

## Review

**Evidence-based treatment of atrial fibrillation around the globe: comparison of the latest ESC, AHA/ACC/HRS, and CCS guidelines on the management of atrial fibrillation**Julian Wolfes<sup>1,\*</sup>, Christian Ellermann<sup>1</sup>, Gerrit Frommeyer<sup>1</sup>, Lars Eckardt<sup>1</sup><sup>1</sup>Clinic of Cardiology II (Electrophysiology), University Hospital Münster, 48149 Münster, Germany\*Correspondence: [julian.wolfes@ukmuenster.de](mailto:julian.wolfes@ukmuenster.de) (Julian Wolfes)

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**Abstract**

Recent versions of evidence-based guidelines on the management of atrial fibrillation (AF) have been published by the European Society of Cardiology (ESC) in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS), the American College of Cardiology, American Heart Association, and the Heart Rhythm Society (AHA/ACC/HRS), and the Canadian Cardiovascular Society/Canadian Heart Rhythm Society (CCS). As all societies refer to the same multicentric and usually multinational studies, the similarities undoubtedly outweigh the differences. Nonetheless, interesting differences can often be found in details, which are usually based on a different assessment of the same study, the availability of data in relation to the publication date and local preferences and availabilities of certain cardiovascular drugs. The following article aims at lining out these similarities and differences.

**Keywords:** Atrial fibrillation; Guidelines; Comparison; ESC; AHA; CCS**1. Introduction**

Evidence-based guidelines on the management of atrial fibrillation (AF) are published and updated to integrate new scientific evidence for multiple years by the large cardiology societies. In 2020, the European Society of Cardiology (ESC) published the third and current version of recommendations for diagnosis and management of atrial fibrillation in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS) [1]. The latest cumulative guidelines from the American College of Cardiology, American Heart Association, and the Heart Rhythm Society (AHA/ACC/HRS) were published in 2014 [2] and underwent a focused update in 2019 [3]. The most recent guidelines on atrial fibrillation were published by the Canadian Cardiovascular Society/Canadian Heart Rhythm Society (CCS) in late 2020 [4].

This article aims at comparing these international guidelines for the management of atrial fibrillation and to identify both similarities and differences. Since all three guidelines largely refer to the same multicentric and usually multinational studies, the similarities undoubtedly outweigh the differences. Nonetheless, interesting differences can often be found in details, which are usually based on a different assessment of the same study, as for example the RACE-II trial [5]. In addition, the recent EAST-AFNET 6 trial [6] is only included in the most recently published CCS guideline due to its publication date. Furthermore, especially when comparing recommendations on drug treatment there are differences between the guidelines, which can be traced back to both common local practice and the

local availability of certain medications.

Focusing on the structure of the guidelines, all three guidelines have an almost textbook-like character and, in addition to their recommendations for action, also offer a deeper understanding of atrial fibrillation and insight into the decision-making of the respective authors. However, the Focused Update of the AHA guidelines from 2019 [3] does not have this character, but rather represents a short summary of the instructions, especially for the topics of stroke prophylaxis and rhythm control.

In the ESC and AHA guidelines the level of recommendation and evidence is presented in the ACCF/AHA methodology, primarily in form of tables. While the CCS guideline uses the GRADE system mainly by offering short recommending texts.

**2. Classification of AF**

In clinical practice, atrial fibrillation should be classified by episode duration and persistence. All three guidelines distinguish between paroxysmal, persistent, long-standing persistent, and permanent AF (“PPP”-pattern), whereas ESC guidelines further define first-diagnosed AF (**Supplementary Table 1**).

Although AF duration is a classification suggested by the three guidelines and relatively easy to define at first glance, this classification bears some shortcomings to be mentioned in the following: (1) the anamnestic AF pattern does not necessarily correlate with the AF burden in ECG monitoring [7], (2) AF duration alone does not predict the risk of AF recurrence or the chance to maintain si-



nus rhythm, respectively [8]. (3) Furthermore, the “PPP”-pattern neither gives mechanistic insights into the underlying pathophysiology in the individual patient nor points it out treatment options and implications.

As a consequence, the CCS and ESC guidelines further classify AF based on pathophysiological or etiological aspects (CCS) or a multidimensional model including clinical and structural aspects (ESC). The CCS guideline subdivides AF into “primary” and “secondary” AF. AF is defined as “primary AF” when it “represents an established pathophysiological course” and “secondary AF” refers to AF in the setting of reversible or self-limited factors. Secondary AF is further subcategorized into “reversible” and “provoked” AF based on the AF susceptibility and the risk of recurrence.

The latest ESC guidelines introduce a newly developed 4S-AF scheme to achieve a structured characterization of the individual patient in view of stroke risk, symptom severity, severity of AF burden, and substrate severity (**Supplementary Fig. 1**). This holistic approach of AF classification is only partially based on established scores and is not validated but points out possible assessment tools and emphasizes that “the most appropriate descriptors of AF domains are yet to be defined” [1]. Up to now, there is no unified classification of different patients in the 4S-AF scheme, but it helps to line out and clarify the most important aspects in AF management and motivates health care providers and scientists to validate diagnostic tools for further classification.

