وزارة الصحة
Ministry of Health

The Saudi Center for
Evidence Based Health Care

Atrial Fibrillation

Clinical Practice Guideline on Antithrombotic Treatment of Patients with Non-valvular Atrial Fibrillation

April 2014

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Acknowledgements

We acknowledge Dr. Ali Al Khathami, Dr. Faisal Al Samadi and Dr. Ahmed Al Sagheir for their contribution to this work

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Disclosure of potential conflict of interest:
Dr. Hersi declares he has served as advisor for Boehringer Ingelheim and received speaker honoraria from Boehringer Ingelheim and Bayer.
Other co-authors have no conflict of interest to declare.

Funding:
This clinical practice guideline was funded by the Ministry of Health, Saudi Arabia.

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Executive Summary

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia. Without antithrombotic treatment, the risk of stroke in patients with atrial fibrillation is around 5% per year, but it can be as high as 10% if other risk factors are present. In recent years, important advances has been made in the management of atrial fibrillation, particularly, the introduction of a new generation of oral anticoagulants.
The objective of this document is to provide guidance for the management of patients with non-valvular atrial fibrillation living in the community in Saudi Arabia.

Methodology

This clinical practice guideline is a part of the larger initiative of the Ministry of Health of the Kingdom of Saudi Arabia (KSA) to establish a program of rigorous adaptation and de novo development of guidelines. The ultimate goals are to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For all selected questions we updated existing systematic reviews that were used for the "Antithrombotic Therapy for Atrial Fibrillation" chapter of the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, 9th edition. We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the systematic reviews we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. We used this information to prepare the evidence to recommendation tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see Appendix 1). The guideline panel met in Riyadh on December 3, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.

How to use these guidelines

The guideline working group developed and graded the recommendations and assessed the quality of the supporting evidence according to the GRADE approach. Quality of evidence (confidence in the available estimates of treatment effects) is categorized as: high, moderate, low, or very low based on consideration of risk of bias, directness, consistency and precision of the estimates. High quality evidence indicates that we are very confident that the *true* effect lies close to that of the estimate of the effect. Moderate quality evidence indicates moderate confidence, and that the *true* effect is likely close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality evidence indicates that our confidence in the effect estimate is limited, and that the *true* effect may be substantially different. Finally, very low quality evidence indicates that the estimate of effect of interventions is very uncertain, the *true* effect is likely to be substantially different from the effect estimate and further research is likely to have important potential for reducing the uncertainty.

The strength of recommendations is expressed as either strong ('guideline panel recommends…') or conditional ('guideline panel suggests…') and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades is essential for sagacious clinical decision making.

Table 1: Interpretation of strong and conditional (weak) recommendations

Implications	Strong recommendation	Conditional (weak) recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful helping individuals making decisions consistent with their values and preferences.
For policy makers	The recommendation can be adapted as policy in most situations	Policy making will require substantial debate and involvement of various stakeholders.

Key questions

1. Should oral anticoagulation rather than no therapy be used in patients with non-valvular atrial fibrillation?
2. Should oral anticoagulation rather than aspirin be used in patients with non-valvular atrial fibrillation?
3. Should oral anticoagulation rather than aspirin + clopidogrel be used in patients with non-valvular atrial fibrillation?
4. Should novel oral anticoagulants (NOACs) rather than Vitamin K Antagonists be used in patients with non-valvular atrial fibrillation?

Recommendations

I. Antithrombotic treatment of patients with non-valvular atrial fibrillation at low risk of stroke:

Recommendations 1-3:
For patients with non-valvular atrial fibrillation at low risk of stroke (e.g. $CHADS_2$ score = 0), the Ministry of Health of Saudi Arabia guideline panel suggests no antithrombotic therapy rather than aspirin [weak recommendation, moderate quality evidence] or oral anticoagulation (weak recommendation, moderate quality evidence)

For patients who choose antithrombotic therapy, the Ministry of Health of Saudi Arabia guideline panel suggests the use of aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation (weak recommendation, moderate quality evidence)

Remarks:
The Ministry of Health of Saudi Arabia guideline panel issued weak recommendations against the use of antithrombotics in patients with atrial fibrillation at low risk of stroke because it considered that the undesirable consequences of antithrombotics (i.e. small increase of the risk of bleeding, burden of treatment and resource utilization) probably outweigh the benefits (i.e. small reduction of the risk of stroke). However, patients who place an exceptional high value in stroke prevention and a relatively low value in the risk of bleeding are likely to opt for antithrombotic therapy. Other factors that may influence the choices above are the individual risk of bleeding and presence of additional risk factors for stroke, not considered by the $CHADS_2$

score: age over 65 years, female gender or the presence of vascular disease (previous myocardial infarction, peripheral artery disease or the existence of an aortic plaque). The concurrence of multiple non-$CHADS_2$ risk factors for stroke may favor oral anticoagulation over aspirin.

II. Antithrombotic treatment of patients with non-valvular atrial fibrillation at intermediate risk of stroke:

Recommendations 4-6:
For patients with non-valvular atrial fibrillation at intermediate risk of stroke (e.g. $CHADS_2$ score = 1), the Ministry of Health of Saudi Arabia guideline panel recommends oral anticoagulation rather than no antithrombotic therapy (strong recommendation, high quality evidence) or aspirin (strong recommendation, moderate quality evidence)
Additionally, the Ministry of Health of Saudi Arabia guideline panel suggests oral anticoagulation rather than aspirin plus clopidogrel (weak recommendation, moderate quality evidence)

Remarks:
The Ministry of Health of Saudi Arabia guideline panel considered that in patients at intermediate risk of stroke, the desirable consequences of using oral anticoagulation rather than aspirin plus clopidogrel (i.e. stroke reduction) probably outweigh the undesirable consequences (i.e. burden of treatment and costs). However, aspirin plus clopidogrel might be an alternative to patients that are unsuitable for or choose to not take anticoagulants (Vitamin K Antagonists or novel anticoagulants) for reasons other than concerns about the risk of bleeding.
III. Antithrombotic treatment of patients with non-valvular atrial fibrillation at high risk of stroke

Recommendations 7-9:
For patients with non-valvular atrial fibrillation at high risk of stroke (e.g. $CHADS_2$ score = 2 or greater), the Ministry of Health of Saudi Arabia guideline panel recommends oral anticoagulation rather than no antithrombotic therapy (strong recommendation, high quality evidence), aspirin (strong recommendation, moderate quality evidence) or aspirin plus clopidogrel (strong recommendation, moderate quality evidence)

IV. Use of Novel Oral Anticoagulants (NOAC) versus Vitamin K Antagonists (VKA)

Recommendation 10:
For patients with non-valvular atrial fibrillation in whom oral anticoagulation is recommended (or suggested), the Ministry of Health of Saudi Arabia guideline panel suggests the use of Novel Oral Anticoagulants (dabigartran 150 mg bid, rivaroxaban 20 mg once a day or apixaban 5 mg bid) rather than Vitamin K antagonists (weak recommendation, moderate quality evidence)

Remarks:
For patients who are well controlled and without complications with VKA, the decision to switch to NOACs should be individualized to the specific clinical circumstances and patients' preferences.
Clinicians and patients should be aware that uncommon but serious adverse effects associated with the use NOACs might emerge over the long term.
Dose adjustments may be necessary for special populations: Dabigatran 110 mg could be an alternative for the elderly (over 75 years) and patients with an increased risk of bleeding, while rivaroxaban 15 mg could be used in patients with mild renal impairment.
Dabigatran is excreted mainly by the kidneys. Rivaroxaban and apixaban also have an important renal excretion. NOACs have not been studied and are contraindicated in patients with severe renal impairment (estimated creatinine clearance of less than 30 mL/min).

Scope and purpose

The purpose of this document is to provide guidance about the antithrombotic treatment of patients with non-valvular atrial fibrillation. The target audience of these guidelines includes primary care physicians and specialists in internal medicine and cardiology in the Kingdom of Saudi Arabia. Other health care professionals and policy makers may also benefit from these guidelines.

Given the importance of this topic, the Ministry of Health (MoH) of Saudi Arabia with the methodological support of the McMaster University working group produced clinical practice guidelines to assist health care providers in evidence-based clinical decision-making. This clinical practice guideline is a part of the larger initiative of the Ministry of Health of Saudi Arabia to establish a program of rigorous adaptation and de novo development of guidelines in the Kingdom; the ultimate goal being to provide guidance for clinicians and reduce variability in clinical practice across the Kingdom.

Introduction

Atrial fibrillation is the most common sustained cardiac arrhythmia, with a prevalence of 1 to 2% of the general population in western countries.[1-3] There are no community-based studies measuring the prevalence of atrial fibrillation in the Middle East. However, a cross-sectional study found a prevalence of 4% among the medical admissions in a hospital in Kuwait.[4] Without antithrombotic treatment, the risk of stroke in patients with atrial fibrillation is around 5% per year, but it can be as high as 10% if other risk factors are present.[5]

In recent years, important advances have been made in the management of atrial fibrillation, particularly, the introduction of a new generation of oral anticoagulants. The objective of this document is to provide guidance for the management of patients with non-valvular atrial fibrillation living in the community in Saudi Arabia.

Methodology

To facilitate the interpretation of these guidelines; we briefly describe the methodology we used to develop and grade recommendations and quality of the supporting evidence. We present the detailed methodology in a separate publication.[6]

The KSA guideline panel selected the topic of this guideline and all clinical questions addressed herein using a formal prioritization process. For the selected questions we updated existing systematic reviews that were used for the "Antithrombotic Therapy for Atrial Fibrillation" chapter of the 2012 Antithrombotic Therapy and Prevention of Thrombosis guidelines, 9th edition.[5] For one clinical question (Novel Oral Anticoagulants versus Vitamin K Antagonists) we developed the evidence synthesis *de novo* for this guideline, following the methods described in **Box 1**. We also conducted systematic searches for information that was required to develop full guidelines for the KSA, including searches for information about patients' values and preferences and cost (resource use) specific to the Saudi context. Based on the updated systematic reviews (see **Appendix 2**) we prepared summaries of available evidence supporting each recommendation following the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach.[8]

Box 1 – Methods for obtaining and summarizing the evidence for the recommendation addressing the comparison of novel oral anticoagulants (NOAC) versus Vitamin K Antagonists.

Data Sources and Searches

We updated the search used for the "Antithrombotic Therapy for Atrial Fibrillation" chapter in MEDLINE and the Cochrane Library (CENTRAL) up to November 2013 (see **Appendix 2**). Also, we identified additional trials hand-searching the references of recent systematic reviews and through the resource Epistemonikos (www.epistemonikos.org).

Study Selection

We used the following inclusion criteria: 1. Study design: randomized clinical trials 2. Population: individuals with atrial fibrillation 3. Intervention: dabigatran, rivaroxaban or apixaban (drugs already or soon available in Saudi Arabia). 4. Comparison: Vitamin K Antagonists 5. Outcomes: Reporting of any of the following outcomes: all-cause mortality, stroke (including ischemic and haemorrhagic strokes), systemic embolism or major bleeding.

Data Extraction and Risk of Bias Assessment

We collected the following information: characteristics of the intervention and control (drug, dose, schedule) and the data regarding the outcomes previously stated. We assessed the risk of bias of the included trials following procedures suggested by the Cochrane Risk of Bias Tool.[7]

Data Synthesis and Analysis

We conducted a standard pair-wise meta-analysis for the comparison NOACs vs Vitamin K Antagonists (see **Appendix 3**). In the trials evaluating two or more doses of NOACs, we restricted the analysis to doses that are currently accepted as standard: dabigartran 150 mg bid, rivaroxaban 15-20 mg once a day and apixaban 5 mg bid. We obtained the pooled Risk Ratios using the Mantel-Haenszel method (random effect model) excluding trials with zero total-events.[7] We also presented the effect estimates in natural frequencies, obtained by multiplying the baseline risks by the pooled risk ratios obtained from the meta-analyses.

We conducted the meta-analyses using RevMan 5.1 (Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). We summarized the findings using the Guideline Development Tool (Hamilton, Ontario. Jan Brozek, Holger Schünemann, 2013).

We assessed heterogeneity with the Chi-square test and with the I^2 statistic. The probability of publication bias was assessed graphically by evaluating symmetry in the funnel plots.

We assessed the quality of evidence using the system described by the GRADE working group.[8]

Quality of evidence is classified as “high”, “moderate”, “low”, or “very low” based on decisions about methodological characteristics of the available evidence for a specific health care problem. The definition of each category is as follows:

- *High*: We are very confident that the true effect lies close to that of the estimate of the effect.
- *Moderate*: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- *Low*: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- *Very low*: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

According to the GRADE approach, the strength of a recommendation is either strong or conditional (weak) and has explicit implications (see **Table 1**). Understanding the interpretation of these two grades – either strong or conditional – of the strength of recommendations is essential for sagacious clinical decision-making.

We used this information to prepare the evidence to recommendation tables that served the guideline panel to follow the structured consensus process and transparently document all decisions made during the meeting (see **Appendix 1**). The guideline panel met in Riyadh on December 3, 2013 and formulated all recommendations during this meeting. Potential conflicts of interests of all panel members were managed according to the World Health Organization (WHO) rules.[6]

Risk Stratification

Patients with non-valvular atrial fibrillation are a heterogeneous group. The net effect of the antithrombotic treatment varies largely with the baseline risks of stroke and bleeding. The recommendations of this guideline were categorized by the risk of stroke.

