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CURRENT OPINION

Atrial fibrillation guidelines across the Atlantic: a comparison of the current recommendations of the European Society of Cardiology/European Heart Rhythm Association/European Association of Cardiothoracic Surgeons, the American College of Cardiology Foundation/American Heart Association/Heart Rhythm Society, and the Canadian Cardiovascular Society

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Introduction

Atrial fibrillation (AF), the most common sustained arrhythmia, has been a major focus for heart rhythm-related research in recent years. The evidence supporting recommendations for the management of AF has markedly increased since the publication of the 2006 ACC/AHA/ESC guidelines on AF (Supplementary material online).

Therefore, the European Society of Cardiology (ESC), together with the European Heart Rhythm Association (EHRA) and the European Association of Cardiothoracic Surgeons (EACTS), mindful of a distinct regulatory, medico-legal and medical practice environment in Europe, published comprehensive new guidelines for the management of patients with AF in 2010,[1,2] and a focused update of these guidelines in 2012.[3] The Canadian Cardiovascular Society (CCS), based on similar considerations, published a full set of AF guidelines in 2011,[4–6] which was updated in 2012.[7] In parallel, the American College of Cardiology Foundation (ACCF), the American Heart Association (AHA), and the Heart Rhythm Society (HRS) issued two focused updates (Supplementary material online, references 7, 8) that were subsequently integrated into the previous 2006 ACC/AHA/ESC guidelines.[8] While ACCF, AHA, and HRS have started to develop a completely new set of guidelines for AF, the present situation provides a unique opportunity to gather insight into the process that leads from new, published evidence to new recommendations. We, therefore, systematically compared the recommendations in the three sets of guidelines and tried to characterize the causes that resulted in differing recommendations.

Methods

We systematically compared all recommendations published in the current versions of the guidelines of ESC, CCS, and ACCF/AHA/HRS, and classified all recommendations as identical/overlapping or differing. The ACCF/AHA/HRS and the ESC guidelines both use the same system to grade strength of recommendation and level of evidence, while the CCS guidelines use an adapted the Grading of Recommendations Assessment, Development and Evaluation (GRADE, www.gradeworkinggroup.org) system (Supplementary material online,

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reference 3). For the purpose of this comparison, we aligned the CCS recommendations with the ESC and US classification system as follows: Strong GRADE recommendations in the CCS documents corresponded to Class I recommendations in the system used by ACCF/AHA/HRS and ESC. Conditional (or weak) GRADE recommendations corresponded to IIa or IIb recommendations in the system used by ACCF/AHA/HRS ESC, where IIb corresponded to low or very low qualities of evidence. Strong negative GRADE recommendations corresponded to Class III recommendations.

Results

Most recommendations are either identical or overlap between all three sets of guidelines: Recommendations for the diagnosis of AF overlap markedly despite a paucity of systematic evidence supporting specific diagnostic strategies (Supplementary material online, *Table S1*). One European recommendation to screen for AF is reflected in the stroke prevention guidelines of AHA,[9] but not in the AF guidelines update. Other differences, e.g. in the use of echocardiography, reflect different practice patterns in Europe, Canada, and the USA (Supplementary material online, *Table S1*). For therapeutic recommendations, most of the overlapping recommendations are based on solid evidence as illustrated by a strong level of supporting evidence ('strong'/level of evidence A or B). This applies to the bulk of recommendations for stroke prevention in AF (Supplementary material online, *Tables S2A–S2C*, *Figure 1*) and for rate control therapy (Supplementary material online, *Table S3*). The target heart rate for rate control differs slightly, reflecting expert consensus in areas of insufficient evidence. For rhythm control therapy, all three guideline sets started off from the practice reflected in the prior 2006 guidelines set (Supplementary material online). Hence, there are no major variations in the recommendations for the older anti-arrhythmic drugs amiodarone, flecainide, propafenone, and sotalol (*Figure 2*). The recommendations differ slightly in their intensity and the level of evidence to recommend catheter ablation as an alternative to anti-arrhythmic drug therapy (*Figure 2*). Furthermore, there are differences in the recommendations on dronedarone and vernakalant, two new anti-arrhythmic drugs. These largely reflect differences in the regulatory approval for these substances.