The AHA and the CCS guidelines both distinguish between valvular and non-valvular AF. According to publication of the latest CCS guideline and the AHA update of 2019, non-valvular AF is defined as “AF in the absence of moderate-to-severe mitral stenosis or a mechanical heart valve” [3,4]. The ESC guidelines do not use this subclassification anymore but nevertheless address it when discussing anticoagulation, as all three guidelines are recommending a vitamin K antagonist (VKA) as the drug of choice only in the setting of moderate-to-severe mitral stenosis or in patients with mechanical heart valves. This is due to the limited data on anticoagulation with non-vitamin K antagonist oral anticoagulants (NOAC) in patients with mitral stenosis [9] and the observed increased thromboembolic and bleeding risks under NOACs in patients with mechanical valves [10].

### 3. Screening for AF

As asymptomatic AF is known to be an independent risk factor for stroke and other arterial thromboembolic events [11,12], the subject of AF screening to detect asymptomatic AF in patients at high risk of stroke has come into focus.

While the AHA guidelines do not address this subject, the ESC and CCS guidelines offer a section on AF screening (**Supplementary Table 2**).

The CCS guidelines recommend opportunistic screening for AF in patients of  $\geq 65$  years at the time of a medical encounter with a suspected number needed to screen (NNS) of 69 [13]. Regarding the mode of screening (opportunistic vs. systematic), the CCS guidelines recommend an opportunistic screening, primarily via pulse-palpation with consecutive diagnostic work-up, based on its cost effectiveness in the SAFE study [14]. The ESC guidelines also recommend opportunistic AF screening by pulse-taking or ECG in patients of  $\geq 65$  years. In contrast to the CCS guidelines, the ESC guidelines recommend (Class IIa, evidence level: B) systematic screening in patients of  $\geq 75$  years or at high risk of stroke.

Furthermore, new screening technologies employing photoplethysmography or single-lead ECG recordings, got into the market. These technologies are addressed in the CCS and ESC guidelines, whereat both guidelines line out their effectiveness especially in population at high AF risk, although a 12-lead-ECG recording remains mandatory to confirm the diagnosis of AF. Notably the topic is not mentioned in the AHA guidelines.

### 4. AF related symptoms

While all guidelines line out the importance of AF-related symptoms, especially for the decision for rhythm control strategies, only the CCS and ESC guidelines recommend specific AF-symptom scales that evaluate the influence of AF-related symptoms on daily life and activities, as presented in **Supplementary Table 3**. To capture AF related symptoms more precisely, the CCS guidelines recommend the EQ-5D as a generic quality of life (QoL) assessment tool and the AFEQT questionnaire as a disease specific tool.

Furthermore, the CCS and ESC guidelines include non-cardiac AF symptoms such as the increased prevalence of depression in AF patients.

### 5. Stroke prevention

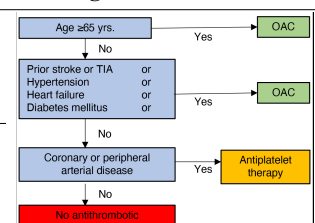
#### 5.1 Stroke-risk assessment

Stroke prevention remains the central part of AF management and a major part of all three clinical practice guidelines.

To weigh the benefit of anticoagulation against the potential bleeding risk, stroke-risk scores were introduced to identify patients at high risk for stroke. To this end, the ESC and AHA guidelines recommend the CHA<sub>2</sub>DS<sub>2</sub>-VASc-Score. Both guidelines recommend oral anticoagulation in men with a CHA<sub>2</sub>DS<sub>2</sub>-VASc-Score of  $\geq 2$  points and  $\geq 3$  in women, while anticoagulation may be considered (IIb; AHA) or should be considered (IIa; ESC) in men with 1 point or women with 2 points.

The CCS guidelines recommend the CHADS<sub>2</sub>-65 score, which generally recommends anticoagulation in patients aged  $\geq 65$  years, due to an independent annual age-attributed stroke risk of 2.1% [15] (Table 1).

Table 1. ESC, AHA/ACC/HRS and CCS guidelines for stroke risk assessment and decision making for anticoagulation.