Several stroke risk stratification schemes have been published. Despite a considerable amount of effort, all the available schemes have only a modest ability to predict the outcome of patients with non-valvular atrial fibrillation.[9-10] The $CHADS_2$ score is the most extensively validated risk scheme: it have been tested in more than 10 separate cohorts after its original introduction.[5] The score gives a single point to each of the following: heart failure, hypertension, age over 75 years and diabetes mellitus; and two points to prior stroke or transient ischemic attack (TIA) (see **Table 2**).[11]

Table 2: The $CHADS_2$ score

Heart failure	1 point
Hypertension	1 point
Age ≥ 75 years	1 point
Diabetes mellitus	1 point
Prior stroke or TIA	2 points

The CHA_2DS_2VASc score is another prominent risk stratification system. It combines the original factors of the $CHADS_2$ score with 3 additional risk factors, which have shown a moderate association with stroke in some studies (age over 65 years, female gender and the presence of vascular disease).[12] Studies comparing the CHA_2DS_2VASc and $CHADS_2$ scores have found that both schemes have similar predictive accuracy.[9]

For the purpose of this Ministry of Health of Saudi Arabia and McMaster University Guideline, the $CHADS_2$ score was chosen in as the principal approach for categorizing recommendations because of its extensive validation and relative simplicity, but also incorporating the consideration of the additional risk factors identified by the CHA_2DS_2VASc score.

Values and preferences used in developing the recommendations

We found no study exploring the values and preferences of patients with atrial fibrillation in Saudi Arabia. A systematic review of 16 studies[13] conducted in western countries showed that in general, informed patients prefer to prevent a stroke rather than preventing a bleeding event. A reasonable trade-off to assume between stroke and bleeds would be a ratio of disutility of net nonfatal stroke (thrombotic or hemorrhagic) to gastrointestinal bleeds in the range of 2:1 to 3:1.
The review also showed that, for most patients, the use of vitamin K antagonists represents an important burden, although it does not have important negative effects on quality of life. Patients' aversion to warfarin treatment may decrease over time once the treatment is initiated.
These findings were considered applicable to the Saudi context by the Ministry of Health of Saudi Arabia guideline panel.

Therefore, in formulating the recommendations, we considered that:

1. Typical informed patients place more value in stroke prevention than in the possibility of bleeds
2. The use of warfarin, and the related laboratory monitoring, lifestyle and diet modifications represent a high burden for patients.
3. The use of aspirin, aspirin plus clopidogrel, or novel oral anticoagulants represents a relatively small burden for patients.

How to use these guidelines

The Ministry of Health of Saudi Arabia and McMaster University Clinical Practice Guidelines provide clinicians and their patients with a basis for rational decisions about the antithrombotic treatment of patients with non-valvular atrial fibrillation. Clinicians, patients, third-party payers, institutional review committees, other stakeholders, or the courts should never view these recommendations as dictates. No guidelines and recommendations can take into account all of the often-compelling unique features of individual clinical circumstances. Therefore, no one charged with evaluating clinicians' actions should attempt to apply the recommendations from these guidelines by rote or in a blanket fashion.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate an accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines.

Key questions

The following is a list of the clinical questions selected by the KSA guideline panel and addressed in this guideline. For details on the process by which the questions were selected for this guideline please refer to the separate methodology publication.[6]

For patients with non-valvular atrial fibrillation at low risk of stroke (e.g. $CHADS_2$ score = 0)

1. Should aspirin rather than no therapy be used in patients with non-valvular atrial fibrillation at low risk of stroke?
2. Should oral anticoagulation rather than no therapy be used in patients with non-valvular atrial fibrillation at low risk of stroke?
3. Should oral anticoagulation rather than aspirin be used in patients with non-valvular atrial fibrillation at low risk of stroke?

For patients with non-valvular atrial fibrillation at intermediate risk of stroke (e.g. $CHADS_2$ score = 1)

4. Should oral anticoagulation rather than no therapy be used in patients with non-valvular atrial fibrillation at intermediate risk of stroke?
5. Should oral anticoagulation rather than aspirin be used in patients with non-valvular atrial fibrillation at intermediate risk of stroke?
6. Should oral anticoagulation rather than aspirin + clopidogrel be used in patients with non-valvular atrial fibrillation at intermediate risk of stroke?

For patients with non-valvular atrial fibrillation at high risk of stroke (e.g. $CHADS_2$ score = 2 or greater)

7. Should oral anticoagulation rather than no therapy be used in patients with non-valvular atrial fibrillation at high risk of stroke?
8. Should oral anticoagulation rather than aspirin be used in patients with non-valvular atrial fibrillation at high risk of stroke?
9. Should oral anticoagulation rather than aspirin + clopidogrel be used in patients with non-valvular atrial fibrillation at high risk of stroke?

For patients in whom anticoagulation is recommended (or suggested)

10. Should novel oral anticoagulants (NOACs) rather than Vitamin K Antagonists be used in patients with non-valvular atrial fibrillation?

Recommendations

I. Antithrombotic treatment of patients with non-valvular atrial fibrillation at low risk of stroke (e.g. $CHADS_2$ score = 0)

Question 1: Should aspirin rather than no therapy be used in patients with non-valvular atrial fibrillation at low risk of stroke (e.g. $CHADS_2$ score = 0)?

Summary of Findings:
The systematic review and meta-analysis included 8 randomized trials.[14-21] We found no additional trials in the update of the literature search. The overall quality of evidence was judged as moderate.

Benefits of the Option:
The meta-analysis of the 8 included trials showed that the use of aspirin rather than no therapy reduces the risk of stroke by 21% (Risk Ratio (RR) 0.79, 95% Confidence Interval (CI) 0.65-0.96). For patients at low risk of stroke, we estimated an absolute reduction of 2 strokes per 1000 patients treated for a year (95% CI from 0 to 3 fewer, moderate quality evidence due to imprecision). However, this risk reduction might be larger in patients with additional risk factors, not considered by the $CHADS_2$ score. These risk factors include: age over 65 years, female gender and the presence of vascular disease (previous myocardial infarction, peripheral artery disease or the existence of an aortic plaque).
In comparison with no treatment, the use of aspirin probably does not produce a significant reduction of mortality (moderate quality evidence due to imprecision).

Harms of the Option:
Using additional evidence available from randomized trials evaluating aspirin for the secondary prevention of cardiovascular events, we estimated that the use of aspirin rather than no therapy increases the risk of major extracranial non-fatal bleeding by 60% (RR 1.6, 95% CI 1.4-1.8). In absolute terms, assuming an average risk of bleeding, the use of aspirin rather no therapy can produce 3 major bleeds per 1000 patients treated for a year (95% CI from 2 to 4 more, high quality evidence).

Values and Preferences:
This recommendation places a higher value in the stroke prevention rather than in the bleeding risk. Additionally, this recommendation assumes that for most patients, the use of a daily dose of aspirin represents a small burden.

Resource Use:
We found no economic evaluations addressing the use of aspirin versus no therapy in patients with atrial fibrillation.

Balance between desirable an undesirable consequences:
The Ministry of Health of Saudi Arabia guideline panel considered that the small increment of the risk of bleeding (3 more major bleeds per 1000 patients treated for a year) and of the burden of treatment with the use of aspirin instead of no therapy probably outweighs the small reduction of the risk of stroke (2 fewer strokes per 1000 patients treated for a year). However, patients at low risk of stroke who place an exceptionally high value in stroke prevention, or have additional non-$CHADS_2$ risk factors (age over 65 years, female gender or the presence of vascular disease) might benefit from the use of aspirin.

Question 2: Should oral anticoagulation rather than no therapy be used in patients with atrial fibrillation at low risk of stroke (e.g. $CHADS_2$ score = 0)?

Summary of Findings:
The systematic review and meta-analysis included 6 randomized trials.[22-27] We found no additional trials in the update of the literature search. The overall quality of evidence was judged as moderate.

Benefits of the Option:
The meta-analysis of the 6 included trials showed that the use of VKA rather than no treatment reduces the risk of stroke by 66% (RR 0.34, 95% CI 0.23-0.49). We estimated an absolute reduction of 5 strokes per 1000 patients treated for a year (95% CI from 4 to 6 fewer, high quality evidence) with the use of VKA over no therapy. As was mentioned before, this risk reduction might be larger in patients with additional risk factors (age over 65

years, female gender and the presence of vascular disease)
In comparison with no treatment, the anticoagulation with VKA probably does not produce a significant reduction of mortality (moderate quality evidence due to imprecision as the confidence interval includes a marginal effect).

Harms of the Option:
The meta-analysis of the 6 included trials showed that anticoagulation with VKA produces a 2.5-fold increase in the risk of major extracranial non-fatal bleeding (RR 2.58, 95% CI 1.12-5.97). Assuming an average risk of bleeding, the anticoagulation with VKA rather than no-therapy can produce 8 major bleeds per 1000 patients treated for a year (95% CI from 1 to 25 more, high quality evidence).

Values and Preferences:
This recommendation places a higher value in the stroke prevention rather than in the bleeding risk. Also, this recommendation considered that for most patients, the use of warfarin, and the related necessity of laboratory monitoring, life-style and diet modifications represent a high burden.

Resource Use:
A systematic review of 5 economic evaluations[28] showed that the use of VKA over no therapy is not cost-effective in patients with atrial fibrillation at low risk of stroke. The studies identified by the review, however, were conducted more than 10 years ago and in western health care settings.

Balance between desirable an undesirable consequences:
The Ministry of Health of Saudi Arabia guideline panel considered that the increment of the risk of bleeding (8 more major bleeds per 1000 patients treated for a year) and of the burden of treatment with the use of VKA instead of no therapy probably outweighs the small reduction of the risk of stroke (5 fewer strokes per 1000 patients treated for a year).
Additionally, the resource utilization associated with the anticoagulation with VKA is high, since a considerable amount of resources are necessary for the laboratory monitoring and follow-up of patients. Probably, this incremental cost is not justified by the small benefits in most circumstances.
However, patients at low risk of stroke who place an exceptionally high value in stroke prevention, or have several additional non-$CHADS_2$ risk factors (age over 65 years, female gender or the presence of vascular disease) might benefit from anticoagulation with VKA.

Question 3: Should oral anticoagulation rather than aspirin be used in patients with atrial fibrillation at low risk of stroke (e.g. $CHADS_2$ score = 0)?

Summary of Findings:
The systematic review and meta-analysis included 11 randomized trials.[29-40] We found no additional trials in the update of the literature search. The overall quality of evidence was judged as moderate.

Benefits of the Option:
The meta-analysis of the 11 included trials showed that, in comparison with aspirin, the use of VKA reduces the risk of stroke by 52% (RR 0.48, 95% CI 0.33-0.70). In patients at low risk of stroke, we estimated an absolute reduction of 3 strokes per 1000 patients treated for a year (95% CI from 2 to 4 fewer, high quality evidence). As it has been previously stated, this risk reduction might be larger in patients with additional risk factors (age over 65 years, female gender or the presence of vascular disease). The use of VKA probably does not produce a significant reduction of mortality in comparison with aspirin (moderate quality evidence due to imprecision)

Harms of the Option:
The meta-analysis of the 11 included trials showed that the use of VKA rather than aspirin increases the risk of major extracranial non-fatal bleeding by 42% (RR 1.42, 95% CI 0.89-2.49). For patients at average risk of bleeding, the use of VKA rather than aspirin can produce 3 more bleeds per 1000 patients treated for a year (95% CI from 1 fewer to 10 more, moderate quality evidence due to imprecision).

Values and Preferences:
This recommendation places a higher value in the stroke prevention rather than in the bleeding risk, and assumes, that for most patients, the use of VKA is more burdensome than the use of aspirin.

Resource Use:
Seven economic evaluations showed that the use of VKA over aspirin in patients with atrial fibrillation at low risk of stroke is not cost-effective.[40-42]

Balance between desirable an undesirable consequences:
The Ministry of Health of Saudi Arabia guideline panel considered that for most patients at low risk of stroke who choose antithrombotic therapy, the high burden of treatment of VKA and the small increment of the risk of bleeding (3 more major bleeds per 1000 patients treated for a year) probably outweigh the additional reduction of the risk of stroke (3 fewer strokes per 1000 patients treated for a year).

Also, the resource utilization associated with anticoagulation with the use of VKA is significantly higher than with the use of aspirin. This incremental cost is probably not justified by the small additional protection of VKA in most of the circumstances.

However, when multiple non-$CHADS_2$ risk factors for stroke are present, the stroke risk reduction may be larger than we have estimated on average, and therefore, the benefits of oral anticoagulation may outweigh the undesirable consequences (harms and cost).

Recommendations 1-3:

For patients with non-valvular atrial fibrillation at low risk of stroke (e.g. CHADS2 score = 0), the Ministry of Health of Saudi Arabia guideline panel suggests no antithrombotic therapy rather than aspirin (weak recommendation, moderate quality evidence) or oral anticoagulation (weak recommendation, moderate quality evidence)

For patients who choose antithrombotic therapy, the Ministry of Health of Saudi Arabia guideline panel suggests the use of aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation (weak recommendation, moderate quality evidence)

Remarks:
The Ministry of Health of Saudi Arabia guideline panel issued weak recommendations against the use of antithrombotics in patients with non-valvular atrial fibrillation at low risk of stroke because it considered that the undesirable consequences of the use of antithrombotics (i.e. small increase of the risk of bleeding, burden of treatment and resource utilization) probably outweigh the benefits (i.e. small reduction of the risk of stroke). However, patients who place an exceptional high value in stroke prevention and a relatively low value in the risk of bleeding are likely to opt for antithrombotic therapy. Other factors that may influence the choices above are the individual risk of bleeding and presence of additional risk factors for stroke, not considered by the $CHADS_2$ score: age over 65 years, female gender or the presence of vascular disease (previous myocardial infarction, peripheral artery disease or the existence of an aortic plaque). The concurrence of multiple non-$CHADS_2$ risk factors for stroke may favor oral anticoagulation over aspirin.