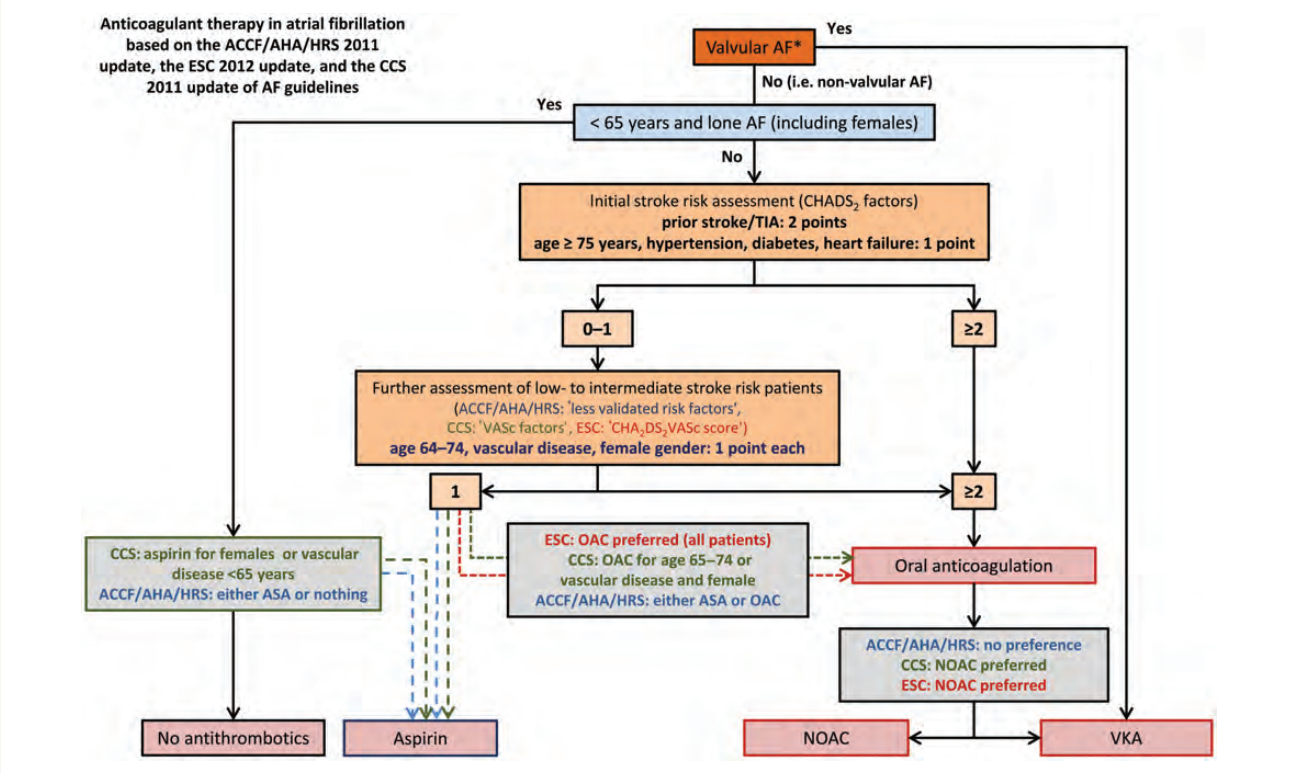

Figure 1 Decision tree for antithrombotic therapy in patients with non-valvular atrial fibrillation. The figure combines the recommendations described in the 2010 ESC/EHRA/EACTS guidelines and in the updated ACCF/AHA/HRS guidelines: Blue boxes indicate parts of the tree that are common to the ESC and ACCF/AHA/ESC recommendations. Pink boxes indicate parts in which the two sets of recommendations differ. These are also areas where clear evidence is lacking. *Valvular AF, rheumatic valvular disease, prosthetic valves; hypertrophic cardiomyopathy. AF, atrial fibrillation; OAC, oral anticoagulant; TIA, transient ischaemic attack; NOAC, Novel oral anticoagulants; VKA, vitamin K antagonist; ACCF/AHA/HRS, American College of Cardiology Foundation, American Heart Association, Heart Rhythm Society. CCS, Canadian Cardiovascular Society; ESC, European Society of Cardiology. *The suggestion to use oral anticoagulants rather than aspirin is substantiated by the safety data from BAFTA and AVERROES.