ESC AHA/ACC/HRS			CCS	
Risk factors	Points awarded	Definitions	Risk factors	Definitions
<b>C</b>	1	<b>Congestive heart failure</b> Symptoms of heart failure, or objective evidence of moderate to severe LV dysfunction, or HCM	<b>C</b>	<b>Congestive heart failure</b>
<b>H</b>	1	<b>Hypertension</b> or on antihypertensive therapy	<b>H</b>	<b>Hypertension</b>
<b>A</b>	2	<b>Age <math>\geq 75</math> yrs.</b>	<b>A</b>	<b>Age <math>\geq 65</math> yrs.</b>
<b>D</b>	1	<b>Diabetes mellitus</b> Treatment with oral hypoglycaemic drugs and/or insulin or fasting blood glucose $> 125$ mg/dL	<b>D</b>	Diabetes mellitus
<b>S</b>	2	<b>Stroke</b> Previous Stroke, transient ischemic attack, or thrombembolism	<b>S</b>	<b>Previous stroke</b> or transient ischemic attack
<b>V</b>	1	<b>Vascular disease</b> Angiographically significant coronary artery disease, previous myocardial infarction, peripheral artery disease, or aortic plaque		
<b>A</b>	1	<b>Age 65–74 yrs.</b>		
<b>Sc</b>	1	<b>Sex category (female)</b>		
<b>Indications for anticoagulation</b>				
<b>ESC</b>	<b>AHA/ACC/HRS</b>		<b>CCS algorithm</b>	
OAC recommended in AF pts. with a CHA <sub>2</sub> DS <sub>2</sub> -VASc $\geq 2$ in men and $\geq 3$ in women Class: I	For patients with AF and a CHA <sub>2</sub> DS <sub>2</sub> -VASc of $\geq 2$ in men or $\geq 3$ women, OAC is recommended. Class: I		 <pre> graph TD     A[Age <math>\geq 65</math> yrs.] -- Yes --&gt; B[OAC]     A -- No --&gt; C[Prior stroke or TIA or Hypertension or Heart failure or Diabetes mellitus]     C -- Yes --&gt; D[OAC]     C -- No --&gt; E[Coronary or peripheral arterial disease]     E -- Yes --&gt; F[Antiplatelet therapy]     E -- No --&gt; G[No antithrombotic]           </pre>	
OAC should be considered in AF pts. with a CHA <sub>2</sub> DS <sub>2</sub> -VASc of 1 in men and 2 in women Class: IIa	For patients with AF and a CHA <sub>2</sub> DS <sub>2</sub> -VASc of 1 in men and 2 in women, OAC may be considered. Class: IIb			

AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; OAC, oral anticoagulation; TIA, transient ischemic attack; yrs., years. Levels of recommendation as presented in the ESC and AHA guidelines.

**Table 2. ESC, AHA/ACC/HRS and CCS guidelines on indications for rhythm control.**

Indications for rhythm control		
ESC	AHA/ACC/HRS	CCS
Favouring rhythm control:	Favouring rhythm control:	Favouring rhythm control:
<ul style="list-style-type: none"> <li>• Younger age</li> <li>• First AF episode or short history</li> <li>• Arrhythmia induced cardiomyopathy</li> <li>• Normal to moderate increased LAVI/atrial conduction delay (limited atrial remodeling)</li> <li>• No or few comorbidities/heart disease</li> <li>• Rate control difficult to achieve</li> <li>• AF precipitated by a temporary event</li> <li>• Patient's choice</li> </ul>	<ul style="list-style-type: none"> <li>• Symptoms under rate control</li> <li>• Failed rate control</li> <li>• Younger age</li> <li>• Arrhythmia induced cardiomyopathy</li> <li>• First AF episode</li> <li>• Patient's choice</li> </ul>	<ul style="list-style-type: none"> <li>• Recently diagnosed (&lt;1 year)</li> <li>• Highly symptomatic or significant QoL impairment</li> <li>• Multiple recurrences</li> <li>• Difficulty to achieve rate control</li> <li>• Arrhythmia induced cardiomyopathy</li> </ul>

AF, atrial fibrillation; QoL, Quality of life, LAVI, Left atrial volume-index.

The application of these different risk assessment tools results in different treatment recommendations as demonstrated in the following examples (Fig. 1). A 70-year-old male patient, without comorbidities would have a clear indication for anticoagulation in the CCS guidelines, anticoagulation should be considered (IIa) in the ESC guidelines and anticoagulation may be considered (IIb) in the AHA guidelines. In contrast, a 50-year-old female patient with peripheral artery disease would receive sole antiplatelet therapy in accordance with the CCS guidelines, while ESC and AHA guidelines imply different levels of recommendation for effective oral anticoagulation (IIa: ESC; IIb: AHA).

Furthermore, aortic plaque is not included in the CHADS-65 score, although previous studies have indicated independent stroke-risk associated with aortic plaques [16].

We think that the cumulative nature of the CHA<sub>2</sub>DS<sub>2</sub>-VASc-Score offers more than the binary question of whether a patient should receive OAC, as it allows to identify individual patients at very high risk for stroke, in whom interruption of OAC would be evaluated differently than in patients with a borderline OAC indication.

## 5.2 Aspirin

Aspirin alone is not suitable for stroke prevention in AF according to the ESC, CCS guidelines. In the previous ESC and in the AHA guidelines from 2014 aspirin could be considered in borderline indications (CHA<sub>2</sub>DS<sub>2</sub>-VASc 1 in men and 2 in women) [17], which is not recommended in the recent ESC guidelines, without being reformatted in the 2019 AHA guidelines update.

All guidelines do only recommend aspirin in combination with OAC in certain clinical settings, as for example post-PCI (see below) and after LAA occluder implantation.

## 5.3 NOAC vs. VKA

All three guidelines prefer NOACs over VKA for anticoagulation in patients eligible for NOACs. The preference for NOACs is based on their non-inferiority regarding stroke prevention [18–21] and simultaneously significantly reduced bleeding risk with NOACs compared to VKA [22,23]. The criteria for dose reduction of NOACs differ between the guidelines with a trend to stricter dose reduction criteria in the CCS guidelines as presented in **Supplementary Table 4**.