II. Antithrombotic treatment of patients with non-valvular atrial fibrillation at intermediate risk of stroke (e.g. $CHADS_2$ score = 1)

Question 4: Should anticoagulation with Vitamin K Antagonists rather than no therapy be used in patients with atrial fibrillation at intermediate risk of stroke (e.g. $CHADS_2$ score = 1)?

Summary of Findings:
The systematic review and meta-analysis included 6 randomized trials.[22-27] We found no additional trials in the update of the literature

search. The overall quality of evidence was judged as high.

Benefits of the Option:
The meta-analysis of the 6 included trials showed that the use of VKA rather than no treatment reduces the risk of stroke by 66% (RR 0.34, 95% CI 0.23-0.49). In absolute terms, we estimated a reduction of 15 strokes per 1000 patients treated for a year (95% CI from 11 to 17 fewer, high quality evidence) among patients at intermediate risk of stroke.

Harms of the Option:
The meta-analysis of the 6 included trials showed that anticoagulation with VKA produces a 2.5-fold increase in the risk of major extracranial non-fatal bleeding (RR 2.58, 95% CI 1.12-5.97). In patients at average risk of bleeding, the use of VKA rather than no-therapy can produce 8 more major bleeds per 1000 patients treated for a year (95% CI from 1 to 25 more, high quality evidence).

Values and Preferences:
This recommendation places a higher value in the stroke prevention rather than in the bleeding risk. Also, this recommendation assumes that for most patients, the use of warfarin, and the related necessity of laboratory monitoring, life-style and diet modifications represent a high burden.

Resource Use:
A systematic review of 5 economic evaluations[28] showed that the use of VKA over no therapy is probably cost-effective in patients with atrial fibrillation at intermediate risk of stroke. The studies identified by the review, however, were conducted more than 10 years ago and in western health care settings.

Balance between desirable an undesirable consequences:
The Ministry of Health of Saudi Arabia guideline panel considered that for all or almost all the patients at intermediate risk of stroke, the benefit of using VKA rather than no therapy (15 fewer strokes per 1000 patients treated for a year) clearly outweighs the increment of the risk of bleeding (8 more major bleeds per 1000 patients treated for a year) and the high burden of treatment.
Also, although the resource utilization associated with the use of VKA is high, the panel considered that it is justified by the benefits of the intervention.

Question 5: Should oral anticoagulation rather than aspirin be used in patients with atrial fibrillation at intermediate risk of stroke (e.g. $CHADS_2$ score = 1)?

Summary of Findings:
The systematic review and meta-analysis included 11 randomized trials.[29-40] We found no additional trials in the update of the literature search. The overall quality of evidence was judged as moderate.

Benefits of the Option:
The meta-analysis of the 11 included trials showed that, in comparison with aspirin, the use of VKA reduces the risk of stroke by 52% (RR 0.48, 95% CI 0.33-0.70). We estimated that in patients at intermediate risk of stroke, the use of VKA instead of aspirin results in an absolute reduction of 9 strokes per 1000 patients treated for a year (95% CI from 5 to 11 fewer, high quality evidence).
The use of VKA probably does not produce a significant reduction of mortality in comparison with aspirin (moderate quality evidence due to imprecision).

Harms of the Option:
The meta-analysis of the 11 included trials showed that the use of VKA rather than aspirin increases the risk of major extracranial non-fatal bleeding by 42% (RR 1.42, 95% CI 0.89-2.49). In absolute terms, the use of VKA rather than aspirin can produce 3 more major bleeds per 1000 patients treated for a year (95% CI from 1 fewer to 10 more, moderate quality evidence due to imprecision) in patients at average risk of bleeding.

Values and Preferences:
This recommendation places a higher value in the stroke prevention rather than in the bleeding risk, and assumes that for most pa-

tients, the use of VKA is more burdensome than the use of aspirin.

Resource Use:
Seven economic evaluations showed that the use of VKA over aspirin in patients with atrial fibrillation at intermediate risk of stroke is probably cost-effective.[40-42]

Balance between desirable an undesirable consequences:
The Ministry of Health of Saudi Arabia guideline panel considered that for all or almost all the patients at intermediate risk of stroke, the benefit of using VKA rather than aspirin (9 fewer strokes per 1000 patients treated for a year) clearly outweighs the increment of the risk of bleeding (3 more major bleeds per 1000 patients treated for a year) and the high burden of treatment.

Also, although the resource utilization associated with anticoagulation with VKA is high, the panel considered that it is justified by the benefits of the intervention.

Question 6: Should oral anticoagulation rather than aspirin plus clopidogrel be used in patients with atrial fibrillation at intermediate risk of stroke (e.g. $CHADS_2$ score = 1)?

Summary of Findings:
The systematic review and meta-analysis included 1 randomized trial (ACTIVE W trial).[43] We found no additional trials in the update of the literature search. The overall quality of evidence was judged as moderate.

Benefits of the Option:
The ACTIVE W trial showed that the use of VKA rather than aspirin plus clopidogrel reduces the risk of stroke by 44% (RR 0.56, 95% CI 0.39-0.82). In patients at intermediate risk of stroke, we estimated that the use of VKA instead of aspirin plus clopidogrel reduces 6 strokes per 1000 patients treated for a year (95% CI from 2 to 8 fewer, high quality evidence).
The trial did not rule out a potential decrease or increase of mortality with the use of VKA instead of aspirin plus clopidogrel (moderate quality evidence due to imprecision).

Harms of the Option:
The ACTIVE W trial showed that the use of VKA rather than aspirin plus clopidogrel probably produces less major extracranial non-fatal bleeds (RR 0.91, 95% CI 0.67-1.23). In absolute terms, for patients at average risk of bleeding, the use of VKA would result in 1 less major bleeding event per 1000 patients treated for a year (95% CI from 4 fewer to 3 more, moderate quality evidence due to imprecision).

Values and Preferences:
This recommendation places a higher value in the stroke prevention rather than in the bleeding risk, and assumes that for most patients, the use of VKA is more burdensome than the use of aspirin plus clopidogrel.

Resource Use:
We found no economic evaluation addressing the use of VKA versus aspirin plus clopidogrel in patients with atrial fibrillation.

Balance between desirable an undesirable consequences:
The Ministry of Health of Saudi Arabia guideline panel considered that for most patients at intermediate risk of stroke, the benefit of using anticoagulation with VKA rather than aspirin plus clopidogrel (a reduction of 6 strokes and a potential reduction of 1 bleeding event per 1000 patients treated for a year) probably outweighs the high burden of treatment.

Also, although the resource utilization associated with anticoagulation with VKA is high, the panel considered that it is probably justified by the benefits of the intervention.
Aspirin plus clopidogrel might be an alternative to patients with atrial fibrillation at intermediate risk of stroke that are unsuitable for or choose to not take anticoagulation with VKA or novel oral anticoagulants for reasons other than concerns about the risk of bleeding.

Recommendations 4-6:

For patients with non-valvular atrial fibrillation at intermediate risk of stroke (e.g. $CHADS_2$ score = 1), the Ministry of Health of Saudi Arabia guideline panel recommends oral anticoagulation rather than no antithrombotic therapy (strong recommendation, high quality evidence) or aspirin (strong recommendation, moderate quality evidence) and suggests oral anticoagulation rather than aspirin plus clopidogrel (weak recommendation, moderate quality evidence)

Remarks:
The Ministry of Health of Saudi Arabia guideline panel considered that in patients at intermediate risk of stroke, the desirable consequences of using oral anticoagulation rather than aspirin plus clopidogrel (i.e. stroke reduction) probably outweigh the undesirable consequences (i.e. burden of treatment and costs). However, aspirin plus clopidogrel might be an alternative to patients that are unsuitable for or choose to not take oral anticoagulants (Vitamin K Antagonists or novel anticoagulants) for reasons other than concerns about the risk of bleeding.

III. Antithrombotic treatment of patients with non-valvular atrial fibrillation at high risk of stroke (e.g. $CHADS_2$ score = 2 or greater)

Question 7: Should oral anticoagulation rather than no therapy be used in patients with atrial fibrillation at high risk of stroke (e.g. $CHADS_2$ score = 2 or greater)?

Summary of Findings:
The systematic review and meta-analysis included 6 randomized trials.[22-27] We found no additional trials in the update of the literature search. The overall quality of evidence was judged as high.

Benefits of the Option:
The meta-analysis of the 6 included trials showed that the use of VKA rather than no treatment decreases the risk of stroke by 66% (RR 0.34, 95% CI 0.23-0.49). In patients at high risk of stroke, we estimated an absolute reduction of 30 ($CHADS_2$ score 2) to 63 ($CHADS_2$ score 3-6) strokes per 1000 patients treated for a year (95% CI from 23 fewer to 35 fewer ($CHADS_2$ score 2) and from 49 fewer to 74 fewer ($CHADS_2$ score 3-6), high quality evidence).
The meta-analysis also found that in patients at intermediate to high risk of stroke, the use of VKA rather than no treatment decreases all-cause mortality (RR 0.72, 95% CI 0.55-0.94). In absolute terms, 15 deaths per 1000 patients treated for a year can be prevented with the use of oral anticoagulation (95% CI 3 to 24 fewer deaths, high quality evidence).

Harms of the Option:
The meta-analysis of the 6 included trials showed that anticoagulation with VKA produces a 2.5-fold increase in the risk of major extracranial non-fatal bleeding (RR 2.58, 95% CI 1.12-5.97). For patients at average risk of bleeding, the use of VKA rather than no-therapy results in 8 more major bleeds per 1000 patients treated for a year (95% CI from 1 to 25 more, high quality evidence).

Values and Preferences:
This recommendation places a higher value in the stroke prevention rather than in the bleeding risk. Also, this recommendation assumes that for most patients, the use of warfarin, and the related necessity of laboratory monitoring, lifestyle and diet modifications represent a high burden.

Resource Use:
A systematic review of 5 economic evaluations[28] showed that the use of VKA over no therapy is cost-effective in patients with atrial fibrillation at high risk of stroke. The studies identified by the review, however, were conducted more than 10 years ago and in western health care settings.

Balance between desirable an undesirable consequences:
The Ministry of Health of Saudi Arabia guideline panel considered that for all or almost all the patients at high risk of stroke, the benefit

of using oral anticoagulation rather than no therapy (a reduction of 15 deaths and between 30 to 63 strokes per 1000 patients treated for a year) clearly outweighs the increment of the risk of bleeding (8 more major bleeds per 1000 patients treated for a year), the high burden of treatment and the increased resource utilization.

Question 8: Should oral anticoagulation rather than aspirin be used in patients with atrial fibrillation at high risk of stroke (e.g. $CHADS_2$ score = 2 or greater)?

Summary of Findings:
The systematic review and meta-analysis included 11 randomized trials.[29-40] We found no additional trials in the update of the literature search. The overall quality of evidence was judged as moderate.

Benefits of the Option:
The meta-analysis of the 11 included trials showed that, in comparison with aspirin, the use of VKA reduces the risk of stroke by 52% (RR 0.48, 95% CI 0.33-0.70). We estimated that in patients at high risk of stroke, the use of VKA instead of aspirin produces an absolute reduction of 19 ($CHADS_2$ score 2) to 40 ($CHADS_2$ score 3-6) strokes per 1000 patients treated for a year (95% CI from 11 fewer to 24 fewer ($CHADS_2$ score 2) and from 23 fewer to 51 fewer ($CHADS_2$ score 3-6), high quality evidence).
The use of VKA probably does not produce a significant reduction of mortality in comparison with aspirin (moderate quality evidence due to imprecision).

Harms of the Option:
The meta-analysis of the 11 included trials showed that the use of VKA rather than aspirin increases the risk of major extracranial non-fatal bleeding by 42% (RR 1.42, 95% CI 0.89-2.49). In absolute terms, for patients at average risk of bleeding, the use of VKA rather than aspirin can produce 3 more major bleeds per 1000 patients treated for a year (95% CI from 1 fewer to 10 more, moderate quality evidence due to imprecision).

Values and Preferences:
This recommendation places a higher value in the stroke prevention rather than in the bleeding risk, and assumes that for most patients, the use of VKA is more burdensome than the use of aspirin.

Resource Use:
Seven economic evaluations showed that the use of VKA over aspirin in patients with atrial fibrillation at high risk of stroke is cost-effective.[40-42]

Balance between desirable an undesirable consequences:
The Ministry of Health of Saudi Arabia guideline panel considered that for all or almost all the patients at high risk of stroke, the benefit of using anticoagulation with VKA rather than aspirin (a reduction of 19-40 strokes per 1000 patients treated for a year) clearly outweighs the increment of the risk of bleeding (3 more major bleeds per 1000 patients treated for a year), the high burden of treatment and the increased resource utilization.

