to be evaluated before starting treatment	Saudi Arabia
8	Emren *et al*.,2018	Dabigatran, rivaroxaban, apixapan	8-item Morisky scale	- The level of adherence to NOACs - Reasons for non-adherence were identified as low levels of education, advanced age, poor knowledge about their drug and disease, - and living in rural areas with limited access to a specialist.	Turkey

9	Ababneh *et.al.,*2016	Warfarin	Designed questionnaire & 8-item Morisky scale	- Rate of adherence to warfarin. - Factors associate with adherence to warfarin. - Association between adherence to warfarin and gender, BMI, warfarin weekly dose, number of medications, or duration of warfarin use.	Jordan
10	Shilbayeh *et al.,* 2018	warfarin	Designed questionnaire & 8-item Morisky scale TTR was calculated using the Rosendaal Method	- Rate of adherence - Significant proportion of participating patients showed satisfactory knowledge of warfarin - No correlation was found between anticoagulation control and knowledge about warfarin. - No statistically significant association between adherence and level of knowledge	Saudi Arabia
11	Zubaid *et al*.,2014	Warfarin	Patients' medical records PMR	- AF patients in the Middle East are relatively young with high burden of atherosclerotic risk factors. - 10% of patients spontaneously cardioverted to sinus rhythm. - 75% of patients were managed with rate control strategy. - Amiodarone is usually used in pharmacological cardioversion. - Sinus rhythm was restored in 43% of patients when pharmacological cardioversion compared to 76% of patients when electrical cardioversion was attempted. - 40% of patients with CHADS2 score 2 were not on warfarin at discharge.	Multi centre (UAE,Kuwait,Bahrain,Qatar,Yemen).

				- Reasons for discharge without warfarin were: physician preference/decision, high bleeding risks, anticipated noncompliance, and other reasons. - INRs at 1-, 6-, and 12-month follow-up, 28% were <2, 56% were between 2 and 3, and 16% were >3.	
12	Salam *et al.*,2012	Warfarin	Patients' medical records PMR	- On admission, there was no ethnic preference in the use of anticoagulant warfarin. - On discharge Asian patients were more likely than Arabs to be prescribed warfarin. - Non treatment patients declined between 1991 to 2010.	Qatar
13	Shehab et al., 2015	dabigatran	Patients' Medical Records PMR	- The main indication for dabigatran use was AF. - Rate of bleeding with dabigatran was reported - Melena was the leading cause of bleeding - Hospitalisation rate was - Dabigatran withdrawal rate and mortality rate. - Dabigatran represents a suitable alternative to warfarin; however, it may need plasma drug monitoring.	UAE
14	Elewa *et al.*,2018	dabigatran and rivaroxaban	Patients' medical records PMR	- - Dabigatran and rivaroxaban were prescribed for inappropriate indication for the patients in the study sites. - Inappropriate dosing was found in prescriptions. - There were significantly more inappropriate dabigatran prescriptions compared to rivaroxaban in the study sites. - Logistic regression analysis confirmed that dabigatran prescribing was the only factor associated with inappropriate indications. - Factors associated with inappropriate dosing included dabigatran prescriptions and poor renal function.	Qatar