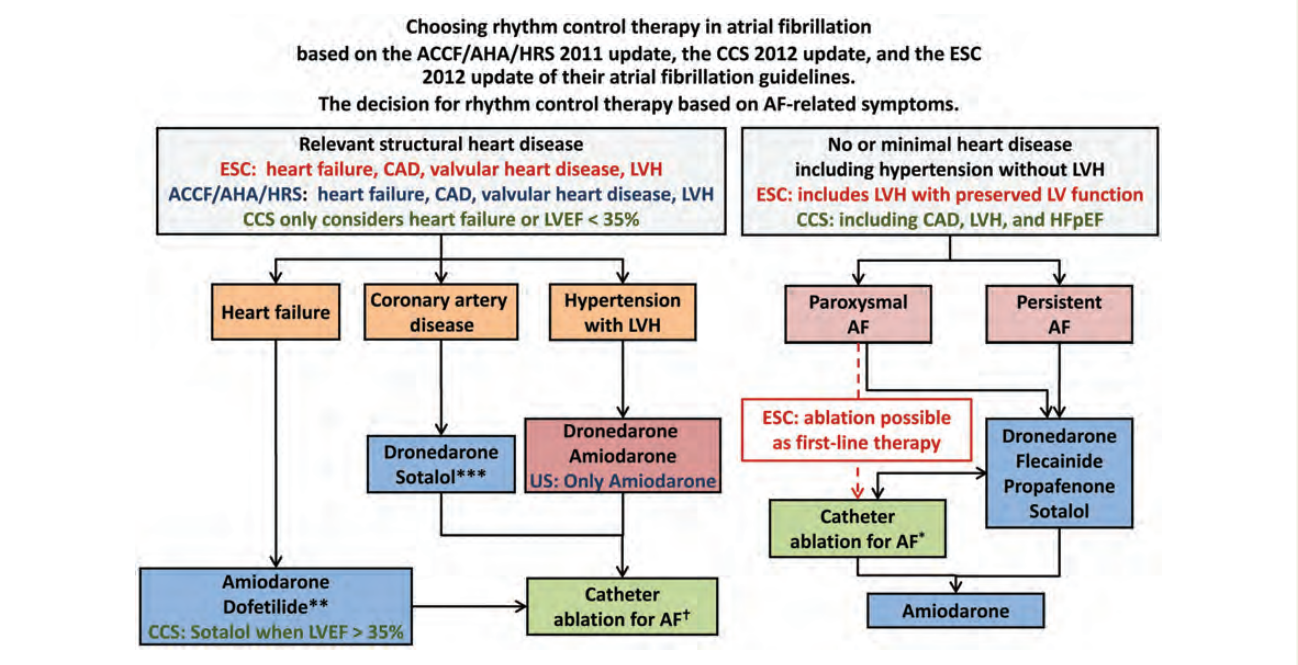

Figure 2 Flow chart for selecting specific rhythm control therapies in patients with atrial fibrillation. Blue boxes for anti-arrhythmic drugs and green boxes for catheter ablation indicate parts of the flow charts that are common to the ESC and ACCF/AHA/ESC recommendations. Pink boxes indicate parts in which the two sets of recommendations differ. Note that the main differences occur in the upper part of the chart, where patient categories are defined. Owing to its nature as an update, the ACCF/AHA/HRS guidelines kept the patient categories unchanged compared with the 2006 guidelines, while the ESC writing group adapted patient categories to better reflect the amended body of data. Anti-arrhythmic agents are listed in alphabetical order within each treatment box. *Usually pulmonary vein isolation is appropriate. **Dofetilide is not available in most parts of Europe. ***This recommendation may be revisited in the planned update of the ESC guidelines in 2012. †More extensive left atrial ablation may be needed. AF, atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; HFpEF, heart failure with preserved ejection fraction; HT, hypertension; LVH, left ventricular hypertrophy; NYHA, New York Heart Association; ACCF/AHA/HRS, American College of Cardiology Foundation, American Heart Association, Heart Rhythm Society. CCS, Canadian Cardiovascular Society; ESC, European Society of Cardiology.

Discussion

Main findings

The published changes in the AF management guidelines in Canada, Europe, and the USA between 2010 and 2012 exemplify that guidelines are not meant to be universal truths, but are comprehensive, living documents which attempt to authoritatively represent a constantly changing knowledge base. This systematic comparison of the recommendations of three major cardiological guideline sets yielded two major observations:

(1) When solid evidence exists, guidelines tend to put forward identical or largely overlapping recommendations. This applies to many aspects of AF management, especially to anticoagulant therapy and rate control therapy.