Question 9: Should oral anticoagulation rather than aspirin plus clopidogrel be used in patients with atrial fibrillation at high risk of stroke (e.g. $CHADS_2$ score = 2 or greater)?

Summary of Findings:
The systematic review and meta-analysis included 1 randomized trial (ACTIVE W trial).[43] We found no additional trials in the update of the literature search. The overall quality of evidence was judged as moderate.

Benefits of the Option:
The ACTIVE W trial showed that the use of VKA rather than aspirin plus clopidogrel reduces the risk of stroke by 44% (RR 0.56, 95% CI 0.39-0.82). In patients at high risk of stroke, we estimated that the use of VKA rather than aspirin plus clopidogrel reduces 11 ($CHADS_2$ score 2) to 24 ($CHADS_2$ score 3-6) strokes per 1000 patients treated for a year (95% CI from 5 fewer to 16 fewer ($CHADS_2$ score 2) and from 10 fewer to 34 fewer ($CHADS_2$ score 3-6), high quality evidence).

The trial did not rule out a potential decrease or increase of mortality with the use of VKA instead of aspirin plus clopidogrel (moderate quality evidence due to imprecision).

Harms of the Option:
The ACTIVE W trial showed that the use of VKA rather than aspirin plus clopidogrel probably produces fewer major extracranial non-fatal bleeds (RR 0.91, 95% CI 0.67-1.23). In absolute terms, for patients at average risk of bleeding, the use of VKA would result in 1 less major bleeding event per 1000 patients treated for a year (95% CI from 4 fewer to 3 more, moderate quality evidence due to imprecision).
Values and Preferences:

This recommendation places a higher value in the stroke prevention rather than in the bleeding risk, and assumes that for most patients, the use of VKA is more burdensome than the use of aspirin plus clopidogrel.

Resource Use:
We found no economic evaluations addressing the use of VKA versus aspirin plus clopidogrel in patients with atrial fibrillation.

Balance between desirable an undesirable consequences:
The Ministry of Health of Saudi Arabia guideline panel considered that for all or almost all the patients at high risk of stroke, the benefit of using anticoagulation with VKA rather than aspirin plus clopidogrel (a reduction of 11-24 strokes per 1000 patients treated for a year) clearly outweighs the high burden of treatment and the increased resource utilization.

Recommendations 7-9:

For patients with non-valvular atrial fibrillation at high risk of stroke (e.g. $CHADS_2$ score = 2 or greater), the Ministry of Health of Saudi Arabia guideline panel recommends oral anticoagulation rather than no antithrombotic therapy (strong recommendation, high quality evidence), aspirin (strong recommendation, moderate quality evidence) or aspirin plus clopidogrel (strong recommendation, moderate quality evidence)

IV. Use of Novel Oral Anticoagulants (NOAC) versus Vitamin K Antagonists (VKA)

Question 10: Should novel oral anticoagulants (NOACs) rather than Vitamin K Antagonists be used in patients with non-valvular atrial fibrillation?

Summary of Findings:
The evidence synthesis was developed specifically for this guideline. We identified 7 randomized trials evaluating dabigatran, rivaroxaban or apixaban against VKA.[44-50] The overall quality of evidence was judged as high.

Benefits of the Option:
The meta-analysis of the 7 included trials showed that, in comparison with VKA, the use of NOAC reduces the risk of death (RR 0.89, 95% CI 0.82- 0.95) and stroke (RR 0.75, 95% CI 0.66- 0.86). In absolute terms, 6 deaths (95% CI from 3 fewer to 11 fewer) and 8 strokes (95% CI from 5 fewer to 10 fewer) per 1000 patients treated for 2.5 years can be prevented with the use of NOACs (high quality evidence).
Additionally, the use of NOAC rather than VKA may decrease the risk of major bleeding (RR 0.87, 95% CI 0.72- 1.05). For patients at average risk of bleeding, the use of NOAC may prevent 7 bleeds per 1000 patients treated for 2.5 years (95% CI from 15 fewer to 3 more, low quality evidence due to imprecision and inconsistency).

Harms of the Option:
It is important to note that there is no long-term data regarding the safety of NOACs. Uncommon but serious adverse effects might emerge with large-scale use of these drugs.
In a meta-analysis of 7 trials (including 2 studies of stroke prophylaxis in atrial fibrillation, 1 in acute venous thromboembolism, 1 in acute coronary syndrome, and 3 of short-term prophylaxis of deep venous thrombosis, n= 30,514) dabigatran was associated with an increment of the risk of myocardial infarction or acute coronary syndrome (OR 1.27, 95% CI

1.00-1.61). However, the absolute difference was small: 2 more events per 1000 patients (95% CI form 0 to 4 more).[51]
Dabigatran is excreted mainly by the kidneys. Rivaroxaban and apixaban also have an important renal excretion. NOACs have not been studied and are contraindicated in patients with severe renal impairment (estimated creatinine clearance of less than 30 mL/min).
Finally, clinicians and patients should be aware that there is no antidote to immediately revert the anticoagulant effect of NOACs.

Values and Preferences:
This recommendation places a higher value in the stroke prevention rather than in the bleeding risk, and assumes that for most patients, the use of VKA is more burdensome than the use of NOAC.

Resource Use:
A systematic review of 16 economic evaluations (13 evaluating dabigatran, 3 apixaban and 2 rivaroxaban) found that NOACs are cost-effective across a broad range of health care settings and perspectives.[52]
Balance between desirable an undesirable consequences:
The Ministry of Health of Saudi Arabia guideline panel considered that for most patients in whom anticoagulation is recommended (or suggested), the benefits of using NOACs (i.e. reduction of mortality, strokes and bleeds) probably outweigh the potential harms (unknown long-term adverse events and lack of antidote).

Even though the direct cost of NOACs is high, their overall resource utilization is probably lower than with the use of VKA, since NOACs do not require frequent laboratory monitoring. Although it has not been studied, NOACs are probably cost-effective in the context of Saudi Arabia.

Recommendation 10:

For patients with non-valvular atrial fibrillation in whom oral anticoagulation is recommended (or suggested), the Ministry of Health of Saudi Arabia guideline panel suggests the use of Novel Oral Anticoagulants (dabigatran 150 mg bid, rivaroxaban 20 mg once a day or apixaban 5 mg bid) rather than Vitamin K antagonists (weak recommendation, high quality evidence)

Remarks
For patients who are well controlled and without complications with VKA, the decision to switch to NOACs should be individualized to the specific clinical circumstances and patients' preferences.
Clinicians and patients should be aware that uncommon but serious adverse effects associated with the use NOACs might emerge over the long term.
Dose adjustments may be necessary for special populations: Dabigatran 110 mg could be an alternative for the elderly (over 75 years) and for patients with an increased risk of bleeding, while rivaroxaban 15 mg could be used in patients with mild renal impairment (Creatinine clearance 30 to 60 mL/min)
Dabigatran is excreted mainly by the kidneys. Rivaroxaban and apixaban also have an important renal excretion. NOACs have not been studied and are contraindicated in patients with severe renal impairment (estimated creatinine clearance of less than 30 mL/min).

Implementation considerations

Maintaining adherence to anticoagulation is crucial to reduce the risk of death and stroke in patients with non-valvular atrial fibrillation at intermediate and high risk of stroke. The Ministry of Health of Saudi Arabia guideline panel encourages the instauration of organized systems (e.g. anticoagulation clinics or the like) for the monitoring and follow-up of patients with atrial fibrillation using anticoagulants.
The implementation of novel oral anticoagulants or home-based monitoring of VKA may help to maintain adherence in patients living far from urban centers.

Monitoring and evaluation

The Ministry of Health of Saudi Arabia guideline panel suggests periodic and formal evaluations of the adherence to the recommendations of this guideline according to their strength:

- Strong recommendations should be applied to the large majority of patients. Therefore, the adherence to the course of action proposed by strong recommendations could be used as a quality criterion or performance indicator.
- For weak recommendations, however, it is important to recognize that different choices could be appropriate for different patients. Therefore, measuring the adherence to the course of action proposed by weak recommendations is not appropriate for quality criteria or performance indicators.

The Ministry of Health of Saudi Arabia guideline panel suggests periodic updates of this guideline every 2-3 years. Early updates could be considered in case of the emergence of new evidence relevant to the interventions covered in the guideline.

Research priorities

The Ministry of Health of Saudi Arabia guideline panel suggests local research in the following topic areas:

- Baseline risks for stroke and bleeding among the patients with atrial fibrillation living in the community in Saudi Arabia.
- Values and preferences of the Saudi population regarding the relative value (utility) of preventing strokes versus bleeds; and also regarding the burden of treatment of the different antithrombotics.
- Economic evaluation of the novel anticoagulants compared with Vitamin K Antagonist in the context of Saudi Arabia.

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Appendices

1. Appendix 1: Evidence-to-Recommendation Tables
2. Appendix 2: Search Strategies and Results
3. Appendix 3: Novel Oral Anticoagulants vs. Vitamin K Antagonists Meta-Analysis

Appendix 1: Evidence to Recommendation Tables

Evidence to recommendation framework 1

Guideline Question: Should aspirin rather than no therapy be used in patients with atrial fibrillation?

Problem: Patients with non-valvular atrial fibrillation

Option: Aspirin

Comparison: No antithrombotics

Setting: Outpatient

Perspective: The KSA MoH

Background and Objective: The guideline will address this question in the people living in the community in Saudi Arabia.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐		

Outcome	Assumed Baseline Risk in Systematic Review: Overall risk (Without treatment - 1 yr. time-frame)	High risk population (Without treatment - 1 yr. time-frame)
Death	53 per 1000	-
Nonfatal stroke	-	96 per 1000
Nonfatal major extracranial bleeds	5 per 1000	-
Systemic em-bolism	4 per 1000	-
Burden of treatment	High with VKA	-

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
BENEFITS & HARMS OF THE OPTIONS	**What is the overall quality of this evidence?**	*No included studies* ☐ | *Very low* ☐ *Low* ☐ *Moderate* ☐ *High* ■	***The relative importance or values of the main outcomes of interest:***	These findings were considered applicable to the context of Saudi Arabia by the KSA MoH guideline panel.
	Is there important uncertainty about how much people value the main outcomes?	*Important uncertainty or variability* ☐ *Possibly important uncertainty or variability* ☐ *Probably no important uncertainty or variability* ☐ *No important uncertainty or variability* ■ *No known undesirable outcomes* ☐	***Summary of the evidence for patients' values and preferences:***	

Outcome	Relative importance	Quality of the evidence
Mortality	Critical	High
Nonfatal stroke	Critical	High
Nonfatal major extracranial bleeds	Important	High
Systemic embolism	Important	Moderate
Burden of treatment	Important	High

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
	Are the desirable anticipated effects large?	$CHADS_2 = 0$ *No* ☐ *Probably No* ■ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐	A systematic review of 16 studies conducted in western countries showed that, in general, informed patients prefer to prevent a stroke rather than preventing a bleeding event. A reasonable trade-off to assume between stroke and bleeds would be a ratio of disutility of net nonfatal stroke (thrombotic or hemorrhagic) to gastro-intestinal bleeds in the range of 2:1 to 3:1. **Reference:** MacLean S et al. Chest. 2012;141(2)(suppl):e1S-e23S.	

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
Are the undesirable anticipated effects small?	CHADS$_2$ = 0 No ☐ Probably No ☐ Uncertain ☐ Probably Yes ■ Yes ☐ Varies ☐	**Summary of findings: Should aspirin rather than no therapy be used in patients with non-valvular atrial fibrillation?** (ref: 14-21)	The reduction of the risk of stroke might be larger in patients with additional risk factors, not considered by the CHADS2 score. These risk factors include: age over 65 years, female gender and the presence of vascular disease (previous myocardial infarction, peripheral artery disease or the existence of an aortic plaque).
Are the desirable effects large relative to undesirable effects?	CHADS$_2$ = 0 No ☐ Probably No ■ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☐		

Outcome	Estimation of absolute effects 1 year time frame: With no therapy	Estimation of absolute effects 1 year time frame: Difference with VKA (95%CI)	Relative effect (RR) (95%CI)	Quality of the evidence (GRADE)
Death	53 per 1000[1]	6 fewer deaths per 1000 (from 13 fewer to 3 more)	RR 0.89 (0.75 to 1.05)	⊕⊕⊕O MODERATE[2]
Nonfatal stroke *Ischemic stroke and intracranial hemorrhage*[3]	CHADS$_2$ 0 points		RR 0.79 (0.65 to 0.96)	⊕⊕⊕O MODERATE[5]
	8 per 1000	2 fewer strokes per 1000[4] (from 0 fewer to 3 fewer)		
	CHADS$_2$ 1 points			
	22 per 1000	5 fewer strokes per 1000[4] (from 1 fewer to 8 fewer)		
	CHADS$_2$ 2 points			
	45 per 1000	9 fewer strokes per 1000[4] (from 2 fewer to 16 fewer)		
	CHADS$_2$ 3-6 points			
	96 per 1000	20 fewer strokes per 1000[4] (from 4 fewer to 34 fewer)		
Major extracranial bleeds *(fatal and non-fatal)*[6]	5 per 1000	3 more bleeds per 1000 (from 2 more to 4 more)	RR 1.60 (1.40 to 1.80)	⊕⊕⊕⊕ HIGH
Systemic embolism	4 per 1000	1 fewer events per 1000[7] (from 2 fewer to 2 more)	RR 0.80 (0.43 to 1.52)	⊕⊕⊕O MODERATE[2]

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐	No evidence identified	
	Is the incremental cost small relative to the net benefits?	$CHADS_2 = 0$ *No* ☐ *Probably No* ■ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ☐ ***Varies*** ☐		
EQUITY	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ☐ *Uncertain* ☐ *Probably reduced* ■ *Reduced* ☐ ***Varies*** ☐	No evidence identified	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐	No evidence identified	

FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐	No evidence identified	

Question 1: Should aspirin rather than no therapy be used in patients with atrial fibrillation at low risk of stroke (e.g. $CHADS_2$ score = 0)?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	■	☐	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	■	☐	☐

Recommendation (text)

For patients with non-valvular atrial fibrillation at low risk of stroke (e.g. $CHADS_2$ score = 0), the KSA MoH guideline panel suggests no antithrombotic therapy rather than aspirin [weak recommendation, moderate quality evidence]

Footnotes:

1. Baseline risk from the ATRIA Cohort (Go et al. JAMA 2003;290:2685-2592).

2. The quality of the evidence was rated down by imprecision, since the 95% confidence interval does not exclude the possibility of no effect or harm.