				- NOACs have been gradually replacing warfarin in Qatar; however, they are not always prescribed appropriately specially in patients on dabigatran and those with renal impairment.	
15	Anouassi et al., 2021	Apixaban, dabigatran, rivaroxaban	Patients' medical records PMR	- The mean CHA2DS2-VASc score was 3.8 ± 2.0. - 346 patients (56.9%) were on apixaban, 123 (20.2%) were on dabigatran, and 139 (22.9%) were on rivaroxaban. - Inappropriate prescribing of DOACs was associated with eGFR, major bleeding history, and history of prior stroke. - major bleeding occurred in 13 patients (11.7%) with inappropriate dosing compared with 29 patients (6.0%) with appropriate dosing. - Ischemic stroke occurred in 11 patients (9.9%) with inappropriate dosing compared with 15 patients (3.1%) with appropriate dosing ($P < 0.01$). - inappropriate DOAC underdosing is common in the Middle East, particularly with apixaban and rivaroxaban.	UAE
16	Elewa *et al.,*2016 a	Warfarin	PMR& 24-item Duke Anticoagulation Satisfaction Scale (DASS)	- Mean number of (INR) tests carried out by pharmacists. - The participants who were naıve to anticoagulation treatment reported a significantly greater satisfaction with warfarin than patients who have experience with taking the drug.	Qatar
17	Elewa *et al.*,2016	warfarin		- Pharmacist-based clinics had a superior TTR compared to those managed at the doctor-based clinics. - The % of visits within therapeutic range was significantly higher in the pharmacist's group compared to doctor's group (76.5% vs. 71.2%). - Percentage of visits with extreme sub-therapeutic INR was reduced in the pharmacist-managed clinic (5.17% vs. 7.05%).	Qatar

			TTR & no. of visits	- Pharmacist-based anticoagulation has better INR control when compared to the traditional anticoagulation management.	
18	Elewa *et al.*,2017	warfarin, dabigatran, rivaroxaban	PMR	- 84% of patients were on warfarin and 16% were on NOACs. - 78% of patients prescribed warfarin for AF, 22% was on NOACs. - For VTE patients 79% were on warfarin, 21% on NOACs. - Prescriptions of NOACs increased from 0.5% to 23% between 2011 and 2015. - Rivaroxaban prescriptions increased significantly compared to dabigatran (40.9%) in 2014 vs. (64.1%) in 2015. - 23.9% of NOACs patients were on warfarin while (16.9%) of NOACs users were switched back to warfarin. - Rapid uptake of NOACs in Qatar as they currently account for more than 20% of all anticoagulant use. - A shift towards more use of rivaroxaban compared to dabigatran since its approval in the country in 2014. - Despite NOACs adoption, warfarin remains the main anticoagulant prescribed	Qatar
19		warfarin	8-MMAS &	- INR control (TTR) measurement - Association between satisfaction with oral anticoagulant warfarin and TTR.	Saudi Arabia

	Shelbayeh et al., 2018 a		TSQ		
20	Alyousif*et. al.*,2016	warfarin	TTR calculated by Rosendaal method	- - 28.2% of the patients had a history of stroke. - 32.7% had poor anticoagulation control; TTR of <50%. Poor anticoagulation control was significantly associated with higher CHADS2 score. - TTR was not significantly different between men and women. - TTR was not associated with age or duration of anticoagulation. - There was no adequate information to assess the effect of other factors such as diet, compliance, and level of education on anticoagulation. - The overall quality of anticoagulation was not significantly different between patients with and without stroke	Saudi Arabia
21	Martínez et al., 2018	Rivaroxaban	Cohort	- middle eastern AF patients are younger than those in other parts of the world - comorbidities were not present in Middle eastern patients - Rates of major bleeding was 1% when using rivaroxaban	Muti countries Bahrain, Jordan, Lebanon, Saudi Arabia, UAE
22	El Kadri et al., 2021	Warfarin, apixaban, dabigatran	Real-World Claims Database, (PDC), High medication possion	- the mean CHA2DS2-VASc risk score was 2.4 - high medication possession ratio (MPR) was 86.8% - proportion of days covered (PDC) was 43.1% - time to first major bleeding was shorter for warfarin users than for DOACs users - longer times to first stroke/systemic embolism (SE) were observed for rivaroxaban and warfarin.	UAE

Appendix III

Patient Information, Participants' consent, Hills-Bone Scale, and patients Experience with Oral Anticoagulants questionnaire

UNIVERSITY OF BIRMINGHAM

Patient Information Sheet

My name is Abdel Rahman Medani, I am a DPharm student at the University of Birmingham, I am conducting a research about how patients are taking their oral anticoagulants, also I would like to get information about your thoughts around taking medications.

