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Review

Stroke Prevention, Evaluation of Bleeding Risk, and Anticoagulant Treatment Management in Atrial Fibrillation Contemporary International Guidelines

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ABSTRACT

In recent years the management of atrial fibrillation patients has progressively and substantially changed because of the introduction of new treatments and the availability of new data regarding the epidemiology and clinical management of these patients. In the past 2 years alone, there have been 7 new guidelines or guideline updates that have been published, which have introduced new recommendations and significantly revised previously published ones. Two updates for Canadian guidelines were published in 2016 and 2018, whereas guidelines from the European Society of Cardiology in 2016, Asia Pacific Heart Rhythm Society were published in 2017, National Heart Foundation of Australia/Cardiac Society of Australia and New Zealand, American College of Chest Physicians, and Korean Heart Rhythm Society have been published in 2018. In this narrative review we provide a comparison of these contemporary international guidelines, with particular attention on the evaluation of thromboembolic and bleeding risks and management of oral anticoagulant therapy. From the analysis of contemporary guidelines on the management of atrial

RÉSUMÉ

Ces dernières années, la prise en charge des patients atteints de fibrillation auriculaire a progressivement et considérablement changé en raison de l'introduction de nouveaux traitements et de la disponibilité de nouvelles données sur l'épidémiologie et la prise en charge clinique de ces patients. Au cours des deux dernières années seulement, les sept nouvelles lignes directrices ou mises à jour de lignes directrices qui ont été publiées ont introduit de nouvelles recommandations et ont tenu compte de l'importante révision des lignes directrices publiées antérieurement. Deux mises à jour des lignes directrices canadiennes ont été publiées en 2016 et en 2018, alors que les lignes directrices de la Société européenne de cardiologie ont été publiées en 2016, celles de la Asia Pacific Heart Rhythm Society, en 2017, et celles de la National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand, du American College of Chest Physicians et de la Korean Heart Rhythm Society, en 2018. Dans la présente revue narrative, nous faisons la comparaison de ces lignes directrices internationales contemporaines et portons

In the past 10 years, clinical practice on stroke prevention in patients with atrial fibrillation (AF) has markedly changed.[1] The introduction of non-vitamin K antagonist oral anticoagulants (NOACs) as an alternative to the vitamin K antagonists (VKAs),[2] has significantly increased the prescription and use of oral anticoagulant (OAC) therapy in AF patients, as shown by several epidemiological and observational studies.[3-6]

There has been much interest in expanding the understanding of AF pathophysiology, epidemiology, and natural history, leading to an increasing number of reports on AF being published (Fig. 1). The deluge of data available has informed how several new issues are managed and have led to a change in clinical practice regarding patients with AF, regarding the evaluation and reduction of thromboembolic risk as well as the general management of such patients. There is also an increasing focus on how the risk of cardiovascular and all-cause death is becoming an even more relevant issue in clinical history and clinical management of these patients.[7-10] This change in the risk profile has led to appeals for a new

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fibrillation, a general agreement is evident about the baseline evaluation of thromboembolic and bleeding risk, as well as a preference for the use of non-vitamin K antagonist oral anticoagulants. Also, regarding the concomitant use of oral anticoagulant and antiplatelet drugs in patients with acute coronary syndromes, undergoing elective percutaneous coronary intervention, catheter ablation, and cardioversion procedures, all of the guidelines agree on the general principles and are supported by evidence. More data are still needed to better substantiate recommendations for specific atrial fibrillation subpopulations. The need for an integrated approach and holistic management is highlighted in the more recently published guidelines.

une attention particulière à l'évaluation du risque thromboembolique et du risque hémorragique, et à la prise en charge de l'anticoagulothérapie par voie orale. À partir de l'analyse des lignes directrices contemporaines sur la prise en charge de la fibrillation auriculaire, on remarque un consensus évident sur l'évaluation initiale du risque thromboembolique et du risque hémorragique, ainsi que sur la préférence pour l'utilisation d'anticoagulants antivitamine K par voie orale. De plus, pour ce qui est de l'utilisation concomitante de médicaments anticoagulants et de médicaments antiplaquettaires par voie orale chez les patients atteints de syndromes coronariens aigus, qui subissent une intervention coronarienne percutanée non urgente, une ablation par cathéter et des cardioversions, l'ensemble des lignes directrices s'harmonisent aux principes généraux et sont fondées sur des données probantes. Plus de données sont encore nécessaires pour mieux étayer les recommandations de certaines sous-populations atteintes de fibrillation auriculaire. La nécessité d'une approche intégrée et d'une prise en charge holistique est mise en évidence dans les plus récentes lignes directrices publiées.

approach to the management of AF patients, involving a more integrated and holistic approach.[11,12]

In the past 2 years alone, there have been several new guidelines or guideline updates that have been published, that have introduced new recommendations and significantly revised the previously published ones.[13-19] In this narrative review we aim to provide a comparison of these contemporary international guidelines or updates, with particular attention to the evaluation of thromboembolic and bleeding risks and management of OAC therapy.

Overview and General Features of Contemporary International Guidelines

We provide an overview of the new guidelines published in the past 2 years.[13-19] General characteristics of these new guidelines are reported in Table 1.

In 2016 the Canadian Cardiovascular Society (CCS) published an update[13] to their 2010 AF clinical guidelines,[20] and also in 2016 the European Society of Cardiology (ESC) published their new guidelines,[14] with a complete revision of the previous main guideline from 2010 and the 2012 focused update.[21,22] In 2017, the Asia Pacific Heart Rhythm Society (APHRS) published their guidelines on stroke prevention in AF.[15] Finally, 3 entirely new guidelines were published in 2018 from the National Heart Foundation of Australia (NHFA)/Cardiac Society of Australia and New Zealand (CSANZ),[16] from the American College of Chest Physicians (ACCP),[17] and the Korean Heart Rhythm Society (KHRS),[19] and a second focused update of the CCS guidelines[18] was published in 2018.

Five of 7 guidelines performed a systematic search of currently available evidence on the basis of a structured and established technique used in evidence-based practice to frame and answer clinical or health-related questions, the Population, Intervention Comparison, Outcomes, in its original or modified form or the clinical questions model.[13,14,16-18] Conversely, the APHRS and KHRS guidelines were substantially on the basis of expert consensus review.[15,19] The "Grading of Recommendations, Assessment, Development and Evaluations" methodology was used to evaluate the quality of scientific evidence in 4 of the 7 guidelines.[13,16-18] Heterogeneity was evident in the grading of the strength of the recommendations and quality of evidence, with APHRS guidelines not explicitly grading their recommendations[15] and with KHRS only grading a limited number of recommendations.[19] Concerning conflict of interests, only the ESC, NHFA/CSANZ, and ACCP guidelines[14,16,17] provided detailed disclosure of direct, indirect, and potential conflicts of interest, with the latter, ACCP, prohibiting voting on issues for which an author reported a potential conflict of interest.

Although we found a considerable variability regarding the classification of clinical types of AF, in particular related to the use of new-onset/first detected AF and long-standing persistent AF, there was a substantial agreement across the various guidelines regarding the definition of nonvalvular AF, which is generally considered as the absence of mitral stenosis, although some guidelines specifically stated the differential rheumatic or nonrheumatic origin and the degree of disease, and of mechanical heart valve. Notwithstanding, 2 guidelines did not assess the definition.[15,19]

Evaluation of Thromboembolic Risk and OAC Prescription

When evaluating thromboembolic risk (Table 2), most guidelines recommended the use of the **C**ongestive Heart Failure, **H**ypertension, **A**ge ($\geq$ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female) (CHA_2DS_2-VASc) score,[14-17,19] although the NHFA/CSANZ guidelines used a modified CHA_2DS_2-VA score (the original CHA_2DS_2-VASc score computed without any point for sex category), which no longer considers the role of sex category in guiding the baseline OAC prescription.[16] This modification of the CHA_2DS_2-VASc score in the NHFA/CSANZ guidelines was justified by differential cutoffs for male and female AF patients or recommendations to exclude the sex category in the evaluation by other guidelines(Table 2).[14,15,17,19] The 5 guidelines that used the CHA_2DS_2-VASc score recommend prescribing OAC therapy in all patients with at least 1 nonsex-related risk factor.[14-17,19] Nonetheless, in the ESC, NHFA/CSANZ, and KHRS guidelines, 2 differential recommendations

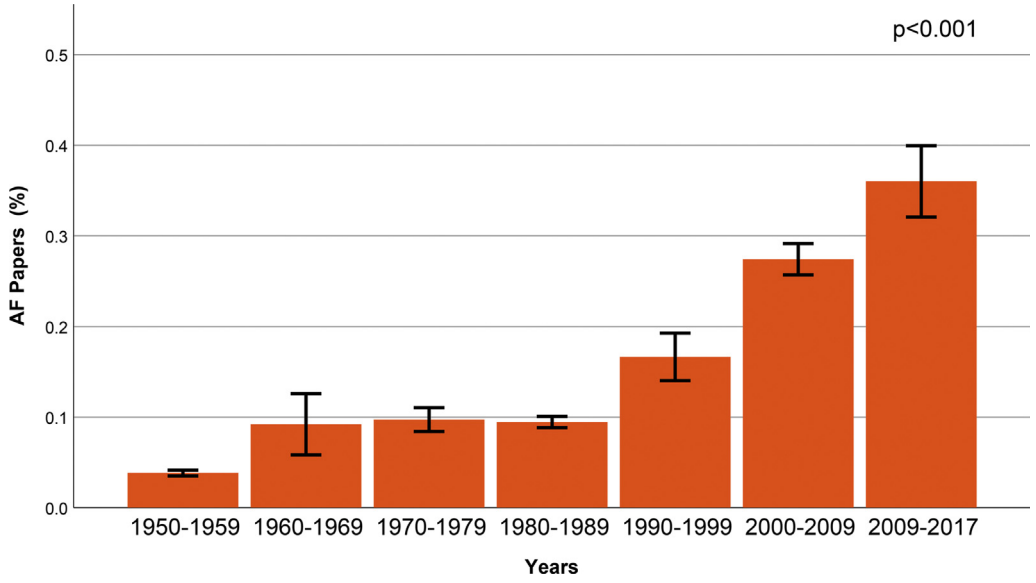

Figure 1. Proportion of articles related to atrial fibrillation (AF) in PubMed from inception to 2017.

are provided about patients with only 1 stroke risk factor and for 2 or more stroke risk factors.[14,16,19] In the latter (CHA_2DS_2-VASc score $\geq$ 2) OAC is recommended, with a strong recommendation on the basis of a high level of evidence, the level of evidence regarding the recommendation for patients with CHA_2DS_2-VASc score of 1 is lower, because fewer such patients were included in the randomized trials.

