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2026 HRS/PACES scientific statement on the use of antiarrhythmic drugs in understudied clinical scenarios

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ABSTRACT

Antiarrhythmic drugs can be an important treatment option for patients with heart rhythm disorders, but not all patients and scenarios are represented in trials related to antiarrhythmic drug use. This Heart Rhythm Society scientific statement identifies common clinical scenarios for which little guidance exists, at least partly because they are understudied. It also provides as much practical advice as possible, sourcing available evidence and the clinical proficiency of a diverse group of experienced clinicians, and provides the rationale for each recommendation.

KEYWORDS Antiarrhythmic; Drug; Arrhythmia; Understudied; Supraventricular tachycardia; Atrial fibrillation; Ventricular tachycardia; Ventricular fibrillation; QT interval

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ABBREVIATION AAD = antiarrhythmic drug; AF = atrial fibrillation; AFL = atrial flutter; AKI = acute kidney injury; AHA = American Heart Association; ATP = antitachycardia pacing; AV = atrioventricular; CABG = coronary artery bypass graft; CAD = coronary artery disease; CCB = calcium channel blocker; CHD = congenital heart disease; CT = computed tomography; CPVT = catecholaminergic polymorphic ventricular tachycardia; CrCl = creatinine clearance; DFT = defibrillation threshold; ERC = early rhythm control; HCM = hypertrophic cardiomyopathy; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HRS = Heart Rhythm Society; IART = intra-atrial reentrant tachycardia; ICD = implantable cardioverter-defibrillator; IST = inappropriate sinus tachycardia; IV = intravenous; LV = left ventricle; LVEF = left ventricular ejection fraction; LQTS = long QT syndrome; LVH = left ventricular hypertrophy; MI = myocardial infarction; NIPS = noninvasive programmed stimulation; NYHA = New York Heart Association; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; PET = positron emission tomography; P-gp = P-glycoprotein; PVC = premature ventricular

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complex; RCT = randomized clinical trial; SHD = structural heart disease; SVT = supraventricular tachycardia; TdP = *torsades de pointes*; VF = ventricular fibrillation; VT = ventricular tachycardia

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Preamble

The Heart Rhythm Society (HRS) has developed scientific and clinical documents guiding the management of cardiac arrhythmias since 1996. This HRS-led scientific statement was developed in collaboration with the Pediatric and Congenital Electrophysiology Society (PACES).

Editorial independence

The statement is sponsored by the HRS and was developed without commercial support. All writing committee members and peer reviewers volunteered their time to the writing and reviewing efforts.

Organization of the writing committee

The writing committee included experts in clinical electrophysiology and clinical research science, bringing together a range of perspectives essential to the topic. HRS strives to ensure that each writing committee reflects both the requisite subject matter expertise and diverse representation from the broader medical community. This includes thoughtful consideration of participants' clinical experience, career stage, and other demographic and professional characteristics.

HRS has rigorous policies and methods to ensure that documents are developed without bias or improper influence. The HRS policy on relationships with industry and other entities can be found in Appendix C of the Heart Rhythm Society Code of Ethics & Professionalism and in the HRS Scientific Documents Methodology Manual. Appendix 1 is a comprehensive list of relationships with industry and other entities (RWIs) disclosed by the writing committee members. Appendix 2 is a comprehensive list of RWIs disclosed by the peer reviewers.

Document review and approval

This statement was approved by the writing committee and underwent internal review and approval by the HRS Scientific Documents Committee. The document was also reviewed and approved by PACES.

Document updates

The HRS Scientific Documents Committee reviews each scientific document for currency every 2–5 years after publication.

Background and methodology

Antiarrhythmic drugs (AADs) can be an important treatment option for patients with heart rhythm disorders. Recommendations on AAD administration are largely based on randomized clinical trials (RCTs) and nonrandomized clinical trials and have been provided in guideline documents authored or endorsed by professional societies.[1–8] Unfortunately, not all patients and scenarios are represented by such trials, which often study a tightly controlled, specific population, with restricted inclusion criteria.