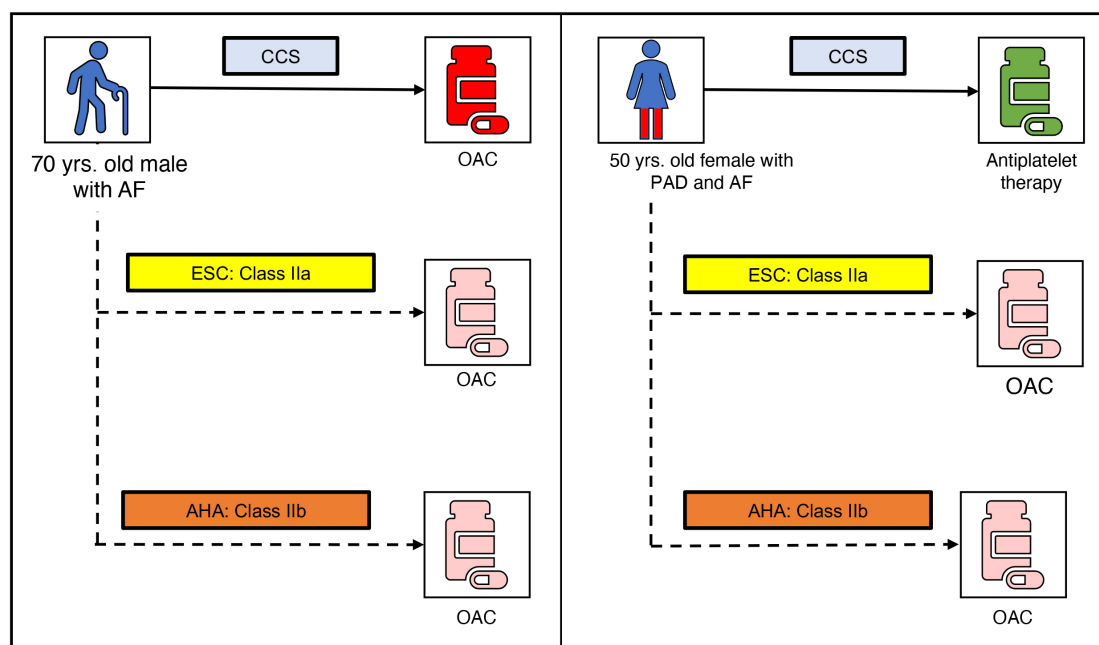
## 5.4 Left atrial appendage occlusion

Left atrial appendage occlusion (LAAO) is considered an alternative to oral anticoagulation in AF patients at medium or high risk of stroke with contraindications for long-term oral anticoagulation according to all three guidelines (**Supplementary Table 5**). As a result of the limited data comparing LAAO with NOACs and the increased stroke risk under LAAO compared to VKA, the recommendations for LAAO are rather weak (level of recommendation: IIb in ESC and AHA guidelines). The indication for surgical occlusion is differing between the CCS and the ESC and AHA guidelines. Compared to ESC and AHA guidelines, the CCS guidelines do only recommend surgical occlusion or exclusion in patients with contraindications for long-term oral anticoagulation. This recommendation must be questioned in the light of the LAAOS III trial [24], which did not enter the guidelines due to its publication date.

## 5.5 Anticoagulation in certain situations

### 5.5.1 Cardioversion

The ESC, CCS, and AHA guidelines emphasize the risk of cardioversion-associated stroke (**Supplementary Table 6**). Therefore, all three guidelines recommend an anticoagulation period of at least three weeks prior to car-



**Fig. 1. Illustrative example of different decision regarding anticoagulation in selected patients between the ESC, AHA/ACC/HRS and CCS guidelines.** AF, atrial fibrillation; OAC, oral anticoagulation; PAD, peripheral arterial disease; yrs., years, levels of recommendation as presented in the ESC and AHA guidelines.

dioversion. In case of an unplanned cardioversion, all guidelines agree that cardioversion can be performed after transoesophageal echocardiography (TOE) for thrombus exclusion.

However, the guidelines differ regarding their recommendation of cardioversion of new-onset AF without TOE: The ESC guidelines allow cardioversion without TOE or previous OAC within 48 hours of AF-onset. The AHA guidelines do not clearly comment on TOE in AF patients with AF duration less than 48 hours; but from the context, cardioversion can be performed without TOE after initiation of OAC in patients with AF onset of less than 48 hours. The CCS guidelines are giving different recommendations depending on AF-duration and individual risk of stroke. If AF-onset is <12 h, cardioversion is recommended without TOE independent of their individual stroke risk. In patients with AF lasting for 12–48 h, TOE is solely abdicable in patients with a low risk of stroke (CHADS<sub>2</sub>-score: 0–1). Since the duration of AF does not necessarily correlate with occurrence of thrombi [25] and AF-onset is often unsure, low-risk TOE [26] prior to cardioversion should be employed.

With regard to anticoagulation post cardioversion, the guideline recommendations only differ for low-risk patients.