In the 2018 ACCP guidelines, the overall recommendation of prescribing all patients with at least 1 stroke risk factor is a stroke recommendation made on the basis of moderate-quality evidence.[17] Of the most recent guidelines, ACCP and KHRS also emphasize how, on the basis of some recent evidence, stroke risk assessment needs to be considered a dynamic process and should be reassessed at the regular follow-up visits.[17,19]

The Canadian guidelines differ from other guidelines because the evaluation of thromboembolic risk is on the basis of the Congestive Heart Failure, Hypertension, Age 65 years, Diabetes, Stroke/Transient Ischemic Attack (CHADS-65) algorithm, also known as the CCS algorithm.[13,18] This algorithm is a 3-step evaluation scheme, that recommends evaluating the patient's age first, with all patients aged $\geq$ 65 years old recommended for OAC, followed by assessment of the presence of stroke risk factors according to the **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack ($CHADS_2$) risk score,[23] according to which, patients with at least 1 risk factor should receive OAC, and last evaluating the presence of coronary artery disease (CAD) or other arterial vascular disease, and recommends the prescription of aspirin in those patients aged $<$ 65 years with isolated CAD.[13,18] The Canadian guidelines remain the only one still to recommend the use of aspirin in AF patients aged $<$ 65 years with isolated CAD and no other $CHADS_2$ stroke risk factors. Conversely, all other guidelines firmly recommend against the use of antiplatelet therapy for thromboembolic risk treatment.[14-17,19]

When OAC is indicated, all guidelines agree about the preferential use of NOACs over VKA therapy,[13-19] with most giving this a strong recommendation.[13,14,18,19] All guidelines concurred with the use of VKAs in patients with valvular AF. When VKAs are used, most guidelines (ESC, APHRS, ACCP, KHRS) recommend to maintain a high quality of OAC control, expressed as time in therapeutic range (TTR) $\geq$ 65%-70%.[14,15,17,19]

Evaluation of Bleeding Risk

After the evaluation of thromboembolic risk, all guidelines point the attention to the bleeding risk evaluation (Table 3). Most strongly recommend the use of the **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly ($>$ 65 Years), **D**rugs/Alcohol Concomitantly (HAS-BLED) risk score to evaluate bleeding risk, with moderate- to high-quality evidence.[13,15,17-19] The ESC guidelines emphasize how the use of clinical risk scores could be helpful tools in evaluating bleeding risk, but do not recommend one scheme over another.[14] Nonetheless, the ESC guidelines emphasize how, irrespectively of the score used, the main aim is to identify patients with modifiable or potentially modifiable bleeding risk factors.[14]

All guidelines agreed that a high bleeding risk should generally not be considered as a reason to withhold OAC treatment, except for specific situations in which the risk/benefit ratio excessively favours no antithrombotic treatment.[13-19] Instead, efforts should be used to identify all of the modifiable bleeding risk factors and address them when possible, discuss these with the patient, and provide more frequent and regular checks and follow-up visits.[13-19] Similar to thromboembolic risk, ACCP and KHRS guidelines recommend a reassessment of bleeding risk on a regular basis in light of its dynamic effect on bleeding risk.[17,19]

Utility of Left Atrial Appendage Closure

All of the guidelines agreed that left atrial appendage (LAA) closure should not be routinely used for the management of

Table 1. Summary of general characteristics and definitions of contemporary atrial fibrillation guidelines

Year	CCS 2016	ESC 2016	APHRS 2017
Bibliographic source	CJC 2016; 32 (10)[13]	EHJ 2016; 37 (38)[14]	J Arrhythmia 2017; 33 (4)[15]
Guidelines methodology	Systematic search according to PICO; GRADE rating of evidence	Systematic search according to PICOT; Experts plenary discussion	Expert consensus review
Strength of recommendations	Strong, conditional, weak	Classes I-IIa-IIb-III	Not explicitly assessed
Quality of evidence	High, moderate, low, very low	Level A-B-C	Not explicitly assessed
Conflict of interest process	Not reported	Detailed disclosure of all real or potential sources of COI publicly available	Reported in acknowledgement
Classification of AF	New onset, paroxysmal, persistent or permanent	First diagnosed, paroxysmal, persistent, long-standing persistent, permanent	Not explicit
Evaluation of valvular origin	Rheumatic mitral stenosis, mitral valve repair, mechanical or bioprosthetic heart valve	Rheumatic valvular disease (predominantly mitral stenosis) or mechanical heart valves	Not explicitly assessed

Year	NHFA/CSANZ 2018	ACCP 2018	CCS 2018	KHRS 2018
Bibliographic source	HLC 2018; 27 (10)[16]	Chest 2018; 154 (5)[17]	CJC 2018; 34 (11)[18]	KCJ 2018; 48 (12)[19]
Guidelines methodology	Systematic search according to clinical questions; GRADE rating of evidence	Systematic search according to PICO-guided clinical questions; GRADE rating of evidence	Systematic search according to PICO; GRADE rating of evidence	Expert consensus review
Strength of recommendations	Strong, weak	Strong, weak	Strong, conditional, weak	Classes I-IIa-IIb-III
Quality of evidence	High, moderate, low	High, moderate, low, very low	High, moderate, low, very low	Level A-B-C
Conflict of interest process	Direct or indirect relationship to any third party, including financial and nonfinancial	Central COIs review. If manageable potential COI, voting on relevant issues was prohibited	Not reported	Reported in acknowledgement
Classification of AF	Paroxysmal, persistent, long-standing persistent, permanent	Paroxysmal, persistent, long-standing persistent, permanent	New onset, paroxysmal, persistent or permanent	Not explicit
Evaluation of valvular origin	Moderate to severe mitral stenosis or mechanical heart valve	Moderate to severe mitral stenosis or mechanical heart valve	Rheumatic mitral stenosis, moderate-severe nonrheumatic mitral stenosis, or a mechanical heart valve	Not explicitly assessed

ACCP, American College of Chest Physicians; AF, atrial fibrillation; APHRS, Asia Pacific Heart Rhythm Society; CCS, Canadian Cardiovascular Society; CJC, *Canadian Journal of Cardiology*; COI, conflict of interest; CSANZ, Cardiac Society of Australia and New Zealand; EHJ, *European Heart Journal*; ESC, European Society of Cardiology; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; HLC, *Heart, Lung and Circulation*; J Arrhythmia, *Journal of Arrhythmia*; KCJ, *Korean Circulation Journal*; KHRS, Korean Heart Rhythm Society; NHFA, National Heart Foundation of Australia; PICO(T), Population, Intervention, Comparison, Outcome, (Time).

thromboembolic risk in patients with AF (Supplemental Table S1). Although the Canadian guidelines suggest, with a low quality of evidence, that LAA closure should be considered only as part of the ablation procedure, although clearly contraindicated in patients at high risk of stroke,[13,18] other guidelines recommend that LAA closure should only be considered in patients with absolute contraindications to OAC use.[14-17,19] Overall, the guidelines judged the quality of evidence regarding LAA closure to be low.

Management of OAC and Antiplatelet Therapy

Several epidemiological studies have shown that AF is often associated with acute coronary syndrome (ACS) and myocardial infarction.[24-26] One of the main concerns in patients who presenting with AF and ACS/myocardial infarction is the management of dual or triple antithrombotic therapy (OAC with single or dual antiplatelet therapy) with respect to balancing atherothrombotic, thromboembolic, and bleeding risk.