3. Intracranial hemorrhage includes: intracerebral, subdural, and subarachnoid bleeds.

4. The absolute risk of stroke with aspirin was estimated from annual rates of ischemic stroke in the aspirin arms of 6 historical trials in atrial fibrillation patients (Gage et al. Circulation 2004;110:2287-2292).

5. The quality of the evidence was rated down by imprecision. When the meta-analysis was restricted to trials evaluating aspirin alone vs. no antithrombotic therapy (i.e., excluding SAFT, which used aspirin in combination with fixed minidose warfarin, and excluding the dipyridamole monotherapy arm of ESPS-2) the relative risk included no effect (relative risk 0.81, 95% confidence interval 0.66 to 1.01).

6. We used the same estimate for the relative effect as in the systematic review, where in addition to the trials evaluating aspirin versus no therapy in people with atrial fibrillation, the authors included evidence from trials evaluating aspirin for the secondary prevention of cardiovascular events. Specific data regarding nonfatal events was not reported

7. The absolute risk of systemic embolism with aspirin was estimated from an IPD meta-analysis of warfarin vs. aspirin (van Walraven et al. JAMA 2002;288:2441-2448)

Evidence to recommendation framework 2

Guideline Question: Should vitamin K antagonists (VKA) rather than no therapy be used in patients with atrial fibrillation?

Problem: Patients with non-valvular atrial fibrillation

Option: Vitamin K antagonists (VKA)

Comparison: No anticoagulation

Setting: Outpatient

Perspective: The KSA MoH

Background and Objective: The guideline will address this question in the people living in the community in Saudi Arabia.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐		

Outcome	Assumed Baseline Risk in Systematic Review: Overall risk (Without treatment - 1 yr. time-frame)	High risk population (Without treatment - 1 yr. time-frame)
Death	53 per 1000	-
Nonfatal stroke	-	96 per 1000
Nonfatal major extracranial bleeds	5 per 1000	-
Systemic em-bolism	4 per 1000	-
Burden of treatment	High with VKA	-

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
What is the overall quality of this evidence?	No included studies ☐ · Very low ☐ · Low ☐ · Moderate ☐ · High ■	***The relative importance or values of the main outcomes of interest:***	These findings were considered applicable to the context of Saudi Arabia by the KSA MoH guideline panel.
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ · Possibly important uncertainty or variability ☐ · Probably no important uncertainty or variability ☐ · No important uncertainty or variability ■ · No known undesirable outcomes ☐		
Are the desirable anticipated effects large?	$CHADS_2 = 0$: No ☐ · Probably No ■ · Uncertain ☐ · Probably Yes ☐ · Yes ☐ · Varies ☐		
	$CHADS_2 = 1$: No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ☐ · Yes ■ · Varies ☐		
	$CHADS_2 = 2$ or greater: No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ☐ · Yes ■ · Varies ☐		

Outcome	Relative importance	Quality of the evidence
Mortality	Critical	High
Nonfatal stroke	Critical	High
Nonfatal major extracranial bleeds	Important	High
Systemic embolism	Important	Moderate
Burden of treatment	Important	High

Summary of the evidence for patients' values and preferences:

A systematic review of 16 studies conducted in western countries showed that, in general, informed patients prefer to prevent a stroke rather than preventing a bleeding event. A reasonable trade-off to assume between stroke and bleeds would be a ratio of disutility of net nonfatal stroke (thrombotic or hemorrhagic) to gastro-intestinal bleeds in the range of 2:1 to 3:1.

The review also showed that, for most patients, the use of vitamin K antagonists represents an important burden, although it does not have important negative effects on quality of life. Patients' aversion to warfarin treatment may decrease over time once the treatment is initiated.

Reference:

MacLean S et al. Chest. 2012;141(2)(suppl):e1S-e23S.

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
Are the undesirable anticipated effects small?	$CHADS_2 = 0$ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ■ Yes ☐ **Varies** ☐ $CHADS_2 = 1$ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ■ **Varies** ☐ $CHADS_2 = 2$ or greater No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ■ **Varies** ☐	**Summary of findings: Should vitamin K antagonists (VKA) rather than no therapy be used in patients with non-valvular atrial fibrillation?** (ref: 22-27)	Although the use of VKA is expected to reduce mortality in general, it is likely that this benefit does not extend to low-risk patients The reduction of the risk of stroke might be larger in patients with additional risk factors, not considered by the CHADS2

Outcome	Estimation of absolute effects 1 year time frame		Relative effect (RR) (95%CI)	Quality of the evidence (GRADE)
	With no therapy	Difference with VKA (95%CI)		
Death	53 per 1000[1]	15 fewer deaths per 1000[2] (from 3 fewer to 24 fewer)	RR 0.72 (0.55 to 0.94)	⊕⊕⊕⊕ HIGH
Nonfatal stroke *Ischemic stroke and intracranial hemorrhage*[3]	$CHADS_2$ 0 points		RR 0.34 (0.23 to 0.49)	⊕⊕⊕⊕ HIGH
	8 per 1000[4]	5 fewer strokes per 1000 (from 4 fewer to 6 fewer)		
	$CHADS_2$ 1 points			

Are the desirable effects large relative to undesirable effects?

$CHADS_2 = 0$

No	Probably No	Uncertain	Probably Yes	Yes	Varies
☐	■	☐	☐	☐	☐

$CHADS_2 = 1$

No	Probably No	Uncertain	Probably Yes	Yes	Varies
☐	☐	☐	☐	■	☐

$CHADS_2 = 2$ or greater

No	Probably No	Uncertain	Probably Yes	Yes	Varies
☐	☐	☐	☐	■	☐

	22 per 1000[4]	15 fewer strokes per 1000 (from 11 fewer to 17 fewer)			
	$CHADS_2$ 2 points				
	45 per 1000[4]	30 fewer strokes per 1000 (from 23 fewer to 35 fewer)			
	$CHADS_2$ 3-6 points				
	96 per 1000[4]	63 fewer strokes per 1000 (from 49 fewer to 74 fewer)			
Nonfatal major extracranial bleeds	5 per 1000	8 more bleeds per 1000 (from 1 more to 25 more)	RR 2.58 (1.12 to 5.97)	⊕⊕⊕⊕ HIGH	
Systemic embolism	4 per 1000	2 fewer events per 1000 (from 3 fewer to 1 more)	RR 0.42 (0.15 to 1.20)	⊕⊕⊕O MODERATE[5]	
Burden of treatment	None	Lifestyle and dietary restrictions, frequent blood testing and clinic visits	NA	⊕⊕⊕⊕ HIGH	

score. These risk factors include: age over 65 years, female gender and the presence of vascular disease (previous myocardial infarction, peripheral artery disease or the existence of an aortic plaque).

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	No ☐ / Probably No ■ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	A systematic review of 5 economic evaluations showed: The use of VKA rather than no therapy is cost-effective in patients with atrial fibrillation at moderate-to-high risk of stroke. The studies identified by the review were conducted more than 10 years ago and in western health care settings. **Reference:** Szucs TD et al. J Thromb Haemost. 2006 Jun;4(6):1180-5	
	Is the incremental cost small relative to the net benefits?	$CHADS_2 = 0$: No ■ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐ $CHADS_2 = 1$: No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ■ / Varies ☐ $CHADS_2 = 2$ or greater: No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ■ / Varies ☐		
EQUITY	**What would be the impact on health inequities?**	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ■ / Reduced ☐ / Varies ☐	No evidence identified	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ■ / Varies ☐	No evidence identified	

FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐	No evidence identified	

Question 2: Should oral anticoagulation rather than no therapy be used in patients with atrial fibrillation at low risk of stroke (e.g. $CHADS_2$ score = 0)?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	■	☐	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	■	☐	☐

Recommendation (text)

For patients with non-valvular atrial fibrillation at low risk of stroke (e.g. CHADS2 score = 0), the KSA MoH guideline panel suggests no antithrombotic therapy rather oral anticoagulation [weak recommendation, moderate quality evidence]

Question 4: Should oral anticoagulation rather than no therapy be used in patients with atrial fibrillation at intermediate risk of stroke (e.g. CHADS2 score = 1)?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	■

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	■

Recommendation (text)	For patients with non-valvular atrial fibrillation at intermediate risk of stroke (e.g. CHADS2 score = 1), the KSA MoH guideline panel recommends oral anticoagulation rather than no antithrombotic therapy [strong recommendation, high quality evidence]

Question 7: Should oral anticoagulation rather than no therapy be used in patients with atrial fibrillation at high of stroke (e.g. CHADS2 score = 2 or greater)?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	■

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	■

Recommendation (text)	For patients with non-valvular atrial fibrillation at high risk of stroke (e.g. CHADS2 score = 2 or greater), the KSA MoH guideline panel recommends oral anticoagulation rather than no antithrombotic therapy [strong recommendation, high quality evidence]

Footnotes:

1. Baseline risk from the ATRIA Cohort (Go et al. JAMA 2003;290:2685-2592).

2. Estimate for patients at intermediate to high of stroke. VKA therapy probably does not lead to any reduction in all-cause mortality compared to no therapy in low risk patients.

3. Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeds.

4. The absolute risk of stroke with aspirin was estimated from annual rates of ischemic stroke in the aspirin arms of 6 historical trials in atrial fibrillation patients (Gage et al. Circulation 2004;110:2287-2292).

5. The quality of the evidence was rated down for imprecision, since the 95% confidence interval does not exclude the possibility of no effect.

Evidence to recommendation framework 3

Guideline Question: Should vitamin K antagonists (VKA) rather than aspirin be used in patients with atrial fibrillation?

Problem: Patients with non-valvular atrial fibrillation
Option: Vitamin K antagonists (VKA)
Comparison: Aspirin
Setting: Outpatient
Perspective: The KSA MoH

Background and Objective: The guideline will address this question in the people living in the community in Saudi Arabia.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐		

	Assumed Baseline Risk in Systematic Review:	
Outcome	**Overall risk (Without treatment - 1 yr. time-frame)**	**High risk population (Without treatment - 1 yr. time-frame)**
Death	53 per 1000	-
Nonfatal stroke	-	96 per 1000
Nonfatal major extracranial bleeds	5 per 1000	-
Systemic em-bolism	4 per 1000	-
Burden of treatment	High with VKA	-

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
What is the overall quality of this evidence?	No included studies ☐ · Very low ☐ · Low ☐ · Moderate ☐ · High ■	***The relative importance or values of the main outcomes of interest:***	These findings were considered applicable to the context of Saudi Arabia by the KSA MoH guideline panel.
Is there important uncertainty about how much people value the main outcomes?	Important uncertainty or variability ☐ · Possibly important uncertainty or variability ☐ · Probably no important uncertainty or variability ☐ · No important uncertainty or variability ■ · No known undesirable outcomes ☐		
Are the desirable anticipated effects large?	$CHADS_2 = 0$: No ☐ · Probably No ■ · Uncertain ☐ · Probably Yes ☐ · Yes ☐ · Varies ☐		
	$CHADS_2 = 1$: No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ■ · Yes ☐ · Varies ☐		
	$CHADS_2 = 2$ or greater: No ☐ · Probably No ☐ · Uncertain ☐ · Probably Yes ☐ · Yes ■ · Varies ☐		

Outcome	Relative importance	Quality of the evidence
Mortality	Critical	High
Nonfatal stroke	Critical	High
Nonfatal major extracranial bleeds	Important	High
Systemic embolism	Important	Moderate
Burden of treatment	Important	High

Summary of the evidence for patients' values and preferences:

A systematic review of 16 studies conducted in western countries showed that, in general, informed patients prefer to prevent a stroke rather than preventing a bleeding event. A reasonable trade-off to assume between stroke and bleeds would be a ratio of disutility of net nonfatal stroke (thrombotic or hemorrhagic) to gastro-intestinal bleeds in the range of 2:1 to 3:1.

The review also showed that, for most patients, the use of vitamin K antagonists represents an important burden, although it does not have important negative effects on quality of life. Patients' aversion to warfarin treatment may decrease over time once the treatment is initiated.

Reference:

MacLean S et al. Chest. 2012;141(2)(suppl):e1S-e23S.