The ESC gives a IIb-recommendation (may be omitted) for anticoagulation in low-risk patients (CHA<sub>2</sub>DS<sub>2</sub>-VASc of 0 in men or 1 in women) after cardioversion of AF with a duration less than 24 hours. The CCS guidelines recommend OAC for all patients following cardioversion for a

minimum of 4 weeks independent of their individual stroke risk. For patients at low risk for stroke (CHA<sub>2</sub>DS<sub>2</sub>-VASc of 0 in men or 1 in women) and AF-onset <48 h the AHA guidelines recommend anticoagulation prior to cardioversion but do not recommend anticoagulation after. Noteworthy, all guidelines generally recommend long-term OAC in high-risk patients, and in patients with AF-duration >24 h (ESC) or >48 h (CCS) prior to cardioversion, respectively.

The CCS recommendations are mainly based on the data from the FinCV [27], ClevelandClinic-Study [28], and the ANTIKogulation registry [25] while the ESC guidelines line out the low thromboembolic risk after cardioversion of AF lasting <12 h [28–30]. The AHA guidelines reach a different conclusion from these studies mentioned previously and recommend anticoagulation prior to cardioversion without recommending long-term anticoagulation in patients with early cardioversion (<48 h) at low risk of stroke.

### 5.5.2 Catheter ablation

Based on previous studies all guidelines emphasize the increased risk for stroke after AF catheter ablation (Supplementary Table 6). All guidelines suggest that OAC should be initiated prior to catheter ablation. The ESC and CCS guidelines incorporate recent studies [31–33] and advise against interruption of OAC or bridging with heparin for ablation. The former AHA guidelines of 2014 do not give clear recommendations for the management of OAC periprocedural and the subject was not revived in the recent 2019 update.

**Table 3. ESC, AHA/ACC/HRS and CCS guidelines on rate control.**

Rate control		
ESC	AHA/ACC/HRS	CCS
<ul style="list-style-type: none"> <li>• <math>\leq 110</math> bpm should be considered the primary target</li> </ul>	<ul style="list-style-type: none"> <li>• Resting heart rate <math>&lt; 80</math> bpm is reasonable to treat symptomatic AF.</li> </ul>	<ul style="list-style-type: none"> <li>• <math>\leq 100</math> bpm should be considered the primary target in the acute care situation</li> </ul>
<ul style="list-style-type: none"> <li>• 1st line drugs when LVEF (<math>\geq 40\%</math>):               <ul style="list-style-type: none"> <li>-betablockers</li> <li>-verapamil</li> <li>-diltiazem</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Resting heart rate <math>&lt; 110</math> bpm seems reasonable when LVEF is normal and patients are asymptomatic.</li> <li>• 1st line drugs for rate control:               <ul style="list-style-type: none"> <li>-betablockers</li> <li>-nondihydropyridine calcium channel antagonist</li> </ul> </li> <li>• AV-node ablation should be considered in patients without effective rhythm control who are not eligible for LA ablation.</li> </ul>	<ul style="list-style-type: none"> <li>• 1st line drugs when LVEF (<math>&gt; 40\%</math>):               <ul style="list-style-type: none"> <li>-betablockers</li> <li>-verapamil</li> <li>-diltiazem (Calcium-antagonists could be favorable for long-term therapy)</li> </ul> </li> <li>• 1st line drugs when LVEF (<math>\leq 40\%</math>):               <ul style="list-style-type: none"> <li>-betablockers</li> </ul> </li> </ul>
<ul style="list-style-type: none"> <li>• 1st line drugs when LVEF (<math>&lt; 40\%</math>):               <ul style="list-style-type: none"> <li>-betablockers</li> <li>-and/or digoxin</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Patients with preexcitation and AF should not be treated with digoxin, non- dihydropyridine calcium channel antagonists, or intravenous amiodarone as they may result in ventricular fibrillation</li> </ul>	<ul style="list-style-type: none"> <li>• Digoxin might be considered in older or sedentary individuals with permanent AF alone or in combination with betablocker</li> </ul>
<ul style="list-style-type: none"> <li>• AV-node ablation should be considered in patients without effective rhythm control who are not eligible for LA ablation.</li> </ul>		<ul style="list-style-type: none"> <li>• In CRT-patients 100% biventricular pacing should be targeted. In cases of biventricular pacing <math>&lt; 95\%</math> under optimal therapy AV-node ablation should be performed.</li> <li>• AV-node ablation should be considered in patients without effective rhythm control who are not eligible for LA ablation.</li> </ul>

AF, atrial fibrillation; bpm, beats per minute; Ca-Ant., calcium channel antagonists; CRT, Cardiac resynchronization therapy; LA, left atrial; LVEF, Left ventricular ejection fraction.