In the antithrombotic decision-making process, a primary distinction has to be drawn between patients who present with ACS and those who undergo elective percutaneous coronary intervention (PCI) with stent (Table 4). For patients who present with ACS and undergo urgent PCI with stent, almost all of the guidelines recommend treatment with triple antithrombotic agents, with the duration varying from 1 to 6 months, with shortening of triple therapy on the basis of bleeding risk.[13-18] For example, the recent ACCP guidelines specifically recommend using triple therapy for 6 months in patients with low bleeding risk, shortening duration to 1-3 months in patients with high bleeding risk, and recommend avoiding it completely in patients with very high bleeding risk.[17] After the period of triple therapy, duration of dual antithrombotic therapy should not be continued longer than 12 months after the PCI. In addition, all guidelines indicate a preference for clopidogrel over aspirin as the choice of antiplatelet drug. Recommendations regarding patients with ACS who undergo urgent PCI (irrespective of stent placement) are generally on the basis of low or moderate quality of evidence (Table 4).[13-18]

Among patients who undergo elective PCI with stent placement, most of the guidelines (ESC, APHRS, NHFA/CSANZ, KHRS) recommend a short duration of triple antithrombotic therapy as very short, up to a maximum of 1 month.[14-16,19] According to ACCP guidelines in patients with low bleeding risk, the duration of triple therapy is recommended for 1 month, followed by 12 months of clopidogrel

Table 2. Baseline thromboembolic risk evaluation and oral anticoagulation prescription algorithm

Year	CCS 2016	ESC 2016	APHRS 2017
Thromboembolic risk assessment	CHADS-65 ("CCS algorithm")	CHA_2DS_2-VASc	CHA_2DS_2-VASc
Rating of evidence	Strong recommendation, high-quality evidence	Class I, level A	Not rated
OAC prescription algorithm	(1) OAC should be considered for all patients $\geq$ 65 years old or with $\geq$ 1 $CHADS_2$ risk factors. (2) < 65 years old and with arterial disease ASA should be considered	(1) OAC is indicated in all patients with a CHA_2DS_2-VASc $\geq$ 2, excluding sex category (2) OAC should be considered in all patients with just 1 CHA_2DS_2-VASc risk factor, excluding sex category	OAC is indicated in all patients with a CHA_2DS_2-VASc $\geq$ 1, excluding sex category
Rating of evidence	(1) Strong recommendation, moderate-quality evidence (2) Conditional recommendation, moderate-quality evidence	(1) Class I, level A (2) Class IIa, level B	Not rated
Use of NOACs	A NOAC is preferred over VKA	A NOAC is preferred over VKA	A NOAC is preferred over VKA
Rating of evidence	Strong recommendation, high-quality evidence	Class I, level A	Not rated

Year	NHFA/CSANZ 2018	ACCP 2018	CCS 2018	KHRS 2018
Thromboembolic risk assessment	CHA_2DS_2-VA	CHA_2DS_2-VASc	CHADS-65 ("CCS algorithm")	CHA_2DS_2-VASc
Rating of evidence	Strong recommendation, moderate-quality evidence	Strong recommendation, moderate-quality evidence	Strong recommendation, high-quality evidence (2014)	Class I, level A
OAC prescription algorithm	(1) OAC is indicated in all patients with CHA_2DS_2-VA $\geq$ 2 (2) OAC should be considered in all patients with CHA_2DS_2-VA 1	OAC is indicated in all patients with a CHA_2DS_2-VASc $\geq$ 1, excluding sex category	(1) OAC should be considered for all patients $\geq$ 65 years old or with $\geq$ 1 $CHADS_2$ risk factors (2) < 65 years old and with arterial disease ASA should be considered	(1) OAC is indicated in all patients with a CHA_2DS_2-VASc $\geq$ 2, excluding sex category (2) OAC should be considered in all patients with just 1 CHA_2DS_2-VASc risk factor, excluding sex category
Rating of evidence	(1) Strong recommendation, high-quality evidence (2) Strong recommendation, moderate-quality evidence	Strong recommendation, moderate-quality evidence	(1) Strong recommendation, moderate-quality evidence (2) Conditional recommendation, moderate-quality evidence (2014)	(1) Class I, level A (2) Class IIa, level B
Use of NOACs	A NOAC is preferred over VKA	A NOAC is preferred over VKA	A NOAC is preferred over VKA	A NOAC is preferred over VKA
Rating of evidence	Strong recommendation, moderate-quality evidence	Strong recommendation, moderate-quality evidence	Strong recommendation, high-quality evidence (2014)	Class I, level A

ACCP, American College of Chest Physicians; APHRS, Asia Pacific Heart Rhythm Society; ASA, acetylsalicylic acid; CCS, Canadian Cardiovascular Society; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; CHADS-65, **C**ongestive Heart Failure, **H**ypertension, **A**ge **65** years, **D**iabetes, **S**troke/Transient Ischemic Attack; CHA_2DS_2 -VA, **C**ongestive Heart Failure, **H**ypertension, **A**ge (75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years); CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge ($\geq$ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); CSANZ, Cardiac Society of Australia and New Zealand; ESC, European Society of Cardiology; KHRS, Korean Heart Rhythm Society; NHFA, National Heart Foundation of Australia; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; VKA, vitamin K antagonist.

with OAC; conversely in patients with high risk of bleeding, whereas the duration of triple therapy is kept to 1 month, the guidelines recommend shortening the dual antithrombotic therapy up to 6 months after the procedure. Finally, in patients with very high bleeding risk use of triple therapy is not recommended, and the duration of dual antithrombotic therapy should be kept up to 6 months.[17]

The Canadian guidelines recommend a bit of a different approach. In the 2016 update they did not recommend at all use of triple therapy for elective PCI, suggesting only dual antithrombotic therapy with clopidogrel. In the 2018 version, they changed the recommendations by introducing the use of triple antithrombotic therapy in elective PCI in consideration of the high risk of thrombotic coronary events associated with some clinical variables (ie, diabetes mellitus, smoking, chronic kidney disease, previous coronary events, etc) and of type of stent.[13,18] Patients with high-risk features are recommended to be treated for up to 6 months with triple antithrombotic therapy, followed by dual therapy for up to 12 months post stent placement. However, in patients without high-risk features, triple therapy is not recommended.[18] It is important to stress that all of the recommendations regarding the use of triple therapy in AF patients who receive elective PCI are weak and on the basis of moderate to low quality of evidence (Table 4).

Regarding OAC prescription, the CCS, APHRS, and KHRS guidelines recommend NOACs over VKAs in ACS patients, although there is less robust evidence,[13,15,18,19] although the NHFA/CSANZ guidelines do not provide any particular recommendation in this regard.[16] The ESC guidelines recommend the use of the lowest approved dosage of

Table 3. Baseline bleeding risk evaluation and associated recommendations

Year	CCS 2016	ESC 2016	APHRS 2017
Bleeding risk assessment	HAS-BLED	Use of clinical risk scores to evaluate modifiable and potentially modifiable risk factors for major bleeding	HAS-BLED
Rating of evidence	Strong recommendation, high-quality evidence (2010)	Class IIa, level B	Not rated
Associated recommendation	Adopt specific measures to mitigate bleeding risk factors	Do not withhold OAC. Identify and correct modifiable bleeding risk factors	For patients with HAS-BLED $\geq$ 3 do not withhold OAC and provide regular review and follow-up of the modifiable bleeding risk factors

Year	NHFA/CSANZ 2018	ACCP 2018	CCS 2018	KHRS 2018
Bleeding risk assessment	Identification of reversible bleeding risk factors	HAS-BLED	HAS-BLED	HAS-BLED
Rating of evidence	Strong recommendation, low-quality of evidence	Strong recommendation, moderate-quality of evidence	Strong recommendation, high-quality evidence (2010)	Class I, level A
Associated recommendation	Minimization of bleeding risk through treating of reversible risk factors	HAS-BLED $\geq$ 3 should not be a reason to withhold OAC. Patients at higher bleeding risk is warranted for more frequent and regular reviews and follow-up	Adopt specific measures to mitigate bleeding risk factors	A high bleeding risk is not a reason to withhold OAC treatment. Modifiable bleeding risk factors should be addressed to reduce bleeding risk

ACCP, American College of Chest Physicians; APHRS, Asia Pacific Heart Rhythm Society; CCS, Canadian Cardiovascular Society; CSANZ, Cardiac Society of Australia and New Zealand; ESC, European Society of Cardiology; HAS-BLED, **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly; KHRS, Korean Heart Rhythm Society; NHFA, National Heart Foundation of Australia; OAC, oral anticoagulant.

NOACs when coadministered with antiplatelet drugs,[14] whereas the ACCP guidelines recommend NOACs as equal to VKAs, but with a weaker recommendation on the basis of a lower quality of evidence (Table 4).[17]

Management of OAC in Cardioversion and Ablation Procedures

With regard to ablation procedures, all guidelines agree on 3 main pillars: (1) uninterrupted OAC is recommended for patients who undergo the ablation procedure; (2) after the procedure, OAC therapy is recommended as compulsory for at least 8 weeks in all patients; and (3) long-term OAC prescription beyond the first 8 weeks, should be on the basis of risk profile and proposed only to patients with high risk of stroke (Table 5).[14,15,17-19]

Regarding the type of OAC to be prescribed for pre- and periprocedural uninterrupted treatment, the ESC, APHRS and CCS 2018 guidelines all recommend NOACs and VKAs as equal alternatives.[14,15,18] As a notable exception, the recent ACCP guidelines only recommend dabigatran or rivaroxaban among the NOACs.[17]

With respect to OAC in patients who undergo a cardioversion procedure, all of the guidelines agreed on some basic principles: (1) in patients with at least 48 hours of proven AF, anticoagulation should be provided for at least 3 weeks to exclude the presence of any left atrial thrombus; (2) as an alternative to OAC, use of a transesophageal echocardiogram to exclude the presence of any left atrial thrombus; and (3) OAC should be continued for at least 4 weeks after the procedure, irrespective of the success of the cardioversion procedure.[13-19] Most of the guidelines agree that long-term OAC, irrespective of the success of the cardioversion procedure, should be considered on the basis of stroke risk factors.[14-19] Several guidelines also explicitly recommended to provide 3-4 weeks of OAC treatment if a thrombus is identified on the transesophageal echocardiogram.[14,15,17,19] ACCP 2018 and CCS 2018 guidelines provided recommendations regarding specific situations. ACCP guidelines provide an indication about not commencing OAC for patients with < 48 hours of AF and hemodynamic instability, rather initiate parenteral anticoagulation as soon as it is possible.[17] In the CCS 2018 guidelines, it is indicated that in patients with very short (< 12 hours) or short (12-48 hours) AF duration, OAC can be avoided if there is no substantial risk of stroke (Table 5).[18]