If you agree to participation in this project, I need to take some information about yourself and your medical condition(s). Also I need you to fill two questionnaires. The first questionnaire is about how you are taking your oral anticoagulants. The second one is about your opinion in taking medications.

The results of this project will help the healthcare providers identify problems that might be as barriers from improving your condition and pave the way for better use of these medications. It also gives an idea about what we can do in order to help patients with their treatment and improve their health. The information which I will get from you is confidential; no sensitive information will be requested, nobody will know what you have said. If you changed your mind about your participation you can withdraw up to two weeks after your participation facing no consequences for your withdrawal and the information will be disposed of safely. The obtained information will be kept safe and secured and nobody has access to it.

Thank you for help.

A.Medani

Doctor of Pharmacy Student

[redacted]

School of Pharmacy- College of Medical and Dental Sciences

University of Birmingham

CONSENT FORM

Patient Identification Number for this study:_____

Title of Study: Measuring Adherence and Assessing Patients' experience with Oral Anticoagulants in Eastern Saudi Arabia

Supervisor: Dr. Zahraa Jalal Researcher: Abdel Rahman Medani (DPharm student)

Please initial all boxes:

1. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

2. I understand that the study will involve the collection of data regarding how I take my oral anticoagulants and what are my thoughts about taking these drugs. ☐

3. I am aware that I might be contacted by phone by the research pharmacist if further information is needed or missing from my participation. ☐

4. I understand that the information will be kept safe and secured and nobody will gain access to it, if I decided to with draw from the study, the obtained information will be disposed of securely in a manner that will not affect my confidentiality ☐

5. I am aware that I will be asked to complete 2 questionnaires about the adherence and beliefs about Medicines ☐

6. I agree to take part in the above study. ☐

Name of Participant_____ Signature_____

Name of Person taking consent_____ Date_____

اقراربالمشاركه في بحث علمي

يهدف البحث لجمع معلومات مباشره من المرضي عن مجموعة ادوية مضادات التجلط. هذه المعلومات تتضمن: نوع الدواء , كيفية اخذ الدواء, بالاضافه لاسئله اخري تتعلق بمدي الالتزام وتاثيره علي الحاله الطبيه المراد علاجها.

مساهمتكم في هذا البحث سوف تساهم في :

التعرف علي انماط كتابة الوصفات بالنسبه لهذه المجموعه من الادويه □

تحديد المشاكل التي تواجه المرضي وقد تلعب دورا في تقليل الالتزام □

تقييم الدور الذي يلعبه الصيدلاني في اعطاء معلومات للمرضي عن هذه الادويه □

ايجاد طرق للمساهمه في تقليل فرص حدوث اثار غير مرغوب فيها عند تناول هذه الادويه □

قد نحتاج لمراجعة بعض التقارير الموجوده في ملفكم الطبي لمعرفة ما اذا كان قد تعرضتم لاثار غير مرغوبه في حال تناولكم لاحد هذه الادويه

التوقيع _____

التاريخ_____

Hill-Bone Medication Adherence Scale (HB-MAS)

No.	Item	Response: 1. All of the Time 2. Most of the Time 3. Some of the Time 4. None of the Time
1	How often do you forget to take your **oral anticoagulants (OACs)**medicine?	
2	How often do you decide NOT to take your **oral anticoagulants (OACs)**medicine?	
3	How often do you forget to get prescriptions filled?	
4	How often do you run out of **oral anticoagulants (OACs)**pills?	
5	How often do you skip your **oral anticoagulants (OACs)**medicine before you go to the doctor?	
6	How often do you miss taking your **oral anticoagulants (OACs)**pills when you feel better?	
7	How often do you miss taking your **oral anticoagulants (OACs)**pills when you feel sick?	
8	How often do you take someone else's **oral anticoagulants (OACs)**pills?	
9	How often do you miss taking your **oral anticoagulants (OACs)**pills when you are careless?	