**Table 4. ESC, AHA/ACC/HRS and CCS guidelines on catheter ablation of atrial fibrillation.**

Catheter ablation of atrial fibrillation		
ESC	AHA/ACC/HRS	CCS
Indications for catheter ablation	Indications for catheter ablation	Indications for catheter ablation
<ul style="list-style-type: none"> <li>• Symptomatic atrial fibrillation</li> </ul>	<ul style="list-style-type: none"> <li>• Rhythm-control desired and paroxysmal atrial fibrillation refractory to at least 1 class I or III AAD</li> </ul>	<ul style="list-style-type: none"> <li>• Recommended in symptomatic atrial fibrillation with desired rhythm-control who remain symptomatic after AAD trial</li> </ul>
<ul style="list-style-type: none"> <li>• Catheter ablation after failed AAD: <ul style="list-style-type: none"> <li>-paroxysmal AF (IA)</li> <li>-persistent AF without risk factors for AF recurrence (IA)</li> <li>-persistent AF with risk factors for AF recurrence (IB)</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Some pts. with persistent AF</li> <li>• Initial strategy in paroxysmal AF after profound risk consideration</li> <li>• May be considered in long-standing persistent AF refractory to at least 1 class I or III AAD</li> </ul>	<ul style="list-style-type: none"> <li>• First-line therapy in selected symptomatic pts.</li> <li>• Success rate higher when performed earlier</li> </ul>
First line catheter ablation <ul style="list-style-type: none"> <li>-paroxysmal AF (IIaB)</li> <li>-persistent AF (IIbC)</li> </ul>	<ul style="list-style-type: none"> <li>• Might be reasonable in selected HFrEF pts. to improve survival and reduce hospitalization for heart failure</li> </ul>	
<ul style="list-style-type: none"> <li>• Recommended in AF-related tachymyopathy independent of symptoms</li> <li>• Selected HFrEF pts. to improve survival and reduce hospitalization for heart failure</li> </ul>		
Ablation technique		
<ul style="list-style-type: none"> <li>• Complete electrical isolation of pulmonary veins in all AF-ablation procedures</li> </ul>	<ul style="list-style-type: none"> <li>• No recommendations regarding the technique of AF ablation</li> </ul>	<ul style="list-style-type: none"> <li>• PVI is the “cornerstone” of all AF ablation procedures</li> </ul>
<ul style="list-style-type: none"> <li>• Cavo-tricuspid isthmus isolation (CTI) may be considered in pts. with history of typical atrial flutter or onset of typical atrial flutter during PVI</li> </ul>		
<ul style="list-style-type: none"> <li>• Additional lesions beyond PVI may be considered but are not well-established</li> </ul>		

AF, atrial fibrillation; AAD, antiarrhythmic drug; CTI, Cavo-tricuspid isthmus isolation; HFrEF, Heart failure with reduced ejection fraction; pts., patients; PVI, pulmonary vein isolation. Levels of recommendation as presented in the ESC and AHA guidelines.

On the other hand, all guidelines agree that postinterventional OAC should be continued for at least eight weeks in all patients and indication for continuing OAC depends on the individual risk of stroke and is not influenced by ablation-success. A randomized-controlled trial to evaluate the need for OAC after successful catheter ablation is still ongoing [34].

### 5.5.3 Anticoagulation and elective or acute PCI

All three guidelines address the subject of anticoagulation in combination with antiplatelet therapy in patients with percutaneous coronary intervention (PCI) (Supplementary Table 7). While the ESC and CCS guidelines discriminate between PCI for acute coronary syndrome (ACS) and elective PCI in the setting of chronic coronary artery disease (CCS), the AHA guidelines only give a recommendation on PCI in ACS.

In general, all guidelines recommend the combination of antiplatelet therapy with oral anticoagulation. The ESC and CCS guidelines recommend all eligible NOAC over VKA for combination with antiplatelet therapy mainly based on the AUGUSTUS [35] and RE-DUAL PCI study [36], whereas the AHA guidelines only mention VKA, rivaroxaban, and dabigatran in combination with antiplatelets without giving a preference for a certain substance class.

For the combination of rivaroxaban with antiplatelet therapy, the CCS guidelines recommend a dose reduction of rivaroxaban to 15 mg (o.d.) while the ESC guidelines limit this recommendation exclusively for patients at high bleeding risk, defined as HAS-BLED score  $\geq 3$ .

The most controversial and ambiguous subject in this field is the use of triple therapy (dual antiplatelet therapy plus anticoagulation) and its duration. The ESC and CCS guidelines suggest triple therapy after PCI in ACS patients for 1 day to 1 month (CCS guideline) or  $\leq 1$  week to  $\leq 1$  month (ESC guideline) depending on the individual relation of stent thrombosis and bleeding risk. The AHA guidelines for AF do not advise when to choose which antiplatelet and anticoagulant combination but line out that (1) dual therapy with OAC and clopidogrel or ticagrelor might be reasonable and (2) limiting triple therapy to 4–6 weeks to reduce bleeding complications can be considered.

## 6. Rate and rhythm control

All guidelines emphasize the different treatment options for AF in terms of rate control and rhythm control.

The ESC, CCS, and AHA guidelines do not significantly differ in patient criteria for a rhythm control strategy and mainly symptomatic, younger patients with limited comorbidities and recent-onset AF are considered suitable candidates. Furthermore, all guidelines recommend rhythm-control strategies in patients who failed a rate control regimen and patients with AF-induced tachymyopathy (Table 2).