Management of OAC in Specific Populations

One of the most debated issues in the management of OAC therapy is the prescription in elderly (very elderly) and frail patients (Supplemental Table S2). Among the guidelines examined, the CCS (had discussed the issue in the previous 2010 and 2012 versions, but did not make any recommendations in 2016 and 2018), and APHRS guidelines did not consider this issue.[13,15,18]

The ESC guidelines state that the available evidence supports the use of OAC in elderly and frail patients, because of the high benefit-risk ratio.[14] The NHFA/CSANZ guidelines highlight the beneficial effect of OAC in elderly patients observed in observational registries, with a preference for the use of NOACs, because of the high prevalence of polypharmacy, although caution is recommended with dose adjustment related to renal function.[16] The ACCP guidelines recommend a specific individual risk assessment before OAC prescription while reaffirming that the benefits of OAC

Table 4. Combination of OAC with antiplatelet drugs in patients with concomitant cardiac disease

Year	CCS 2016	ESC 2016	APHRS 2017
Patients with ACS	(1) In patients < 65 years old and no $CHADS_2$ risk factors 12 months treatment with aspirin and P2Y12 inhibitor (chosen according to risk and implementation of PCI) with indefinite treatment with aspirin if PCI has been performed (2) In patients ≥ 65 years old and $CHADS_2$ ≥ 1 and no PCI is undertaken clopidogrel 75 mg and OAC for 12 months followed by only OAC (3) In patients ≥ 65 years old and $CHADS_2$ ≥ 1 and PCI is undertaken ASA 81 mg and clopidogrel 75 mg and OAC for 3 to 6 months (according to risk) followed by clopidogrel 75 mg and OAC up to 12 months then OAC	(1) In patients not undergoing PCI dual therapy with OAC and aspirin or clopidogrel should be considered up to 12 months (2) In patients undergoing PCI, triple therapy with OAC, aspirin, and clopidogrel should be considered from 1 to 6 months on the basis of bleeding risk, followed by dual therapy with aspirin or clopidogrel (3) Duration of combination therapy, especially triple therapy, should be kept to the minimum, balancing risk of bleeding and recurrent events	In patients with ACS triple therapy can be continued from 1 to 6 months according to bleeding risk (high or low) with dual therapy up to 12 months after the event
Rating of evidence	(1) Strong recommendation, high-quality evidence (2) Conditional recommendation, low-quality evidence (3) Conditional recommendation, low-quality evidence	(1) Class IIa, level C (2) Class IIa, level C (3) Class IIa, level B	Not rated
Elective PCI	(1) In patients < 65 years and no $CHADS_2$ risk factors indefinite treatment with aspirin and 12 months of treatment with clopidogrel is recommended (2) In patients ≥ 65 and $CHADS_2$ risk factors OAC and clopidogrel with no aspirin are indicated for 12 months followed by indefinite OAC	(1) In patients undergoing elective PCI, use of triple therapy with OAC, aspirin, and clopidogrel should be limited to 1 month (2) Dual therapy with OAC and aspirin or clopidogrel, could be continued up to 6 or 12 months according to bleeding risk	In patients with elective PCI triple therapy should be continued for 1 month, with dual therapy continued up to 6 or 12 months, according to bleeding risk (high or low)
Rating of evidence	(1) Strong recommendation, high-quality evidence (2) Strong recommendation, high-quality evidence	(1) Class IIa, level B (2) Class IIa, level C	Not rated
Use of NOACs	When OAC indicated a NOAC is preferred over warfarin	When NOAC is used the lowest recommended dose should be administered together with antiplatelet therapy	A NOAC is preferred over warfarin
Rating of evidence	Not rated	Not rated	Not rated

Year	NHFA/CSANZ 2018	ACCP 2018	CCS 2018	KHRS 2018
Patients with ACS	(1) In patients with ACS or PCI duration of triple therapy should be kept as short as possible to minimize risk of bleeding, still ensuring the coverage of the high risk of recurrent event/stent thrombosis (2) After triple therapy, dual therapy with OAC and aspirin 100 mg or clopidogrel 75 mg is recommended	(1) In patients with ACS and low bleeding risk, triple therapy is suggested up to 6 months, followed by OAC with single antiplatelet agent (preferably clopidogrel) up to 12 months (2) In patients with ACS and high bleeding risk, triple therapy is suggested from 1 to 3 months, followed by OAC with antiplatelet agent (preferably clopidogrel) up to 12 months (3) In patients with very high bleeding risk, a strategy with OAC and single antiplatelet agent (preferably clopidogrel) for 6-9 months is suggested	(1) In patients ≤ 65 years and no $CHADS_2$, use of antiplatelet therapy according to characteristics and extent of disease as directed by other guidelines (2) In patients ≥ 65 years and $CHADS_2$ ≥ 1 not undergoing PCI, OAC with P2Y12 inhibitor (preferably clopidogrel) is indicated for 12 months (3) In patients ≥ 65 years and $CHADS_2$ ≥ 1 undergoing PCI, OAC, aspirin, and clopidogrel are indicated up to 6 months, followed by OAC with clopidogrel up to 12 months	No recommendation
Rating of evidence	(1) Strong recommendation, moderate quality of evidence (2) Strong recommendation, low-quality of evidence	(1) Weak recommendation, low quality of evidence (2) Weak recommendation, low quality of evidence (3) Weak recommendation, low quality of evidence	(1) Not rated (2) Weak recommendation, low quality of evidence (3) Weak recommendation, moderate quality of evidence	–
Elective PCI	(1) In patients with ACS or PCI duration of triple therapy should be kept as short as possible to minimize risk of bleeding, still ensuring the coverage of the high risk of recurrent event/stent thrombosis (2) After triple therapy, dual therapy with	(1) In patients receiving PCI and low bleeding risk, triple therapy is suggested for 1 month, followed by OAC with single antiplatelet agent (preferably clopidogrel) up to 12 months (2) In patients receiving PCI and high bleeding risk, triple therapy is suggested for 1 month,	(1) In patients ≥ 65 years and $CHADS_2$ ≥ 1 receiving PCI without high-risk features, OAC with clopidogrel is suggested for at least 1 month (BMS) or at least 3 months (2) In patients ≥ 65 years and $CHADS_2$ ≥ 1 receiving PCI with high-risk features, OAC, aspirin, and clopidogrel are	Triple therapy is recommended to be as short as possible, in relation to bleeding risk, unless the risk of stent thrombosis/recurrence would not be too high. After

Continued

Table 4. Continued.

Year	NHFA/CSANZ 2018	ACCP 2018	CCS 2018	KHRS 2018
	OAC and aspirin 100 mg or clopidogrel 75 mg is recommended	followed by OAC with antiplatelet agent (preferably clopidogrel) up to 6 months (3) In patients with very high bleeding risk, a strategy with OAC and single antiplatelet agent (preferably clopidogrel) for 6 months is suggested	indicated up to 6 months, followed by OAC with clopidogrel up to 12 months	triple therapy, dual therapy with OAC and P2Y12 inhibitor (preferably clopidogrel) should be continued up to 12 months after PCI.
Rating of evidence	(1) Strong recommendation, moderate quality of evidence (2) Strong recommendation, low quality of evidence	(1) Weak recommendation, low quality of evidence (2) Weak recommendation, low quality of evidence (3) Weak recommendation, low quality of evidence	(1) Weak recommendation, moderate quality of evidence (2) Weak recommendation, moderate quality of evidence	Not rated
Use of NOACs	No specific recommendation done	NOACs are indicated equally to VKAs	A NOAC is preferred over VKA	A NOAC is preferred over VKA
Rating of evidence	–	Weak recommendation, low quality of evidence	Weak recommendation, moderate quality of evidence	Not rated

ACCP, American College of Chest Physicians; ACS, acute coronary syndrome; APHRS, Asia Pacific Heart Rhythm Society; ASA, acetylsalicylic acid; BMS, bare-metal stent; CCS, Canadian Cardiovascular Society; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; CSANZ, Cardiac Society of Australia and New Zealand; ESC, European Society of Cardiology; KHRS, Korean Heart Rhythm Society; NHFA, National Heart Foundation of Australia; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; VKA, vitamin K antagonist.

prescription generally outweigh the risk of harm from serious bleeding, although they highlight a contraindication to OAC prescription for patients with dementia and no caregiver (to administer OAC).[17] Similar recommendations are included in the KHRS guidelines.[19] Guidelines including specific recommendations about elderly patients did not rate these recommendations.