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
Are the undesirable anticipated effects small?	$CHADS_2 = 0$ *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ■ *Yes* ☐ ***Varies*** ☐ $CHADS_2 = 1$ *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐ $CHADS_2 = 2$ or greater *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐	**Summary of findings: Should vitamin K antagonists (VKA) rather than aspirin be used in patients with non-valvular atrial fibrillation?** (ref: 29-40)	

Outcome	Estimation of absolute effects 1 year time frame		Relative effect (RR) (95%CI)	Quality of the evidence (GRADE)
	With aspirin	Difference with VKA (95%CI)		
Death	47 per 1000[1]	1 fewer death per 1000 (from 7 fewer to 6 more)	RR 0.97 (0.85 to 1.12)	⊕⊕⊕O MODERATE[2]
Nonfatal stroke *Ischemic stroke and intracranial hemorrhage*[3]	$CHADS_2$ 0 points		RR 0.48 (0.33 to 0.70)	⊕⊕⊕⊕ HIGH
	6 per 1000[4]	3 fewer strokes per 1000 (from 2 fewer to 4 fewer)		
	$CHADS_2$ 1 points			

Are the desirable effects large relative to undesirable effects?

$CHADS_2 = 0$

No	Probably No	Uncertain	Probably Yes	Yes	Varies
☐	■	☐	☐	☐	☐

$CHADS_2 = 1$

No	Probably No	Uncertain	Probably Yes	Yes	Varies
☐	☐	☐	☐	■	☐

$CHADS_2 = 2$ or greater

No	Probably No	Uncertain	Probably Yes	Yes	Varies
☐	☐	☐	☐	■	☐

	17 per 1000[4]	9 fewer strokes per 1000 (from 5 fewer to 11 fewer)		
	$CHADS_2$ 2 points			
	36 per 1000[4]	19 fewer strokes per 1000 (from 11 fewer to 24 fewer)		
	$CHADS_2$ 3-6 points			
	76 per 1000[4]	40 fewer strokes per 1000 (from 23 fewer to 51 fewer)		
Nonfatal major extracranial bleeds	8 per 1000	3 more bleeds per 1000 (from 1 fewer to 10 more)	RR 1.42 (0.89 to 2.29)	⊕⊕⊕O MODERATE[2]
Systemic embolism	3 per 1000[5]	1 fewer events per 1000 (from 2 fewer to 2 more)	RR 0.81 (0.40 to 1.64)	⊕⊕⊕O MODERATE[2]
Burden of treatment	Daily medication	Lifestyle and dietary restrictions, frequent blood testing and clinic visits	NA	⊕⊕⊕⊕ HIGH

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	No ☐ / Probably No ■ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐	Seven economic evaluations showed: The use of VKA rather than aspirin is cost-effective in patients with atrial fibrillation at moderate-to-high risk of stroke. Among patients at low risk of stroke, the use VKA rather than aspirin is not a cost-effective strategy. **References:** 1. Gage BF et al. JAMA. 1995 Dec 20;274(23):1839-45. 2. Solomon MD et al. J Cardiovasc Med (Hagerstown). 2012 Feb;13(2):86-96. 3. Jowett S. et al. Stroke 2011 42(6): 1717-1721.	
	Is the incremental cost small relative to the net benefits?	$CHADS_2 = 0$: No ☐ / Probably No ■ / Uncertain ☐ / Probably Yes ☐ / Yes ☐ / Varies ☐ $CHADS_2 = 1$: No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ■ / Varies ☐ $CHADS_2 = 2$ or greater: No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ■ / Varies ☐		
EQUITY	**What would be the impact on health inequities?**	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ■ / Reduced ☐ / Varies ☐	No evidence identified	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ■ / Varies ☐	No evidence identified	

FEASIBILITY	**Is the option feasible to implement?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐	No evidence identified

Question 3: Should oral anticoagulation rather than aspirin be used in patients with atrial fibrillation at low risk of stroke (e.g. $CHADS_2$ score = 0)?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	■	☐	☐	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	■	☐	☐

Recommendation (text)

For patients with non-valvular atrial fibrillation at low risk of stroke who choose antithrombotic therapy, the KSA MoH guideline panel suggests the use of aspirin (75 mg to 325 mg once daily) rather than oral anticoagulation [weak recommendation, moderate quality evidence]

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	■

Question 5: Should oral anticoagulation rather than aspirin be used in patients with atrial fibrillation at intermediate risk of stroke (e.g. CHADS2 score = 1)?

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	■

Recommendation (text)	For patients with non-valvular atrial fibrillation at intermediate risk of stroke (e.g. CHADS2 score = 1), the KSA MoH guideline panel recommends oral anticoagulation rather than aspirin [strong recommendation, moderate quality evidence].

Question 8: Should oral anticoagulation rather than aspirin be used in patients with atrial fibrillation at high of stroke (e.g. CHADS2 score = 2 or greater)?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	■

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	■

Recommendation (text)	For patients with non-valvular atrial fibrillation at high risk of stroke (e.g. CHADS2 score = 2 or greater), the KSA MoH guideline panel recommends oral anticoagulation rather than aspirin [strong recommendation, moderate quality evidence]

Footnotes:

1. Baseline risk from the ATRIA Cohort (Go et al. JAMA 2003;290:2685-2592).

2. The quality of the evidence was rated down for imprecision, since the 95% confidence does not exclude the possibility of important harm or benefit with VKA therapy

3. Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeds.

4. The absolute risk of stroke with aspirin was estimated from annual rates of ischemic stroke in the aspirin arms of 6 historical trials in atrial fibrillation patients (Gage et al. Circulation 2004;110:2287-2292).

5. The absolute risk of systemic embolism with aspirin was estimated from an IPD meta-analysis of warfarin vs. aspirin (van Walraven et al. JAMA 2002;288:2441-2448)

Evidence to recommendation framework 4

Guideline Question: Should vitamin K antagonists (VKA) rather than aspirin plus clopidogrel be used in patients with atrial fibrillation?

Problem: Patients with non-valvular atrial fibrillation
Option: Vitamin K antagonists (VKA)
Comparison: Aspirin plus clopidogrel
Setting: Outpatient
Perspective: The KSA MoH

Background and Objective: The guideline will address this question in the people living in the community in Saudi Arabia.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐		

Outcome	Assumed Baseline Risk in Systematic Review: Overall risk (Without treatment - 1 yr. time-frame)	High risk population (Without treatment - 1 yr. time-frame)
Death	53 per 1000	-
Nonfatal stroke	-	96 per 1000
Nonfatal major extracranial bleeds	5 per 1000	-
Systemic embolism	4 per 1000	-
Burden of treatment	High with VKA	-

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
What is the overall quality of this evidence?	☐ No included studies ☐ Very low ☐ Low ☐ Moderate ■ High	***The relative importance or values of the main outcomes of interest:***	These findings were considered applicable to the context of Saudi Arabia by the KSA MoH guideline panel.
Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ■ No important uncertainty or variability ☐ No known undesirable outcomes	***Summary of the evidence for patients' values and preferences:*** A systematic review of 16 studies conducted in western countries showed that, in general, informed patients prefer to prevent a stroke rather than preventing a bleeding event. A reasonable trade-off to assume between stroke and bleeds would be a ratio of disutility of net nonfatal stroke (thrombotic or hemorrhagic) to gastro-intestinal bleeds in the range of 2:1 to 3:1. The review also showed that, for most patients, the use of vitamin K antagonists represents an important burden, although it does not have important negative effects on quality of life. Patients' aversion to warfarin treatment may decrease over time once the treatment is initiated.	
Are the desirable anticipated effects large?	$CHADS_2 = 1$: ☐ No ■ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies $CHADS_2 = 2$ or greater: ☐ No ☐ Probably No ☐ Uncertain ☐ Probably Yes ■ Yes ☐ Varies	**Reference:** MacLean S et al. Chest. 2012;141(2)(suppl):e1S-e23S.	

Outcome	Relative importance	Quality of the evidence
Mortality	Critical	High
Nonfatal stroke	Critical	High
Nonfatal major extracranial bleeds	Important	High
Systemic embolism	Important	Moderate
Burden of treatment	Important	High

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
	Are the undesirable anticipated effects small?	$CHADS_2 = 1$ *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ■ *Yes* ☐ ***Varies*** ☐ $CHADS_2 = 2$ or greater *No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐	**Summary of findings: Should vitamin K antagonists (VKA) rather than aspirin plus clopidogrel used in patients with non-valvular atrial fibrillation?** (ref: 43)	

Outcome	Estimation of absolute effects 1 year time frame		Relative effect (RR) (95%CI)	Quality of the evidence (GRADE)
	With aspirin + clopidogrel	Difference with VKA (95%CI)		
Death	46 per 1000[1]	1 fewer death per 1000 (from 10 fewer to 10 more)	RR 0.98 (0.79 to 1.22)	⊕⊕⊕O MODERATE[2]
Nonfatal stroke *Ischemic stroke and intracranial hemorrhage*[3]	$CHADS_2$ 0 points		RR 0.56 (0.39 to 0.82)	⊕⊕⊕⊕ HIGH
	5 per 1000[4]	2 fewer strokes per 1000 (from 1 fewer to 3 fewer)		

Are the desirable effects large relative to undesirable effects?

$CHADS_2$ = 1

No	Probably No	Uncertain	Probably Yes	Yes	Varies
☐	☐	☐	■	☐	☐

$CHADS_2$ = 2 or greater

No	Probably No	Uncertain	Probably Yes	Yes	Varies
☐	☐	☐	☐	■	☐

	$CHADS_2$ 1 points			
	13 per 1000[4]	6 fewer strokes per 1000 (from 2 fewer to 8 fewer)		
	$CHADS_2$ 2 points			
	26 per 1000[4]	11 fewer strokes per 1000 (from 5 fewer to 16 fewer)		
	$CHADS_2$ 3-6 points			
	55 per 1000[4]	24 fewer strokes per 1000 (from 10 fewer to 34 fewer)		
Nonfatal major extracranial bleeds[5]	12 per 1000	1 fewer bleeds per 1000 (from 4 fewer to 3 more)	RR 0.91 (0.67 to 1.23)	⊕⊕⊕O MODERATE[2]
Systemic embolism	3 per 1000[6]	2 fewer events per 1000 (from 1 fewer to 3 fewer)	RR 0.22 (0.07 to 0.65)	⊕⊕⊕⊕ HIGH
Burden of treatment	Daily medication	Lifestyle and dietary restrictions, frequent blood testing and clinic visits	NA	⊕⊕⊕⊕ HIGH

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
RESOURCE USE	Are the resources required small?	No ☐ Probably No ■ Uncertain ☐ Probably Yes ☐ Yes ☐ Varies ☐	No evidence identified	
	Is the incremental cost small relative to the net benefits?	$CHADS_2 = 1$: No ☐ Probably No ☐ Uncertain ☐ Probably Yes ■ Yes ☐ Varies ☐ $CHADS_2 = 2$ or greater: No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ■ Varies ☐		
EQUITY	What would be the impact on health inequities?	Increased ☐ Probably increased ☐ Uncertain ☐ Probably reduced ■ Reduced ☐ Varies ☐	No evidence identified	
ACCEPTABILITY	Is the option acceptable to key stakeholders?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ■ Varies ☐	No evidence identified	
FEASIBILITY	Is the option feasible to implement?	No ☐ Probably No ☐ Uncertain ☐ Probably Yes ☐ Yes ■ Varies ☐	No evidence identified	

Question 6: Should oral anticoagulation rather than aspirin plus clopidogrel be used in patients with atrial fibrillation at intermediate risk of stroke (e.g. CHADS2 score = 1)?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	■	☐

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	■	☐

Recommendation (text)

For patients with non-valvular atrial fibrillation at intermediate risk of stroke (e.g. CHADS2 score = 1), the KSA MoH guideline panel suggests oral anticoagulation rather than aspirin plus clopidogrel [weak recommendation, moderate quality evidence]

Question 9: Should oral anticoagulation rather than aspirin plus clopidogrel be used in patients with atrial fibrillation at high of stroke (e.g. CHADS2 score = 2 or greater)?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	☐	■

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	☐	■

Recommendation (text)

For patients with non-valvular atrial fibrillation at high risk of stroke (e.g. CHADS2 score = 2 or greater), the KSA MoH guideline panel recommends oral anticoagulation rather than aspirin plus clopidogrel [strong recommendation, moderate quality evidence]

Footnotes:

1. Baseline risk from the ATRIA Cohort (Go et al. JAMA 2003;290:2685-2592).

2. The quality of the evidence was rated down for imprecision, since 95% confidence interval does not exclude important harm or benefit with VKA therapy.

3. Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeds.

4. The absolute risk of stroke with aspirin was estimated from annual rates of ischemic stroke in the aspirin arms of 6 historical trials in atrial fibrillation patients (Gage et al. Circulation 2004;110:2287-2292) and the relative risk observed in ACTIVE A trial.

5. The number of non-fatal major extracranial bleeds was not available. We used the same estimate as in the systematic review, where the pooled relative risk for non-fatal major extracranial bleeds was imputed from aggregate data.

6. The absolute risk of systemic embolism with aspirin + clopidogrel was estimated from an IPD meta-analysis of warfarin vs. aspirin (van Walraven et al. JAMA 2002;288:2441-2448) and the relative risk observed in ACTIVE A trial.

Evidence to recommendation framework 5

Guideline Question: Should Novel Oral Anticoagulants (NOAC) rather than vitamin K antagonists (VKA) be used in patients with non-valvular atrial fibrillation?