Due to its most recent publication date, solely the CCS guidelines incorporate the results from the EAST-AFNET 4 study [6], which demonstrated positive effects of rhythm over rate control regardless of patient's symptoms and recommend that "a rhythm control strategy (should) be considered for most stable patients with recent-onset AF" [4].

### 6.1 Rate control

When focusing on rate control targets, the results of RACE II [5] and AFFIRM [37] are integrated into all three guidelines in different ways (Table 3). The ESC guidelines recommend a lenient rate-control strategy with target heart rates  $< 110$  bpm. The CCS and AHA guidelines recommend a target heart  $< 100$  bpm only in patients with LVEF  $> 40\%$  and stricter rate control targets in patients with LVEF  $< 40\%$ . This is due to the small number of patients with reduced ejection fraction in the lenient rate control group and small differences in the achieved heart rates between both groups in the RACE II study [5].

Furthermore, possible beneficial effects of calcium-antagonists over betablockers in patients with preserved ejection fraction [38,39] are lined out in the CCS guidelines.

The comparative RATE-AF study [40] on bisoprolol vs. digoxin on the quality of life of patients with permanent AF was not included in the three guidelines due to its recent publication date.

In the setting of AF with preexcitation, the AHA and CCS guidelines warn against possible AV conduction slowing medications, with the risk of ventricular fibrillation, a subject which is not included in the ESC guidelines.

Lastly, all guidelines recommend AV-node ablation in case of unachievable rate control and unsuccessful conversion to sinus rhythm, especially in elderly patients and in CRT patients with subtherapeutic biventricular pacing. The ESC and AHA guidelines differ in the recommended lower tracking rate after AV-node ablation, whereas the AHA guidelines recommend 90–100 bpm and the ESC guidelines recommend 70–90 bpm to lower the risk of sudden bradycardia-triggered proarrhythmia [41].

### 6.2 Rhythm control

#### 6.2.1 Cardioversion

All three guidelines include recommendations on cardioversion, while the mode of cardioversion (electrical vs. pharmacological) should be chosen based on patient characteristics, possible side effects, and hemodynamic stability.

The ESC guidelines incorporate data from the RATE-7-trial [42] and therefore offer a watch and wait approach for stable patients with AF and a duration of less than 48 hours.

Electrical cardioversion. The value of electrical cardioversion is mostly its timesaving character especially in the setting of hemodynamic instability.

The preferred mode of electrical cardioversion differs between the guidelines: while the ESC and AHA guide-



lines recommend an anterior-posterior electrodeposition, the CCS guidelines do not give a recommendation as they evaluate the study results as heterogeneous [43–45].

## 6.2.2 Pharmacological rhythm control

**6.2.2.1 Pharmacological cardioversion.** In the setting of hemodynamic stability, pharmacological cardioversion can be performed by intravenous or oral application of different antiarrhythmic drugs. All three guidelines mainly refer to the same drugs and the evaluation of the different drugs is mostly homogeneous. However, they differ in certain details or the local availability of drugs (**Supplementary Table 8**).

All guidelines agree that amiodarone is not the first drug of choice in patients eligible for other drugs due to its side effects and its delayed effectiveness.

The ESC and AHA guidelines recommend flecainide or propafenone for cardioversion in eligible patients (no LV-dysfunction, no structural heart disease, no signs of coronary artery disease, etc.) and consider ibutilide, especially for cardioversion of atrial flutter [46], but also outline its possible proarrhythmic side effects [47]. In contrast, intravenous flecainide or propafenone is not available in Canada and therefore not recommended in the CCS guidelines, while intravenous magnesium is recommended to reduce ibutilide's possible torsadogenic properties [48,49].

The ESC guidelines state the effectiveness of vernakalant whereas the CCS guidelines do not expect it to be significantly more effective than amiodarone or ibutilide based on previous data [50,51].

**6.2.2.2 Long-term antiarrhythmic drug therapy.** In patients with symptomatic AF, antiarrhythmic drugs can be used to reduce symptomatic AF recurrence. All three guidelines collectively recommend the guidance of antiarrhythmic drug therapy based on drug's safety in the individual patient and the patient's symptom relief or reduction of symptomatic AF-burden and not by sole drug efficacy (**Supplementary Table 8**).

Possible and frequently recommended drugs are the class I antiarrhythmic drugs flecainide and propafenone, which are limited to patients without severe structural or ischemic heart disease, without severe conduction disorder. They are preferably combined with betablockers to reduce the risk of atrial flutter with 1:1 conduction. While all three guidelines emphasize ischemic heart disease as a possible contraindication, the CCS guidelines clearly recommend an ischemia risk assessment in patients  $\geq 50$  years of age and patients with severe risk factors and furthermore recommend an annual reassessment of possible symptoms of coronary artery disease.

For amiodarone the three guidelines acknowledge the significant amount of possible severe side effects, by which it has mostly become a second choice in selected cases. Nonetheless, the ESC and AHA guidelines agree that the

risk of proarrhythmia in spite of significant QT prolongation is rare [52,53].