Another important population is patients with chronic kidney disease. Impaired renal function is an independent risk factor for stroke, major bleeding, and major adverse outcomes in patients with AF,[27] thus these patients need careful management to maximize stroke prevention and reduce bleeding risk, and the guidelines differ in their recommendations for managing such patients (Supplemental Table S2) and the lower limit for which OAC use is no longer recommended. Both Canadian guidelines suggest that OAC should not be routinely prescribed for patients with glomerular filtration rate (GFR) $<$ 15 mL/min, but that use of OAC might be appropriate in some patients in whom there is a stronger preference in avoiding stroke despite the uncertain benefit and the associated bleeding risk.[13,18] Lack of data, with limited evidence about efficacy and safety of OAC in patients with GFR $<$ 30 mL/min and $<$ 15 mL/min are claimed by the APHRS,[15] NHFA/CSANZ,[16] and ESC guidelines.[14] Although the APHRS, ACCP, and KHRS guidelines recognize the limited evidence, they suggest that use of VKAs with well managed quality of anticoagulation therapy could be considered.[15,17,19]

In patients with moderate to severe chronic kidney disease (GFR 15-30 mL/min), treatment strategies differ across guidelines. Both Canadian guidelines recommend OAC prescription on the basis of stroke risk, with warfarin the preferred agent,[13,18] whereas the APHRS, ACCP, and KHRS guidelines suggest the use of OAC with caution, with the recommendation to reduce NOAC dosages.[15,17,19] The ESC guidelines also recommend reducing the NOAC dosage, although the reduction is suggested for patients with GRF 25-50 mL/min. The adjustment of NOAC dosage is also suggested in the other guidelines for patients with GFR $>$ 30 and up to 50 or 60 mL/min, according to guidelines.[13,15,17-19] It is relevant to note that most of the recommendations are weak and on the basis of a low quality of evidence, underlining the need for more solid evidence.

One emergent issue is that related to the treatment of patients with cardiac implantable electronic devices, without clinical AF, who are found to have atrial high rate episodes (AHREs). Although some guidelines did not consider this issue,[15,19] others suggest that OAC treatment should be considered in those with prolonged AHREs ($>$ 24 hours) and a high risk of stroke (CHA_2DS_2-VASc $\geq$2),[13,16-18] whereas further data are needed to support the use of OAC in patients with AHREs of shorter duration.

However, the ESC guidelines do not advocate OAC treatment for patients with AHREs.[14]

Use of an Integrated Management in Patients With AF

Because of the increased risk for adverse outcomes other than stroke, such as myocardial infarction, cardiovascular death, and all-cause death,[9,10,24,25] in AF patients, there is a need for a more integrated and holistic management approach

Table 5. Oral anticoagulation management in patients undergoing ablation or cardioversion procedure

Year	CCS 2016	ESC 2016	APHRS 2017
Ablation procedure	OAC should be continued after AF surgical ablation according to CCS algorithm	(1) All patients should receive OAC for at least 8 weeks after catheter ablation (2) OAC should be continued indefinitely after successful catheter ablation in patients at high risk of stroke (3) Continuation of OAC with VKAs or NOACs during procedure is recommended	(1) NOACs can be safe and effective alternatives to VKAs for periprocedural anticoagulation (2) OAC should be continued for at least 3 weeks before procedure in patients with at least 48 hours of AF (3) OAC should be continued for at least 2 months after ablation, and longer in patients with high risk of stroke
Rating of evidence	Strong recommendation, moderate-quality evidence	(1) Class IIa, level B (2) Class IIb, level C (3) Class IIb, level B (VKAs) or level C (NOACs)	Not rated
Cardioversion procedure	OAC should be prescribed for 3 weeks before cardioversion and at least 4 weeks after. If AF recurs OAC should be prescribed on the basis of the CCS algorithm. If SR is achieved, decision on continuing OAC after 4 weeks of treatment should be on the basis of risk of stroke and expert consultation	(1) Effective anticoagulation is recommended for at least 3 weeks before cardioversion (2) Anticoagulation with heparin or NOAC should be initiated before every cardioversion procedure (3) In patients without stroke risk factors anticoagulation is recommended for 4 weeks. In those at risk of stroke anticoagulation should be continued long-term after procedure (4) Perform TEE is recommended as an alternative to OAC (5) If with TEE a thrombus is identified 3 weeks OAC is recommended	(1) Anticoagulation is needed 3 weeks before and 4 weeks after cardioversion procedure (2) In patients undergoing TEE, if thrombus is identified OAC is needed for at least 4 weeks and repeat TEE to ensure thrombus resolution (3) After cardioversion long-term OAC is needed in patients with high risk of stroke (4) For OAC in patients undergoing cardioversion VKAs and NOACs can be considered
Rating of evidence	Strong recommendation, moderate quality of evidence	(1) Class I, level B (2) Class IIa, level B (3) Class I, level B (4) Class I, level B (5) Class I, level C	Not rated

Year	NHFA/CSANZ 2018	ACCP 2018	CCS 2018	KHRS 2018
Ablation procedure	Uninterrupted OAC is recommended for patients undergoing catheter ablation	(1) OAC with VKA, dabigatran or rivaroxaban is recommended for patients undergoing ablation (2) After ablation long-term OAC should be prescribed on the basis of thromboembolic risk profile	Use of uninterrupted OAC, either with NOACs or VKAs is recommended	(1) Uninterrupted OAC is recommended for patients undergoing catheter ablation (2) OAC after ablation should be continued for at least 2 months (3) After 2 months, long-term OAC should be decided on patient's stroke risk
Rating of evidence	Strong recommendation, moderate quality of evidence	(1) Weak recommendation, low quality of evidence (2) Weak recommendation, low quality of evidence	Weak recommendation, moderate quality of evidence	Not rated
Cardioversion procedure	(1) OAC for 3 weeks is recommended (or TEE to document absence of left atrium thrombus) before cardioversion procedure (2) OAC is recommended for at least 4 weeks after cardioversion procedure	(1) In patients with AF for 48 hours or more OAC with VKAs or NOACs is recommended at least 3 weeks before cardioversion or TEE approach with abbreviated OAC treatment (2) In patients with 48 hours or less AF or hemodynamic instability, parenteral anticoagulation should be started as soon as possible before procedure and continued for at least 4 weeks (3) After cardioversion, OAC with VKAs or NOACs should be continued for at least 4 weeks. Continuing OAC beyond 4 weeks	(1) Patients planned to receive cardioversion should receive OAC for 3 weeks before procedure (2) 3 weeks of OAC treatment can be waived if AF is < 12 hours with no recent stroke or within 12 and 48 hours and there is no substantial stroke risk (3) OAC is recommended to be continued for at least 4 weeks (4) TEE can be considered as an alternative to OAC (5) NOACs and heparin/VKAs strategies can be used	(1) OAC is recommended for at least 3 weeks before cardioversion (2) After procedure OAC is recommended for at least for 4 weeks in patients without stroke risk factors. In patients at risk of stroke, long-term OAC is recommended (3) Anticoagulation with heparin or NOAC should be initiated as soon as possible before every cardioversion procedure (4) If a TEE identifies a thrombus in left atrium, effective anticoagulation is recommended for at least 3 weeks

Continued

Table 5. Continued.

Year	NHFA/CSANZ 2018	ACCP 2018	CCS 2018	KHRS 2018
		should be on the basis of general OAC prescription decision-making	(6) OAC continuation after 4 weeks should be decided on the basis of CCS algorithm	
Rating of evidence	Strong recommendation, low quality of evidence	(1) Strong recommendation, moderate quality of evidence (2) Weak recommendation, low quality of evidence (3) Strong recommendation, moderate quality of evidence	(1) Strong recommendation, moderate quality of evidence (2) Weak recommendation, low quality of evidence (3) Weak recommendation, low quality of evidence (4) Weak recommendation, moderate quality of evidence (5) Weak recommendation, low quality of evidence (6) Strong recommendation, moderate quality of evidence	(1) Class I, level B (2) Class I, level B (3) Class IIa, level B (4) Class I, level C

ACCP, American College of Chest Physicians; AF, atrial fibrillation; APHRS, Asia Pacific Heart Rhythm Society; CCS, Canadian Cardiovascular Society; CSANZ, Cardiac Society of Australia and New Zealand; ESC, European Society of Cardiology; KHRS, Korean Heart Rhythm Society; NHFA, National Heart Foundation of Australia; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; SR, sinus rhythm; TEE, transesophageal echocardiography; VKA, vitamin K antagonist.

for AF patients, to reduce overall cardiovascular risk.[11,12] Most guidelines advocate the need for an integrated approach (Supplemental Table S3), for example, in the 2016 ESC guidelines, to improve adherence to treatment, quality of life, and long-term outcomes.[14,16-19] However, the operationalization and implementation of integrated care needs to be simple and practical. To address the latter, the ACCP and KHRS guidelines have suggested that use of the "Atrial Fibrillation Better Care" (ABC)[28] approach as a practical tool to streamline the integrated management of AF patients.[17,19]

Summary and Discussion

In this narrative review, we have discussed the main recommendations regarding OAC management for AF patients from contemporary international guidelines. Most guidelines were compiled with a systematic and well-established approach and rated according to a rigourous evaluation system. There was general agreement in the definition of valvular and nonvalvular AF, although some heterogeneity was evident in the temporal classification of AF. Despite not being considered in the OAC decision-making process, the type of AF can influence the risk of major adverse outcomes.[29] Further, the classification of clinical AF influences rate/rhythm management and lack of concordance between the guidelines can be misleading in the evaluation of patients and differing management strategies between physicians.