(2) Differences in recommendations stem from three main sources, namely the need to fill evidence gaps by writing group consensus, differences in regulatory appraisal of available evidence, and differences in the 'culture of medical practice'. Such differences between guideline recommendations can be found, e.g. in antithrombotic therapy in low-risk patients, or the choice of rhythm control therapy. This obviously calls for further studies to fill evidence gaps.

While the impact of expert consensus in areas of patchy evidence seems widely appreciated and monitored, the impact of differences in regulatory decisions and of 'medical culture' on guideline recommendations warrant further evaluation. A more detailed discussion covering the different areas of AF management can be found in the Supplementary material online of this article.

Tracing the influence of regulators in current AF guidelines

Guidelines are meant to apply to the majority of patients, and laid out in a way that can be followed in clinical practice. Henceforth, medications that are not available or not approved are usually not covered in guidelines written for that part of the world. For example, vernakalant is only covered in the European guidelines. There are other, more subtle effects on the interpretation of regulators on the available clinical trial data that can be traced in the recommendations, e.g. the dosing of the new oral anticoagulants: The dosing recommendations for rivaroxaban are not different between the three sets of guidelines, nor are the dosing recommendations for apixaban, for which approval had not been granted at the time of publication. The recommended doses reflect the doses tested in the trials. The dosing recommendations

for dabigatran, in contrast, show remarkable differences that can be explained by the different regulatory approval in Canada and Europe: Although dabigatran has been tested in two doses (110 and 150 mg b.i.d.), the FDA only approved the use of the higher dose (150 mg b.i.d.). In Canada, both doses are approved. The EMA approved both doses, but the label suggests consideration of a lower dose for some patients >75 years, and only approved the lower dose for patients 80 years and older, thereby limiting the use of the higher, more effective dose. Without clinical outcome data, the FDA furthermore approved the use of a 75 mg b.i.d. dose for patients with severe chronic kidney disease (MDRD IV-V, glomerular filtration rate <30 mL/min), while dabigatran is not available for such patients in Europe or in Canada. These approved dosings are reflected in the different guidelines, resulting in marked dosing differences in the recommendations.

Another area where the influence of regulators on guideline recommendations can be tracked is found in the recommendations for the monitoring of liver function on dronedarone therapy, where the recommended intensity of monitoring during the follow-up varies markedly and directly reflects the revised labels of the drug. The European guidelines furthermore reflect the revised EMA label of dronedarone, which excludes the use of this medication in heart failure, while the FDA did not include such a cautious note in their revised label of dronedarone. The CCS update accepts the use of dronedarone in patients with moderate heart failure symptoms, provided that they have a preserved left ventricular ejection fraction. Likewise, the ACCF/AHA/HRS focused update did not change their statement on the use of dronedarone in heart failure patients.

Overall, there is a marked, traceable influence of the regulatory approval on the recommendations in the three AF guideline sets compared here. These observations raise questions towards the justification of guideline recommendations based on regulatory approval, i.e. regulatory interpretation of evidence, as opposed to evidence itself.

Medical 'culture' impacts guidelines

Cultural issues also influence guideline recommendations. An example relates to the interpretation of a Class I recommendation. In Europe a Class I recommendation is generally regarded as an instruction which should be followed. An echocardiogram for all patients with AF is likely to be a valuable investigation, although there is no evidence to support this. Indeed, the US guidelines recommend and echocardiogram (Class I). However, this is not feasible in many parts of Europe, and the European Class I recommendation is restricted to obviously needful cases, in part reflecting the fact that many patients with AF are managed in a primary care setting without involvement of cardiologists in most of Europe. In addition, estimations of cost-effectiveness are increasingly shaping local decisions for reimbursement and approved use of new therapies, adding a further level of 'cultural' differences that will influence wording and grading of recommendations.

Conclusions

Most recommendations in the recent update of AF management guidelines are either identical or almost entirely overlapping, consistent with the solid evidence-base supporting the recommendations. Evidence gaps are at times filled with expert consensus, resulting in minor differences. Furthermore, the 'regional culture of medical practice' and the regulatory appraisal of the available evidence leave traceable effects in the guidelines. These factors may be considered by future guideline writing groups and guideline oversight committees.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: All authors helped to write one of the three guidelines that were compared here: P.K. and J.C. co-authored the ESC guidelines, A.G. and S.K. the CCS guidelines, and A.C. and S.W. the ACCF/AHA/HRS guidelines update. A detailed list of the financial disclosures of all authors has been published with the full set of guidelines.

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