Dronedarone is a possible alternative to amiodarone, with overall reduced side effects compared to amiodarone, but the ESC and AHA guidelines and presumably most physicians recognize dronedarone as “less effective” compared to amiodarone. In previous randomized trials [54, 55] dronedarone showed reduced cardiovascular morbidity in patients with paroxysmal and persistent AF and further comorbidities, but increased mortality in patients with heart failure, heart failure with reduced ejection fraction (HFrEF), and permanent AF, which resulted in the recommendations in all guidelines as shown in **Supplementary Table 8**. As a result of the profound data regarding dronedarone it might be considered a first-choice antiarrhythmic drug for suitable patients according to the ESC guidelines.

Sotalol is mostly, due to its  $I_{Kr}$  blocking effects with a consecutive significant proarrhythmic, especially torsadogenic potential mainly considered as a second line antiarrhythmic drug. It has to be mentioned that the ESC guidelines present heterogeneous study results [56,57] regarding the all-cause mortality under sotalol while the AHA guidelines are reporting a raised mortality under sotalol based on a retrospective analysis [58].

Long-term antiarrhythmic drug therapy with disopyramide is mentioned in the ESC and AHA guidelines. Both guidelines are evaluating disopyramide as a possible treatment alternative in patients with vagal AF [52] or patients with hypertrophic cardiomyopathy as disopyramide is able to reduce LV outflow tract obstruction [59], but leads to significantly increased mortality [60].

**6.2.3 Catheter ablation.** Catheter ablation for AF is discussed in detail in all three guidelines as a possible option to achieve rhythm control in certain patients. Predominantly, symptomatic patients after an ineffective or impossible antiarrhythmic treatment regimen are considered suitable for catheter ablation (Table 4). The ESC and AHA guidelines prefer catheter ablation in patients with paroxysmal AF, while patients with persistent AF are also suitable candidates for catheter ablation especially in the absence of risk factors for AF recurrence.

Furthermore, all guidelines include the results of the CASTLE-AF trial [61] and consider catheter ablation as a suitable treatment option in patients with symptomatic AF and HFrEF to improve survival and reduce hospitalizations for heart failure.

A difference can be found between AHA and CCS guidelines regarding the interpretation of the results of the CABANA trial [62], in which pulmonary vein isolation (PVI) was not superior to antiarrhythmic drugs in the reduction of death, stroke, and cardiac arrest, when focusing on the intention-to-treat analysis. But, as mentioned in the CCS guidelines, PVI was superior in the as-treated analysis.

Furthermore, the CCS guidelines point out upcoming new data on PVI in heart failure with reduced and preserved ejection fraction from the RAFT-AF study [63], which has closed enrollment.

The ESC and CCS guidelines recommend pulmonary vein isolation in all AF-ablation procedures, whereas the data for left atrial ablation techniques beyond PVI (e.g., additional linear ablations, rotors, fragmented activity, ectopic activity, etc.) are sparse and these procedures are not generally recommended.

## 7. Conclusions

The latest guidelines on the management of atrial fibrillation show great agreement in most aspects. Nevertheless, differences can be found in detail. To sum up, the ESC and CCS guidelines recently introduced different concepts for AF classification, further differences between the three guidelines can be found in the recommendations on stroke prophylaxis, the indications and targets for rate control and the patients eligible for rhythm control concepts.

## Abbreviations

AAD, antiarrhythmic drug; ACS, acute coronary syndrome; AF, atrial fibrillation; AFEQT, Atrial Fibrillation Effect on Quality-of-Life questionnaire; AFL, atrial flutter; Bpm, beats per minute; b.d., bis in die (twice a day); Ca-Ant., calcium channel antagonist; CCS, chronic coronary syndrome; CRT, Cardiac resynchronization therapy; CTI, Cavo-tricuspid isthmus isolation; CV, cardiovascular; EQ-5D, EuroQol-5D; HCM, hypertrophic cardiomyopathy; HFrEF, Heart failure with reduced ejection fraction; HFpEF, Heart failure with preserved ejection fraction; HOCM, Hypertrophic obstructive cardiomyopathy; i.v., intravenous; INR, International normalized ratio; LA, left atrial; LAA, left atrial appendage; LAAO, left atrial appendage occlusion; LAVI, Left atrial volume-index; LV, left ventricle; LVEF, Left ventricular ejection fraction; NOAC, Non-vitamin K antagonist oral anticoagulant; NYHA, New York Heart Association; o.d., omni die (once daily); OAC, oral anticoagulation; PAD, peripheral arterial disease; PCI, Percutaneous coronary intervention; pts., patients; PVI, pulmonary vein isolation; QoL, Quality of life; TdP, Torsade de pointes tachycardia; TIA, transient ischemic attack; TOE, Transoesophageal echocardiography; VKA, Vitamin K antagonist; yrs., years.

## Author contributions

JW—literature research and writing; CE and GF—literature research and corrections; LE—initiation, literature research and corrections.

## Ethics approval and consent to participate

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## Conflict of interest

The authors declare no conflict of interest.

## Supplementary material

Supplementary material associated with this article can be found, in the online version, at <https://www.imrpress.com/journal/RCM/23/2/10.31083/j.rcm2302056>.

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