Problem: Patients with non-valvular atrial fibrillation
Option: Novel Oral Anticoagulants (NOAC)
Comparison: Vitamin K antagonists (VKA)
Setting: Outpatient
Perspective: The KSA MoH

Background and Objective: The guideline will address this question in the people living in the community in Saudi Arabia.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ☐ *Yes* ■ ***Varies*** ☐		

Outcome	Assumed Baseline Risk in Systematic Review: Overall risk (Without treatment - 1 yr. time-frame)	High risk population (Without treatment - 1 yr. time-frame)
Death	53 per 1000	-
Nonfatal stroke	-	96 per 1000
Nonfatal major extracranial bleeds	5 per 1000	-
Systemic em-bolism	4 per 1000	-
Burden of treatment	High with VKA	-

BENEFITS & HARMS OF THE OPTIONS

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
What is the overall quality of this evidence?	☐ No included studies ☐ Very low ☐ Low ☐ Moderate ■ High	***The relative importance or values of the main outcomes of interest:***	These findings were considered applicable to the context of Saudi Arabia by the KSA MoH guideline panel.
Is there important uncertainty about how much people value the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ■ No important uncertainty or variability ☐ No known undesirable outcomes	***Summary of the evidence for patients' values and preferences:*** A systematic review of 16 studies conducted in western countries showed that, in general, informed patients prefer to prevent a stroke rather than preventing a bleeding event. A reasonable trade-off to assume between stroke and bleeds would be a ratio of disutility of net nonfatal stroke (thrombotic or hemorrhagic) to gastro-intestinal bleeds in the range of 2:1 to 3:1. The review also showed that, for most patients, the use of vitamin K antagonists represents an important burden, although it does not have important negative effects on quality of life. Patients' aversion to warfarin treatment may decrease over time once the treatment is initiated.
Are the desirable anticipated effects large?	☐ No ☐ Probably No ☐ Uncertain ■ Probably Yes ☐ Yes ☐ ***Varies***	**Reference:** MacLean S et al. Chest. 2012;141(2)(suppl):e1S-e23S.

Outcome	Relative importance	Quality of the evidence
Mortality	Critical	High
Nonfatal stroke	Critical	High
Nonfatal major extracranial bleeds	Important	High
Systemic embolism	Important	Moderate
Burden of treatment	Important	High

CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
Are the undesirable anticipated effects small?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ■ *Yes* ☐ ***Varies*** ☐	**Summary of findings:** **Should Novel Oral Anticoagulants (NOAC) rather than vitamin K antagonists (VKA) be used in patients with non-valvular atrial fibrillation?** (ref: 44-50)	For patients who are well controlled and without complications with VKA, the decision to switch to NOACs should be individualized to the specific clinical circumstances and patients' preferences There is no long-term data regarding the safety of NOACs. Uncommon but serious adverse effects might emerge with large-scale use of the drugs. Dose adjustments may be necessary for special populations: Dabigatran 110 mg could be an alternative for the elderly (over 75 years) and patients with an increased risk of bleeding, while rivaroxaban 15 mg could be
Are the desirable effects large relative to undesirable effects?	*No* ☐ *Probably No* ☐ *Uncertain* ☐ *Probably Yes* ■ *Yes* ☐ ***Varies*** ☐		

Outcome	Estimation of absolute effects Follow-up up to 2.5 years		Relative effect RR (95%CI)	Quality of the evidence (GRADE)
	With VKA	Difference with NOAC (95%CI)		
Death	61 per 1000[1]	6 fewer deaths per 1000 (from 3 to 11 fewer)	RR 0.89 (0.82- 0.95)	⊕⊕⊕⊕ HIGH
Nonfatal stroke *Ischemic stroke and intracranial hemorrhage*[2]	30 per 1000[1]	8 fewer strokes per 1000 (from 5 to 10 fewer)	RR 0.75 (0.66- 0.86)	⊕⊕⊕⊕ HIGH[3]
Major bleeds[4]	55 per 1000[1]	7 fewer bleeds per 1000 (from 15 fewer to 3 more)	RR 0.87 (0.72- 1.05)	⊕⊕OO LOW[3,5,6]
Systemic embolism	2 per 1000[1]	1 fewer events per 1000 (from 1 fewer to 2 more)	RR 0.61 (0.61- 1.22)	⊕⊕⊕O MODERATE[5,7]
Burden of treatment	Lifestyle and dietary restrictions, frequent blood testing and clinic visits	Daily medication	NA	⊕⊕⊕⊕ HIGH

				used in patients with mild renal impair-ment.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE AND NOTES	GUIDELINE PANEL CONSIDERATIONS
RESOURCE USE	**Are the resources required small?**	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ■ / Yes ☐ / Varies ☐	A systematic review of 16 economic evaluations (13 evaluating dabigatran, 3 apixaban and 2 rivaroxaban) found that NOACs are cost-effective across a broad range of health care settings and perspectives. **Reference:** Best Pract Res Clin Haematol. 2013 Jun;26(2):225-37.	Even though the direct cost of NOACs is high, their overall resource utilization is probably lower than with the use of VKA
	Is the incremental cost small relative to the net benefits?	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ■ / Yes ☐ / Varies ☐		
EQUITY	**What would be the impact on health inequities?**	Increased ☐ / Probably increased ☐ / Uncertain ☐ / Probably reduced ■ / Reduced ☐ / Varies ☐	No evidence identified	
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ■ / Varies ☐	No evidence identified	
FEASIBILITY	**Is the option feasible to implement?**	No ☐ / Probably No ☐ / Uncertain ☐ / Probably Yes ☐ / Yes ■ / Varies ☐	No evidence identified	

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences *is closely balanced or uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings
	☐	☐	☐	■	☐

Question 10: Should Novel Oral Anticoagulants (NOAC) rather than vitamin K antagonists (VKA) be used in patients with non-valvular atrial fibrillation?

Type of recommendation	We recommend against offering this option	We suggest not offering this option	We suggest offering this option	We recommend offering this option
	☐	☐	■	☐

Recommendation (text)	For patients with non-valvular atrial fibrillation in whom oral anticoagulation is recommended (or suggested), the KSA MoH guideline panel suggests the use of Novel Oral Anticoagulants (dabigatran 150 mg bid, rivaroxaban 20 mg once a day or apixaban 5 mg bid) rather than Vitamin K antagonists [weak recommendation, high quality evidence]

Footnotes:

1. Based on the control group of the trials evaluating NOACs vs. VKA

2. Intracranial hemorrhage includes intracerebral, subdural, and subarachnoid bleeds.

3. The funnel plot is asymmetrical suggesting potential publication bias. However, the effect estimates are almost completely based in the results of 3 large trials (which provide more than 95% of the weight). It is unlikely that small non-published trials could appreciable change the effect estimates.

4. The relative risk corresponds to the outcome “major bleeding” (intracranial and extracranial and fatal and nonfatal events), since specific data was not reported in some of the trials.

5. The quality of the evidence was rated down for imprecision, since the 95% confidence interval does not exclude important harm or benefit with NOAC.

6. The quality of the evidence was rated down for inconsistency, since there is substantial heterogeneity (I^2 = 69%) with effect estimates ranging from 0.35 to 1.03

7. Although there was substantial heterogeneity (I^2 49%), the number of events was low. Therefore, chance alone is a plausible explanation for the variability observed among trials. Since the quality of the evidence was already rated-down for imprecision, we decided to not rate-down for inconsistency.

Appendix 2: Search Strategies and Results

Effect Estimates Search

Data base: **MEDLINE (via OVID)**	
Search strategy:	**Date of search: 11/2013**

1. exp Coumarins/
2. warfarin/
3. warfarin$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4. (dicumarol or phenprocoumon or acenocoumarol).mp.
5. fondaparinux.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6. idraparinux.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7. Aspirin/
8. triflusal.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
9. indobufen.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
10. dabigatran.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
11. ximelagatran.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
12. rivaroxaban.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
13. apixaban.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
14. ticlopidine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
15. clopidogrel.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

16. 1 or 3 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. Ablation Techniques/
18. exp Catheter Ablation/
19. watchman.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
20. PLAATO.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
21. maze procedure$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
22. ((ligat$ or remov$) adj2 atrial append$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
23. 20 or 21 or 18 or 19 or 22 or 17
24. cardioversion$.mp.
25. exp atrial fibrillation/ or exp atrial flutter/
26. 16 and 25
27. 25 and 23 and 16
28. 24 and 25 and 16
29. 26 or 27 or 28
30. randomized controlled trial.pt.
31. controlled clinical trial.pt.
32. randomi?ed.ab.

33. placebo.ab. 34. drug therapy.fs. 35. randomly.ab. 36. trial.ab. 37. groups.ab. 38. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 39. exp animals/ not humans.sh. 40. 38 not 39 41. 40 and 29 42. limit 41 to (english language and yr="2010-current")
Date limit: 01/2010 - 11/2013 Study Types: RCTs

Records Retrieved	1009

Data base: **Cochrane Library (CENTRAL)**	
Search strategy:	**Date of search: 11/2013**
#1 Coumarins in Trials (Word variations have been searched) #2 warfarin in Trials (Word variations have been searched) #3 fondaparinux #4 idraparinux in Trials (Word variations have been searched) #5 Aspirin in Trials (Word variations have been searched) #6 triflusal in Trials (Word variations have been searched) #7 indobufen in Trials (Word variations have been searched) #8 dabigatran in Trials (Word variations have been searched) #9 ximelagatran in Trials (Word variations have been searched) #10 rivaroxaban in Trials (Word variations have been searched) #11 apixaban in Trials (Word variations have been searched) #12 ticlopidine in Trials (Word variations have been searched) #13 clopidogrel in Trials (Word variations have been searched) #14 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 #15 Ablation Techniques in Trials (Word variations have been searched) #16 Catheter Ablation in Trials (Word variations have been searched) #17 watchman in Trials (Word variations have been searched) #18 PLAATO in Trials (Word variations have been searched) #19 maze procedure in Trials (Word variations have been searched) #20 #15 or #16 or #17 or #18 or #19 1 #21 cardioversion in Trials (Word variations have been searched) #22 atrial fibrillation in Trials (Word variations have been searched) #23 atrial flutter in Trials (Word variations have been searched) #24 #22 or #23 #25 #14 and #24 #26 #14 and #24 and #20 #27 #14 and #24 and #21 #28 #25 or #26 or #27 from 2010 to 2013	
Date limit: 01/2010 - 11/2013 Study Types: RCTs	

Records Retrieved	93

Summary of Searches: Effect Estimates

No. Total Retrieved:	**1102**
Medline:	1009
Cochrane:	93
No. Total without duplicates:	**923**
Screening (Title and Abstract Review)	
No. Excluded:	916
Selection (Full Text Review)	
No. Excluded:	14
Reasons for exclusions:	
1. Not comparison of interest (7)	
Included in the update:	**7**

Patients' Values and Preferences Search

Data base: **MEDLINE (via OVID)**	
Search strategy:	**Date of search: 11/2013**
1. Saudi Arab$.mp,in. or Saudi Arabia/ 2. Riyadh.mp,in. 3. Jeddah.mp,in. 4. Kh*bar.mp,in. 5. Dammam.mp,in. 6. 1 or 2 or 3 or 4 or 5 7. Kuwait$.mp,in. or Kuwait/ 8. United Arab Emirates.mp,in. or United Arab Emirates/ 9. Qatar$.mp,in. or Qatar/ 10. Oman$.mp,in. or Oman/ 11. Yemen$.mp,in. or Yemen/ 12. Bahr*in$.mp,in. or Bahrain/ 13. 7 or 8 or 9 or 10 or 11 or 12 14. Middle East$.mp,in. or Middle East/ 15. Jordan$.mp,in. or Jordan/ 16. Libya$.mp,in. or Libya/ 17. Egypt$.mp,in. or Egypt/ 18. Syria$.mp,in. or Syria/ 19. Iraq$/ or Iraq.mp,in. 20. Morocc$.mp,in. or Morocco/ 21. Tunisia$.mp,in. or Tunisia/ 22. Leban$.mp,in. or Lebanon/ 23. West Bank.mp,in. 24. Iran$.mp,in. or Iran/ 25. Turkey/ or (Turkey or Turkish).mp,in. 26. Algeria$.mp,in. or Algeria/ 27. Arab$.mp,in. or Arabs/ 28. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 29. 27 or 28 30. 6 or 13 or 29 31. patient$ participation.mp. or exp patient participation/ 32. patient$ satisfaction.mp. or exp patient satisfaction/ 33. attitude to health.mp. or exp Attitude to health/ 34. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or patient$ view$ or patient$ value$).mp. 35. (patient$ utilit$ or health utilit$).mp. 36. health related quality of life.mp. or exp "quality of life"/	

37. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp. or exp Health Status Indicators/ 38. 31 or 32 or 33 or 34 or 35 or 36 or 37 39. atrial fibrillation.mp. or Atrial Fibrillation/ 40. atrial flutter.mp. or Atrial Flutter/ 41. Warfarin$.mp. or exp Warfarin/ 42. vitamin k antagonist$.mp. 43. aspirin$.mp. or Aspirin/ 44. clopidogrel.mp. 45. 39 or 40 46. 41 or 42 or 43 or 44 47. 45 or 46 48. 30 and 38 and 47
Date limit: None Study Types: Any