Demographic Data

- *Age*

18-30_____ 31-60_____ > 60_____

- *Gender*

Male_____ Female_____

- *Education*

None_____ Primary school_____ Secondary school_____

University_____ Postgraduate_____

- *Comorbidities*

Hypertension_____ DM II_____ CVD_____

Other_____

- *Reason for prescribing OAC*

_____

- *Name of the OAC used by patient*

Warfarin_____ DOAC_____

- *Duration on OAC*

3 month_____ 6 month_____

1 year_____ > 1 year_____

Patients experience with taking OACs

- Do you know why you are taking OACs. Yes-------- No------
- How do you take OACs: As prescribed---------- Other----------
- Do you think you are getting benefits from taking OACs : Yes---------- No---------
- How often you miss a dose: none-------- Occasionally. --------- Regularly----------
- Do you have a problem with your OACs: Yes---------- No----------
- If ye, which one is causing the problem and stop you from taking OACs:
- Side effects---------- do not know how many tablets should I take----------
- Food interaction---------- drug interaction---------- Other----------
- Do you know your INR targe?. Yes--------- No----------
- Do you think any of the reported barriers, if any, affect your beliefs about oral anticoagulants?
- Yes---------- No----------

Appendix IV

Interview Schedule of Health Care Professionals

Schedule for Exploring Views of Healthcare Providers on patients' adherence to Oral Anticoagulants in Eastern Saudi Arabia

An interview to explore views of health care providers about patients' adherence to oral anticoagulants and patients' beliefs about these medications

- This interview will take about 30- 45 minutes to complete
- It will be distributed among physicians, pharmacists, and nurses

About this interview

Adherence to oral anticoagulants (OACs) is important for successful treatment for patients who are prescribed these drugs. Patients' beliefs about OACs influence adherence as well as the treatment outcome. In this study, we are assessing the level of adherence to OACs among patients who are receiving their treatment at the Prince Sultan Cardiac Centre. In addition, we are exploring views of both patients and professionals (physicians, pharmacists, nurses) about OACs and the problems that may affect adherence to these medications.

This interview is anonymous and participation is voluntary. The collected data will only be for the purpose of this research. .

Consent

(Please tick the circle if you are happy to participate in this interview)

I am hereby voluntarily accept to participate in this interview ◯

1. Could you please share your experience with patients on oral anticoagulants what extent do you think patients are adherent to their OACs?

Prompts:

adherence to warfarin

Adherence to NOACs/DOACs

_____
_____
_____
_____
_____

2. Do you take any measures to help patients with adherence to their OACs?

Prompts:

Do you provide any counselling for adherence?

Do you assess adherences?

Do you recommend adherence aids? Could you please describe this further?

Are there any interventions that you may implement when you find that a patient is non-adherent?

Any advice you would give to your patients?

How can patients' adherence be improved?

Do you work with a pharmacist to help patients who are non-adherent?

_____
_____
_____

3. What are the reasons that make patients non-adherent to their OACs from your experience?

Prompts:

Add a list here look up from previous literature reasons for non-adherence to OACs

side effects

- Knowledge about their disease
- Knowledge about their medications
- costs

 other

4. Could you please share factors that, as a prescriber, you consider when prescribing an OAC for patients?

Prompts:

Does this involve an informed discussion with a patient?

Could you please describe how you help a patient reach a decision about their medication choice?

Do you have a similar discussion when prescribing for warfarin?

Do you have a similar discussion when prescribing for DOACs

Any particular information you share with your patients? For example leaflets, online information etc.

5. From your experience, do you think there is any correlation between medication taking behaviour and the condition that they are taking OAC for?

Prompts:

Add the conditions that you are mentioning above in question 5.

Could you share with us reasons why medication-taking behaviour varies according to the condition?

_____

_____

Any additional thoughts/comments you would like to share with me?

_____

_____

_____

_____

_____

Thank you for your time today.