Evaluation of thromboembolic risk at baseline is very similar across all the guidelines with most adopting the CHA_2DS_2-VASc score, with the notable exception of Canadian guidelines. The almost universal adoption of CHA_2DS_2-VASc score reflects the strength of the current data supporting its use as a clinical risk score that provides a balance between evidence, practicality, and precision.[30] A recent comparative effectiveness review about the ability of the scores to predict thromboembolic and bleeding events reported that $CHADS_2$, CHA_2DS_2-VASc, and the recent ABC-Stroke[31] scores were best and had a similar predictive capacity for stroke occurrence.[32] Nonetheless, CHA_2DS_2-VASc differs from other scores for its capacity to effectively identify patients with very low risk and does not require expensive and time-consuming laboratory tests to be undertaken compared with the ABC-Stroke score.[30] Furthermore, recently a systematic review and meta-regression showed that CHA_2DS_2-VASc score represents the score with the highest probability to perform best in predicting the occurrence of all-cause death in AF patients.[33]

The role of female sex as an independent risk factor, in relation to stroke risk is addressed by all 7 guidelines examined (Table 2).[13-19] The increased stroke risk in female AF patients has been long discussed.[34,35] A comprehensive meta-analysis including almost 1 million AF patients showed that female patients with AF were at increased risk of stroke, with a 24% relative risk increase.[36] However, a significant relationship was found between increasing age and a progressively higher risk of stroke in female AF patients.[36] Compelling data from the Danish registries showed that although there were no profound differences between "low risk" male and female AF patients with no additional stroke risk factors, a sex difference in stroke risk increased with the increasing number of risk factors, suggesting that female sex was "risk modifier" rather

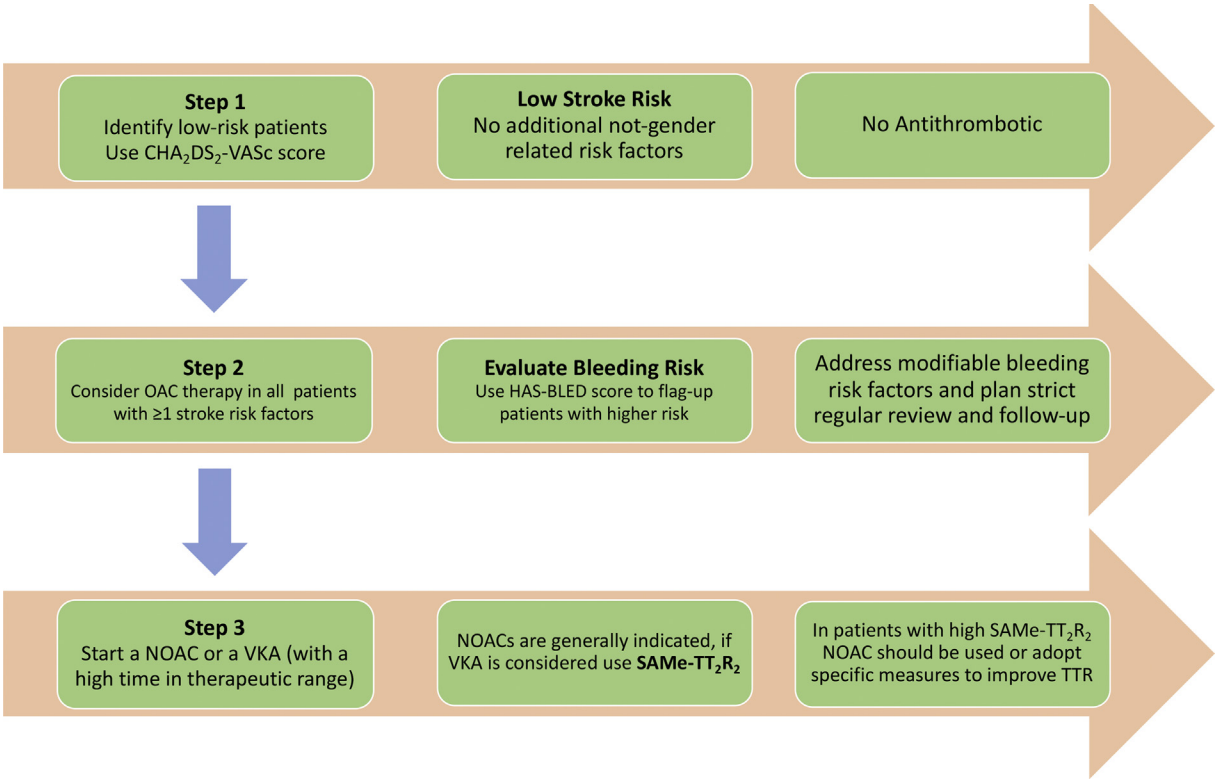

Figure 2. The "Birmingham 3-Step" management strategy for anticoagulation in patients with atrial fibrillation. CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge (≥ 75 years), **D**iabetes, **S**troke/Transient Ischemic Attack, **V**ascular Disease, **A**ge (65-74 years), **S**ex (Female); HAS-BLED, **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulant; SAMe-TT_2R_2, **S**ex, **A**ge, **Me**dical History, **T**reatment, **T**obacco Use, **R**ace; TTR, time in therapeutic range.

than a risk factor per se.[37] Ignoring the female sex criterion would lead to underestimation of stroke risk in female patients with ≥ 1 additional stroke risk factor, an important consideration when discussing risks with AF patients.

The second pivotal step on which all the guidelines agree is the evaluation of baseline bleeding risk. Although 5 of 7 of the guidelines examined adopted HAS-BLED as the clinical risk score to evaluate bleeding risk,[13,15,17-19] the ESC and NHFA/CSANZ guidelines recognize the utility of the clinical scores to evaluate bleeding risk, but do not recommend the use of any particular score.[14,16] Conversely, these guidelines adopt an approach on the basis of the identification of modifiable and potentially modifiable bleeding risk factors,[14,16] despite evidence showing the superiority of HAS-BLED to **O**lder Age, **R**educed Haemoglobin/Hematocrit/Anemia, **B**leeding History, **I**nsufficient Kidney Function, **T**reatment With Antiplatelets (ORBIT), **An**ticoagulation and **R**isk Factors **i**n **A**trial Fibrillation (ATRIA) Bleeding, **H**epatic or Renal Disease, **E**thanol Abuse, **M**alignancy, **O**lder (Age > 75 Years), **R**educed Platelet Count or Function, **R**ebleeding Risk, **H**ypertension (Uncontrolled), **A**nemia, **G**enetic Factors, **E**xcessive Fall Risk, and **S**troke ($HEMORR_2HAGES$) scores[38,39] and to the most recent ABC-Bleeding and **G**lobal **A**nticoagulant **R**egistry in the **Field** **A**trial **F**ibrillation (GARFIELD-AF) Bleeding scores.[40,41] Furthermore, compared with an approach exclusively on the basis of modifiable bleeding risk factors as promoted by the ESC guidelines, using the HAS-BLED score was a superior strategy for bleeding risk assessment.[42,43]

Regarding the prescription of OAC, the Canadian guidelines still recommend prescribing antiplatelet drugs in patients aged < 65 years with isolated CAD and no other stroke risk factors,[13,18] but all other guidelines support the prescription of OAC in patients with at least 1 stroke risk factor not related to sex. All of the recommendations regarding OAC prescription are strong recommendations and hence supported by solid evidence. Similarly, as largely supported by phase III randomized clinical trials[2] and observational studies,[44-46] all of the guidelines recommend the use of NOACs in preference to VKAs. Notwithstanding that globally VKAs are still widely used as OACs, the use of the **S**ex, **A**ge, **Me**dical History, **T**reatment, **T**obacco Use, **R**ace (SAMe-TT_2R_2) score is mentioned in some guidelines related to where VKAs are used to help assess the likelihood of patients to achieve optimal anticoagulation control when prescribed with VKAs, that could guide more intense international normalized ratio monitoring or the alternative prescription of VKAs and NOACs.[47]

On the basis of the guideline recommendations and evidence presented, and because the default should be to offer stroke prevention unless the patient is "low risk," the so-called "Birmingham 3-Step" management strategy has been advocated (Fig. 2).[1] In the first step, AF patients who are low risk are identified through CHA_2DS_2-VASc score, and no antithrombotic therapy is recommended. In the second step, OAC therapy is considered in all AF patients with at least 1 additional non-sex stroke risk factor and risk of bleeding is assessed, to identify patients at high risk of bleeding

(HAS-BLED $\geq$ 3), to address modifiable bleeding risk factors and plan more frequent follow-up checks. In the third step, treatment with OACs should be started with NOACs as the preferred option—and if a VKA is considered, the SAMe-TT_2R_2 score can help to identify patients who would more likely obtain a low time in therapeutic range (SAMe-TT_2R_2 > 2) who can be identified for more regular international normalized ratio monitoring, education/counselling, or to reconsider being prescribed a NOAC.

Regarding the concomitant use of OAC and antiplatelet drugs, the guidelines examined agree on a similar basis. It is recognized that the use of triple antithrombotic therapy in AF with ACS should be on the basis of the balance between atherothrombotic/thromboembolic risk and bleeding risk and that such strategy should be kept as short as possible.