Records Retrieved	94

Data base: **EMBASE (via OVID)**	
Search strategy:	**Date of search: 11/2013**
1. Saudi Arab$.mp,in. or Saudi Arabia/ 2. Riyadh.mp,in. 3. Jeddah.mp,in. 4. Kh*bar.mp,in. 5. Dammam.mp,in. 6. 1 or 2 or 3 or 4 or 5 7. Kuwait$.mp,in. or Kuwait/ 8. United Arab Emirates.mp,in. or United Arab Emirates/ 9. Qatar$.mp,in. or Qatar/ 10. Oman$.mp,in. or Oman/ 11. Yemen$.mp,in. or Yemen/ 12. Bahr*in$.mp,in. or Bahrain/ 13. 7 or 8 or 9 or 10 or 11 or 12 14. Middle East$.mp,in. or Middle East/ 15. Jordan$.mp,in. or Jordan/ 16. Libya$.mp,in. or Libya/ 17. Egypt$.mp,in. or Egypt/ 18. Syria$.mp,in. or Syria/ 19. Iraq$/ or Iraq.mp,in. 20. Morocc$.mp,in. or Morocco/ 21. Tunisia$.mp,in. or Tunisia/ 22. Leban$.mp,in. or Lebanon/ 23. West Bank.mp,in. 24. Iran$.mp,in. or Iran/ 25. Turkey/ or (Turkey or Turkish).mp,in. 26. Algeria$.mp,in. or Algeria/ 27. Arab$.mp,in. or Arabs/ 28. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 29. 27 or 28 30. 6 or 13 or 29 31. patient$ participation.mp. or exp patient participation/ 32. patient$ satisfaction.mp. or exp patient satisfaction/ 33. attitude to health.mp. or exp Attitude to health/ 34. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or	

patient$ view$ or patient$ value$).mp. 35. (patient$ utilit$ or health utilit$).mp. 36. health related quality of life.mp. or exp "quality of life"/ 37. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp. or exp Health Status Indicators/ 38. 31 or 32 or 33 or 34 or 35 or 36 or 37 39. atrial fibrillation.mp. or heart atrium fibrillation/ 40. atrial flutter.mp. or heart atrium flutter/ 41. 39 or 40 42. Warfarin$.mp. or warfarin/ 43. vitamin k antagonist$.mp. or antivitamin K/ 44. (aspirin$ or acetylsalicylic acid$).mp. or acetylsalicylic acid/ 45. clopidogrel/ or acetylsalicylic acid plus clopidogrel/ or clopidogrel$.mp. 46. 42 or 43 or 44 or 45 47. 41 or 46 48. 30 and 38 and 47
Date limit: None Study Types: Any

Records Retrieved	123

Data base: **PsycINFO (via OVID)**	
Search strategy:	**Date of search: 11/2013**
1. Saudi Arab$.mp,in. or Saudi Arabia/ 2. Riyadh.mp,in. 3. Jeddah.mp,in. 4. Kh*bar.mp,in. 5. Dammam.mp,in. 6. 1 or 2 or 3 or 4 or 5 7. Kuwait$.mp,in. or Kuwait/ 8. United Arab Emirates.mp,in. or United Arab Emirates/ 9. Qatar$.mp,in. or Qatar/ 10. Oman$.mp,in. or Oman/ 11. Yemen$.mp,in. or Yemen/ 12. Bahr*in$.mp,in. or Bahrain/ 13. 7 or 8 or 9 or 10 or 11 or 12 14. Middle East$.mp,in. or Middle East/ 15. Jordan$.mp,in. or Jordan/ 16. Libya$.mp,in. or Libya/ 17. Egypt$.mp,in. or Egypt/ 18. Syria$.mp,in. or Syria/ 19. Iraq$/ or Iraq.mp,in. 20. Morocc$.mp,in. or Morocco/ 21. Tunisia$.mp,in. or Tunisia/ 22. Leban$.mp,in. or Lebanon/ 23. West Bank.mp,in. 24. Iran$.mp,in. or Iran/ 25. Turkey/ or (Turkey or Turkish).mp,in. 26. Algeria$.mp,in. or Algeria/ 27. Arab$.mp,in. or Arabs/ 28. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 29. 27 or 28 30. 6 or 13 or 29	

31. client$ participation.mp. or exp client participation/ 32. client$ satisfaction.mp. or exp client satisfaction/ 33. exp Health Attitudes/ 34. (patient$ preference$ or patient$ perception$ or patient$ decision$ or patient$ perspective$ or user$ view$ or patient$ view$ or patient$ value$ or patient$ attitude$).mp. 35. (patient$ utilit$ or health utilit$).mp. 36. health related quality of life.mp. or exp "quality of life"/ 37. (health stat$ utilit$ or health stat$ indicator$ or (health stat$ adj 2 valu$)).mp. 38. (standard gambl$ or time trade off or willingness to pay or visual analog scale or (VAS or "visual analog$ adj 2 scal$")).mp. 39. 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 40. "fibrillation (heart)"/ 41. atrial fibrillation.mp. or exp "Fibrillation (Heart)"/ 42. atrial flutter.mp. 43. 40 or 41 or 42 44. warfarin$.mp. 45. vitamin k antagonist$.mp. 46. aspirin.mp. or Aspirin/ 47. clopidogrel.mp. 48. 44 or 45 or 46 or 47 49. 43 or 48 50. 30 and 39 and 49
Date limit: None Study Types: Any

Records Retrieved	1

Summary of Searches: Patients' Values and Preferences

No. Total Retrieved:	**218**
Medline:	94
EMBASE:	123
PsychINFO:	1
No. Total without duplicates:	**203**
Screening (Title and Abstract Review)	
No. Excluded:	203
Included in the update:	**0**

Economic Evaluations Search

Data base: **MEDLINE (via OVID)**	
Search strategy:	**Date of search: 11/2013**
1. atrial fibrillation.mp. or Atrial Fibrillation/ 2. atrial flutter.mp. or Atrial Flutter/ 3. Warfarin$.mp. or exp Warfarin/ 4. vitamin k antagonist$.mp. 5. aspirin$.mp. or Aspirin/ 6. clopidogrel.mp. 7. dabigatran.mp. 8. rivaroxaban.mp. 9. apixaban.mp 10. 1 or 2	

11. 3 or 4 or 5 or 6 or 7 or 8 or 9 12. 7 and 8 13. economics/ or exp economics, hospital/ or exp economics, medical/ or economics, nursing/ or economics, pharmaceutical/ 14. exp "Costs and Cost Analysis"/ 15. Value-Based Purchasing/ 16. exp "Fees and Charges"/ 17. budget$.mp. or Budgets/ 18. (low adj cost).mp. 19. (high adj cost).mp. 20. (health?care adj cost$).mp. 21. (cost adj estimate$).mp. 22. (cost adj variable$).mp. 23. (unit adj cost$).mp. 24. (fiscal or funding or financial or finance).tw. 25. (economic$ or pharmacoeconomic$ or price$ or pricing).tw. 26. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 27. 26 and 12	
Date limit: None Study Types: Any	
Records Retrieved	372

Summary of Searches: Economic Evaluations

No. Total Retrieved:	**372**
Medline:	372
No. Total without duplicates:	**335**
Screening (Title and Abstract Review)	
No. Excluded:	306
Selection (Full Text Review)	
No. Excluded:	25
Reasons for exclusions:	
1. Included in the original guideline (22) 2. Not economic evaluation (3)	
Included in the update:	**4**

Appendix 3: Novel Oral Anticoagulants vs Vitamin K Antagonists Meta-Analysis

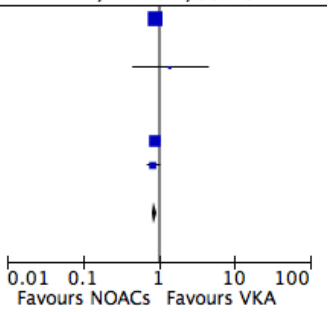
Risk of Bias of included studies:

Trial	Sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting
RE-LY	Yes	Yes	No	Yes	Yes	Yes
ROCKET AF	Yes	Yes	Yes	Probably no	Yes	Yes
ARISTOTLE	Probably yes	Probably yes	Yes	Yes	Yes	Yes
J-ROCKET AF	Probably yes	Probably yes	Yes	Yes	Yes	Yes
ARISTOTLE-J	Probably yes	Probably yes	No	Probably no	Probably yes	Yes
PETRO	Probably yes	Probably yes	No	Yes	No	Yes
NCT01136408	No information	No information	No information	No information	No information	No information

Outcome 1: all-cause mortality

Study or Subgroup	NOACs Events	NOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE	603	9120	669	9081	48.0%	0.90 [0.81, 1.00]
ARISTOTLE-J	0	71	0	75		Not estimable
J-ROCKET AF	7	637	5	637	0.4%	1.40 [0.45, 4.39]
NCT01136408	0	58	0	62		Not estimable
PETRO	0	169	0	70		Not estimable
RE-LY	438	6076	487	6022	35.1%	0.89 [0.79, 1.01]
ROCKET AF	208	7061	250	7082	16.5%	0.83 [0.70, 1.00]
Total (95% CI)		**23192**		**23029**	**100.0%**	**0.89 [0.82, 0.95]**
Total events	1256		1411			

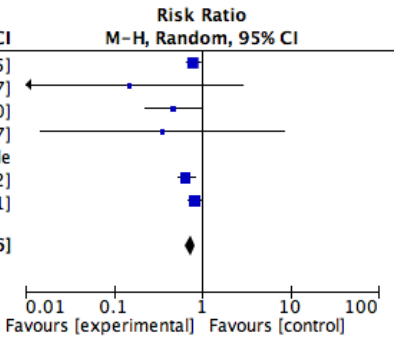
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.10$, df = 3 (P = 0.78); $I^2 = 0\%$
Test for overall effect: Z = 3.22 (P = 0.001)



Outcome 2: Stoke

Study or Subgroup	NOACs Events	NOACs Total	VKA Events	VKA Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE	199	9120	250	9081	36.2%	0.79 [0.66, 0.95]
ARISTOTLE-J	0	71	3	75	0.2%	0.15 [0.01, 2.87]
J-ROCKET AF	10	637	21	637	3.0%	0.48 [0.23, 1.00]
NCT01136408	0	58	1	62	0.2%	0.36 [0.01, 8.57]
PETRO	0	169	0	70		Not estimable
RE-LY	122	6076	185	6022	26.6%	0.65 [0.52, 0.82]
ROCKET AF	184	7061	221	7082	33.8%	0.84 [0.69, 1.01]
Total (95% CI)		**23192**		**23029**	**100.0%**	**0.75 [0.66, 0.86]**
Total events	515		681			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.72$, df = 5 (P = 0.33); $I^2 = 13\%$
Test for overall effect: Z = 4.28 (P < 0.0001)

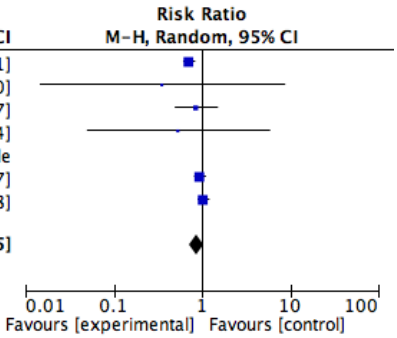


Outcome 3: major bleeding

Study or Subgroup	NOACs Events	Total	VKA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE	327	9120	462	9081	29.9%	0.70 [0.61, 0.81]
ARISTOTLE-J	0	71	1	75	0.3%	0.35 [0.01, 8.50]
J-ROCKET AF	23	639	27	639	8.9%	0.85 [0.49, 1.47]
NCT01136408	1	58	2	62	0.6%	0.53 [0.05, 5.74]
PETRO	0	169	0	70		Not estimable
RE-LY	375	6076	397	6022	30.1%	0.94 [0.82, 1.07]
ROCKET AF	395	7111	386	7125	30.1%	1.03 [0.89, 1.18]
Total (95% CI)		**23244**		**23074**	**100.0%**	**0.87 [0.72, 1.05]**
Total events	1121		1275			

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 15.97$, df = 5 (P = 0.007); $I^2 = 69\%$

Test for overall effect: Z = 1.45 (P = 0.15)

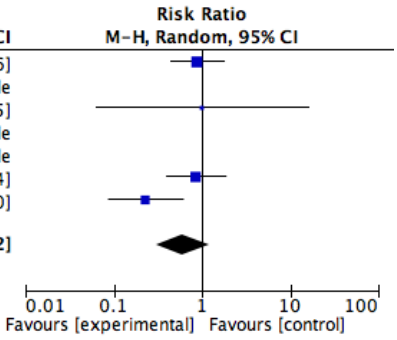


Outcome 4: Systemic embolism

Study or Subgroup	NOACs Events	Total	VKA Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ARISTOTLE	15	9120	17	9081	35.4%	0.88 [0.44, 1.76]
ARISTOTLE-J	0	71	0	75		Not estimable
J-ROCKET AF	1	637	1	637	5.6%	1.00 [0.06, 15.95]
NCT01136408	0	58	0	62		Not estimable
PETRO	0	169	0	70		Not estimable
RE-LY	12	6076	14	6022	32.7%	0.85 [0.39, 1.84]
ROCKET AF	5	7061	22	7082	26.4%	0.23 [0.09, 0.60]
Total (95% CI)		**23192**		**23029**	**100.0%**	**0.61 [0.31, 1.22]**
Total events	33		54			

Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 5.85$, df = 3 (P = 0.12); $I^2 = 49\%$

Test for overall effect: Z = 1.39 (P = 0.17)




المركز السعودي للرعاية الصحية المبنية على البراهين
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وزارة الصحة
Ministry of Health