Use of triple antithrombotic therapy has been traditionally associated with an increased risk of bleeding, with several studies reporting an increased rate of major bleeding events with no relative benefit in terms of thromboembolic and atherosclerotic events.[48,49] For example, the **W**hat Is the **O**ptimal Antiplat**e**let and Anticoagulation Therapy in Patients With Oral Anticoagulation and Coronary **S**ten**t**ing (WOEST) trial reported that a strategy of clopidogrel with OAC compared with triple antithrombotic therapy was associated with a lower risk of major bleeding with no difference in terms of efficacy.[48] Nevertheless, if good-quality anticoagulation control is attained, the risk of major bleeding in such patients who undergo PCI and stent seems to be significantly reduced.[49] The 2018 joint European consensus document emphasized the need to shorten triple antithrombotic therapy in AF patients as much as possible, related to clinical presentation, bleeding risk, etc.[50] In this situation, a strategy on the basis of NOACs was associated with a reduced risk of major bleeding events.[51,52] However, a network meta-analysis concluded that the best treatment strategy for these high-risk patients still appears to be the use of a VKA and single antiplatelet drugs when considering efficacy and safety, although the use of low-dose rivaroxaban appears to be a valid alternative.[53] Nevertheless, this network meta-analysis did not include data from the Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention (RE-DUAL PCI) trial.[52] Future results from other ongoing trials, the Open-Label, 2 × 2 Factorial, Randomized, Controlled Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome and or Percutaneous Coronary Intervention (AUGUSTUS) (ClinicalTrials.gov: NCT02415400) and the **E**doxaba**n** **Tr**eatment vers**us** VKA in Pa**t**ients With **AF** Undergoing **PCI** (ENTRUST-AF PCI) (ClinicalTrials.gov: NCT02866175) will provide further evidence.

In the clinical scenarios of catheter ablation and cardioversion procedures, the guidelines reviewed shared similar approaches regarding the use of OAC and NOACs. Several studies have examined the use of uninterrupted NOACs in the catheter ablation setting and all data support better safety profile compared with VKAs, with no differences in terms of efficacy.[54,55] In the cardioversion setting NOACs were similar to VKAs in terms of efficacy and safety.[56]

With regard to specific populations (patients with chronic kidney disease, the elderly, and frail patients with AHREs), the guidelines highlight the absence of specific controlled studies on the efficacy and safety of OAC and NOACs in these populations. Although observational data are available and subgroup analysis provided some evidence to draft some recommendations, this evidence was not considered solid enough to provide strong recommendations. Future studies are still needed in patients with chronic kidney disease and elderly and frail patients to better substantiate current clinical practice. Regarding patients with AHREs, some studies are currently in progress and will elucidate the risk-benefit ratio of treating these patients with OAC.[57,58]

In some of the contemporary guidelines, the need for integrated management for AF patients is highlighted. On the basis of the evidence that AF patients are burdened with an increased risk of major adverse outcomes beyond their mere thromboembolic risks,[9,10,24,25] an approach that would account for the multiple issues related to the clinical management of these patients is needed.[11,12] The 2016 ESC guidelines refer to the "domains of AF management" and the need for a multidisciplinary approach to AF management (with so-called "heart team") but the operationalization of such an approach requires simple and practical approaches for the AF patient management pathway.

Indeed, the use of an integrated management approach to AF is associated with a reduced risk of all-cause death, cardiovascular death, and rehospitalization.[59-61] Compliance with the ABC pathway is also associated with reduced health care costs.[62] As recently highlighted by some guidelines,[17,19] the ABC pathway has been proposed to streamline an integrated and holistic management approach for patients with AF (Fig. 3).[28]

Significant differences are evident between the various guidelines examined for some key issues. For example, the CCS guidelines do not indicate the use of OAC in patients < 65 years with isolated CAD,[13,18] as one example. This notable exception has been first reported in the CCS guidelines in the 2012 update[63] and it stands on the assumption that CAD implies a low risk of stroke in AF patients (< 1.5% per year).[63] Several data exist to show that in AF patients, the presence of vascular disease and CAD are associated with a significant independent increase in stroke risk.[64-66]

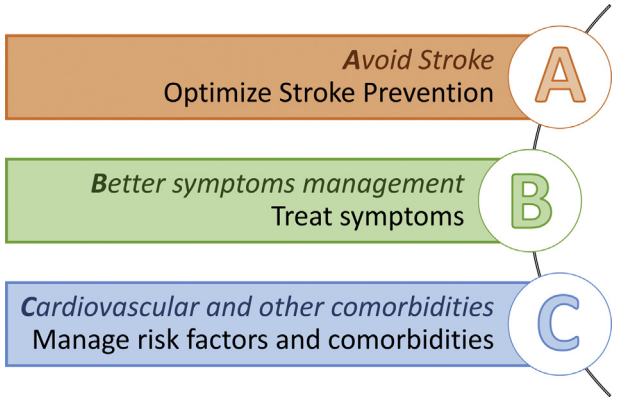

Figure 3. Atrial Fibrillation Better Care (ABC) pathway for integrated care in atrial fibrillation patients.

Even more differences are related to issues for which a lower quality of evidence and strength of recommendations is available. These reflect the lack of high-quality data obtained from randomized controlled trials and highlight the need for future well designed and adequately powered studies.

The use of an approach on the basis of expert consensus review of the published evidence for the APHRS and KHRS guidelines[15,19] could affect the daily clinical decision-making process, but when a high quality of evidence is available these guidelines are still able to provide solid recommendations. For all other aspects for which there is a significant degree of uncertainty, there might be a less objective evaluation of the limited scientific evidence available. In any case, many guidelines that use systematic reviews still include many recommendations with level of evidence C, which represents expert consensus.

Conclusion

In this narrative review of contemporary guidelines, we show that there is general agreement on the baseline evaluation of thromboembolic and bleeding risk, as well as a preference for the use of NOACs. More data are still needed to better substantiate recommendations for specific AF subpopulations. The need for an integrated approach and holistic management is emphasized in the more recently published guidelines.

Disclosures

M.P. reports consulting activity for Boehringer Ingelheim; D.A.L. reports investigator-initiated educational grants from Bristol-Myers Squibb and Boehringer Ingelheim, speaker activity for Boehringer Ingelheim, Bayer, and Bristol-Myers Squibb/Pfizer, consultant activity for Bristol-Myers Squibb, Bayer, Boehringer Ingelheim, and Daiichi-Sankyo, and she is a member of the ACCP 2018 writing committee. G.B. has received small speaker's fee from Medtronic, Boston, Boehringer, and Bayer, outside of the submitted work, and is a member of the ACCP 2018 writing committee. G.Y.H.L. has served as consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo, and as speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo, and is member and chair of the ACCP 2018 writing committee. No fees are received personally.

References

1. Lip G, Freedman B, De Caterina R, Potpara TS. Stroke prevention in atrial fibrillation: past, present and future. Comparing the guidelines and practical decision-making. Thromb Haemost 2017;117:1230-9.
2. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014;383:955-62.
3. Gadsbøll K, Staerk L, Loldrup Fosbøl E, et al. Increased use of oral anticoagulants in patients with atrial fibrillation: temporal trends from 2005 to 2015 in Denmark. Eur Heart J 2017;38:899-906.
4. Marzec LN, Wang J, Shah ND, et al. Influence of direct oral anticoagulants on rates of oral anticoagulation for atrial fibrillation. J Am Coll Cardiol 2017;69:2475-84.
5. Camm AJ, Accetta G, Ambrosio G, et al. Evolving antithrombotic treatment patterns for patients with newly diagnosed atrial fibrillation. Heart 2017;103:307-14.
6. Boriani G, Proietti M, Laroche C, et al. Contemporary stroke prevention strategies in 11 096 European patients with atrial fibrillation: a report from the EURObservational Research Programme on Atrial Fibrillation (EORP-AF) Long-Term General Registry. Europace 2018;20:747-57.
7. Marijon E, Le Heuzey JY, Connolly S, et al. Causes of death and influencing factors in patients with atrial fibrillation: a competing-risk analysis from the randomized evaluation of long-term anticoagulant therapy study. Circulation 2013;128:2192-201.
8. Fauchier L, Villejoubert O, Clementy N, et al. Causes of death and influencing factors in patients with atrial fibrillation. Am J Med 2016;129:1278-9.
9. Proietti M, Laroche C, Opolski G, et al. "Real-world" atrial fibrillation management in Europe: observations from the 2-year follow-up of the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase. Europace 2017;19:722-33.
10. Proietti M, Laroche C, Nieuwlaat R, et al. Increased burden of comorbidities and risk of cardiovascular death in atrial fibrillation patients in Europe over ten years: a comparison between EORP-AF pilot and EHS-AF registries. Eur J Intern Med 2018;55:28-34.
11. Kotecha D, Breithardt G, Camm AJ, et al. Integrating new approaches to atrial fibrillation management: the 6th AFNET/EHRA Consensus Conference. Europace 2018;20:395-407.
12. Kirchhof P. The future of atrial fibrillation management: integrated care and stratified therapy. Lancet 2017;390:1873-87.
13. Macle L, Cairns J, Leblanc K, et al. 2016 Focused Update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol 2016;32:1170-85.
14. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893-962.
15. Chiang CE, Okumura K, Zhang S, et al. 2017 Consensus of the Asia Pacific Heart Rhythm Society on stroke prevention in atrial fibrillation. J Arrhythmia 2017;33:345-67.
16. NHFA CSANZ Atrial Fibrillation Guideline Working Group, Brieger D, Amerena J, et al. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Heart Lung Circ 2018;27:1209-66.
17. Lip GYH, Banerjee A, Boriani G, et al. Antithrombotic therapy for atrial fibrillation: CHEST Guideline and Expert Panel Report. Chest 2018;154:1121-201.
18. Andrade JG, Verma A, Mitchell LB, et al. 2018 Focused update of the Canadian Cardiovascular Society guidelines for the management of atrial fibrillation. Can J Cardiol 2018;34:1371-92.
19. Joung B, Lee JM, Lee KH, et al. 2018 Korean guideline of atrial fibrillation management. Korean Circ J 2018;48:1033.
20. Gillis AM, Skanes AC; CCS Atrial Fibrillation Guidelines Committee. Canadian Cardiovascular Society atrial fibrillation guidelines 2010: implementing GRADE and achieving consensus. Can J Cardiol 2011;27:27-30.
21. Camm AJ, Kirchhof P, Lip GYH, et al. Guidelines for the management of atrial fibrillation. Eur Heart J 2010;31:2369-429.

22. Camm A, Lip G, De Caterina R, et al. 2012 Focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012;33:2719-47.

23. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 2001;285:2864-70.

24. Soliman EZ, Safford MM, Muntner P, et al. Atrial fibrillation and the risk of myocardial infarction. JAMA Intern Med 2014;174:107-14.

25. Soliman EZ, Lopez F, O'Neal WT, et al. Atrial fibrillation and risk of ST-segment-elevation versus non-ST-segment-elevation myocardial infarction: the Atherosclerosis Risk in Communities (ARIC) Study. Circulation 2015;131:1843-50.

26. Violi F, Davì G, Proietti M, et al. Ankle-Brachial Index and cardiovascular events in atrial fibrillation: the ARAPACIS study. Thromb Haemost 2016;115:856-63.

27. Lau YC, Proietti M, Guiducci E, Blann AD, Lip GYH. Atrial fibrillation and thromboembolism in patients with chronic kidney disease. J Am Coll Cardiol 2016;68:1452-64.

28. Lip GYH. The ABC pathway: an integrated approach to improve AF management. Nat Rev Cardiol 2017;14:627-8.

29. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. Eur Heart J 2016;37:1591-602.

30. Proietti M, Mujovic N, Potpara TS. Optimizing stroke and bleeding risk assessment in patients with atrial fibrillation: a balance of evidence, practicality and precision. Thromb Haemost 2018;118:2014-7.

31. Oldgren J, Hijazi Z, Lindbäck J, et al. Performance and validation of a novel biomarker-based stroke risk score for atrial fibrillation: clinical perspective. Circulation 2016;134:1697-707.

32. Borre ED, Goode A, Raitz G, et al. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. Thromb Haemost 2018;118:2171-87.

33. Proietti M, Farcomeni A, Romiti GF, et al. Association between clinical risk scores and mortality in atrial fibrillation: systematic review and network meta-regression of 669,000 patients. Eur J Prev Cardiol 2018. 204748731881766.

34. Lane DA, Lip GYH. Female gender is a risk factor for stroke and thromboembolism in atrial fibrillation patients. Thromb Haemost 2009;101:802-5.

35. Poli D, Antonucci E. Epidemiology, diagnosis, and management of atrial fibrillation in women. Int J Womens Health 2015;7:605-14.

36. Marzona I, Proietti M, Farcomeni A, et al. Sex differences in stroke and major adverse clinical events in patients with atrial fibrillation: a systematic review and meta-analysis of 993,600 patients. Int J Cardiol 2018;269:182-91.

37. Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation: should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? Circulation 2018;137:832-40.

38. Senoo K, Proietti M, Lane DA, Lip GYH. Evaluation of the HAS-BLED, ATRIA and ORBIT bleeding risk scores in atrial fibrillation patients on warfarin. Am J Med 2016;129:600-7.

39. Proietti M, Senoo K, Lane DA, Lip GYH. Major bleeding in patients with non-valvular atrial fibrillation: impact of time in therapeutic range on contemporary bleeding risk scores. Sci Rep 2016;6:24376.

40. Esteve-Pastor MA, Rivera-Caravaca JM, Roldan V, et al. Long-term bleeding risk prediction in "real world" patients with atrial fibrillation: comparison of the HAS-BLED and ABC-Bleeding risk scores. The Murcia Atrial Fibrillation Project. Thromb Haemost 2017;117:1848-58.

41. Proietti M, Rivera-Caravaca JM, Esteve-Pastor MA, et al. Predicting bleeding events in anticoagulated patients with atrial fibrillation: a comparison between the HAS-BLED and GARFIELD-AF bleeding scores. J Am Heart Assoc 2018;7:e009766.

42. Chao TF, Lip GYH, Lin YJ, et al. Incident risk factors and major bleeding in patients with atrial fibrillation treated with oral anticoagulants: a comparison of baseline, follow-up and delta HAS-BLED scores with an approach focused on modifiable bleeding risk factors. Thromb Haemost 2018;118:768-77.

43. Esteve-Pastor MA, Rivera-Caravaca JM, Shantsila A, et al. Assessing bleeding risk in atrial fibrillation patients: comparing a bleeding risk score based only on modifiable bleeding risk factors against the HAS-BLED score. The AMADEUS trial. Thromb Haemost 2017;117:2261-6.

44. Carmo J, Moscoso Costa F, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation. Meta-analysis of observational comparison studies with vitamin K antagonists. Thromb Haemost 2016;116:754-63.

45. Bai Y, Deng H, Shantsila A, Lip GYH. Rivaroxaban versus dabigatran or warfarin in real-world studies of stroke prevention in atrial fibrillation. Stroke 2017;48:970-6.

46. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH. Real-world use of apixaban for stroke prevention in atrial fibrillation: a systematic review and meta-analysis. Stroke 2018;49:98-106.

47. Zulkifly H, Lip GYH, Lane DA. Use of the SAMe-TT 2 R 2 score to predict anticoagulation control in atrial fibrillation and venous thromboembolism patients receiving vitamin K antagonists: a review. Heart Rhythm 2018;15:615-23.

48. Dewilde WJM, Oirbans T, Verheugt FWA, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet 2013;381:1107-15.

49. Proietti M, Airaksinen KEJJ, Rubboli A, et al. Time in therapeutic range and major adverse outcomes in atrial fibrillation patients undergoing percutaneous coronary intervention: the Atrial Fibrillation Undergoing Coronary Artery Stenting (AFCAS) registry. Am Heart J 2017;190:86-93.

50. Lip GYH, Collet JP, Haude M, et al. 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventions: a joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Interventions (EAPCI), and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LAHRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). Europace 2019;21:192-3.

51. Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med 2016;375:2423-34.

52. Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med 2017;377:1513-24.

53. Gong X, Tang S, Li J, et al. Antithrombotic therapy strategies for atrial fibrillation patients undergoing percutaneous coronary intervention: a systematic review and network meta-analysis. PLoS One 2017;12:e0186449.

54. Ge Z, Faggioni M, Baber U, et al. Safety and efficacy of nonvitamin K antagonist oral anticoagulants during catheter ablation of atrial fibrillation: a systematic review and meta-analysis. Cardiovasc Ther 2018;36:e12457.

55. Zhao Y, Lu Y, Qin Y. A meta-analysis of randomized controlled trials of uninterrupted periprocedural anticoagulation strategy in patients undergoing atrial fibrillation catheter ablation. Int J Cardiol 2018;270:167-71.

56. Brunetti ND, Tarantino N, De Gennaro L, et al. Direct oral anticoagulants compared to vitamin-K antagonists in cardioversion of atrial fibrillation: an updated meta-analysis. J Thromb Thrombolysis 2018;45:550-6.

57. Lopes RD, Alings M, Connolly SJ, et al. Rationale and design of the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA) trial. Am Heart J 2017;189:137-45.

58. Kirchhof P, Blank BF, Calvert M, et al. Probing oral anticoagulation in patients with atrial high rate episodes: rationale and design of the non-vitamin K antagonist oral anticoagulants in patients with atrial high rate episodes (NOAH-AFNET 6) trial. Am Heart J 2017;190:12-8.

59. Gallagher C, Elliott AD, Wong CX, et al. Integrated care in atrial fibrillation: a systematic review and meta-analysis. Heart 2017;103:1947-53.

60. Proietti M, Romiti GF, Olshansky B, Lane DA, Lip GYH. Improved outcomes by integrated care of anticoagulated patients with atrial fibrillation using the simple ABC (Atrial Fibrillation Better Care) pathway. Am J Med 2018;131:1359-1366.e6.

61. Pastori D, Pignatelli P, Menichelli D, Violi F, Lip GYH. Integrated care management of patients with atrial fibrillation and risk of cardiovascular events [e-pub ahead of print]. Mayo Clin Proc, https://doi.org/10.1016/j.mayocp.2018.10.022.

62. Pastori D, Farcomeni A, Pignatelli P, Violi F, Lip GY. ABC (Atrial fibrillation Better Care) pathway and healthcare costs in atrial fibrillation. The ATHERO-AF study[e-pub ahead of print]. Am J Med, https://doi.org/10.1016/j.amjmed.2019.01.003.

63. Skanes AC, Healey JS, Cairns JA, et al. Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol 2012;28:125-36.

64. Anandasundaram B, Lane DA, Apostolakis S, Lip GYH. The impact of atherosclerotic vascular disease in predicting a stroke, thromboembolism and mortality in atrial fibrillation patients: a systematic review. J Thromb Haemost 2013;11:975-87.

65. Steensig K, Olesen KKW, Thim T, et al. Coronary artery disease is independent risk factor for stroke among patients with atrial fibrillation. J Am Coll Cardiol 2018;118:2162-70.

66. Steensig K, Olesen KKW, Thim T, et al. Should the presence or extent of coronary artery disease be quantified in the CHA2DS2-VASc score in atrial fibrillation? A report from the Western Denmark Heart Registry. Thromb Haemost 2018;118:2162-70.

Supplementary Material

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