This scientific statement identifies common clinical scenarios for which little guidance exists, at least partly because they are understudied. It then provides as much practical advice as possible, sourcing available evidence and the clinical proficiency of a diverse group of experienced clinicians, and provides the rationale for each recommendation. The authors hope that this guidance facilitates potentially challenging clinical decision-making. However, it must be recognized that decisions in individual cases sometimes must take into account subtle details particular to individual patient cases. The concept of shared decision-making was employed to indicate that available evidence, expert consensus, and patient values should be considered when implementing the recommendations in this document. The writing committee recognizes that this patient-centered shared decision-making can best be accomplished through patient and clinician education, engagement of multidisciplinary team members, and if available, use of purpose-built decision aid tools.[8,9] In addition, although procedural therapy (eg, implanted device-based therapy, catheter ablation) might be more appropriate in many of these clinical scenarios, this document approaches scenarios with the assumption that standalone invasive therapy is either not desired or not appropriate. The writing committee also recognizes that some clinical scenarios require both invasive and pharmacologic therapy for optimal treatment.

When considering how to organize this document, the writing committee acknowledged the existence of the commonly used Vaughan–Williams classification of AADs, and the more recently proposed "modern" classification.[10,11] However, as the scope of understudied clinical scenarios is not evenly distributed among these class schemes, this document does not discuss every AAD class. Rather than producing a comprehensive overview of all aspects of AAD use, this document focuses on gaps in knowledge.

In some cases, relatively little directly relevant published information exists about these understudied clinical scenarios, but we made every effort to apply what published data were available. An additional challenge was the frequently used term structural heart disease (SHD) as a disqualifier for AAD therapy—especially for sodium channel-blocking AADs. Because SHD is poorly defined, the term

can be interpreted variably in clinical practice as signifying heart failure (HF), coronary disease, myocardial scar, or valvular disease, among other diagnoses. Each kind of SHD may or may not be relevant depending on the scenario. To address this challenge, we have avoided the umbrella term SHD and instead focused on identifying and discussing the impact of specific diagnoses that must be considered in the context of AAD selection. Furthermore, because the use of AADs in pediatric patients has not been evaluated in large RCTs, this entire population may be considered "understudied." A comprehensive review of the nuances of AAD use in pediatrics is out of the scope of the document. However, many of the recommendations made in this document may be applicable in pediatric patients for whom, as for adults, there are understudied arrhythmia scenarios.

Draft recommendations were reviewed, discussed, and edited by the writing committee. The final recommendations were sent to all writing committee members, who voted anonymously. All members voted on each recommendation unless a significant conflict of interest was identified by that individual or the writing committee chair or vice chair. Our writing committee chose to indicate "consensus" when at least 70% of the group agreed with the majority recommendation and "strong consensus" when 90% or more were in agreement. On secret-ballot voting, each of the 49 recommendations contained in this document received strong consensus. In contrast to more formal clinical practice guidelines, classes of recommendations are not given, nor are levels of evidence. We also recognize that many of these fields are still evolving, and our consensus represents the current state of practice and science at this time.

Initiation, transition, and discontinuation of AADs

Is a stress test needed before initiation of class 1C AAD therapy?

Scenario

In patients with atrial fibrillation (AF) with a low clinical suspicion of ischemia, including a normal echocardiogram and a normal QRS, is stress testing required before initiation of a class 1C AAD, such as flecainide or propafenone?

Recommendations

1. In patients with AF who are at low clinical suspicion for coronary artery disease (CAD), a stress test is not required before initiating a class 1C AAD.
2. In patients with AF in whom there is reasonable clinical suspicion for CAD and myocardial ischemia, a stress test is recommended before initiating a class 1C AAD.

Discussion

Although retrospective and inferential, substudies from the Cardiac Arrhythmia Suppression Trial (CAST) strongly implicate the interaction between ischemia and class 1C AADs as an important, if not the, causal factor related to the risk of mortality attributed to these drugs.[12–14] All patients in the CAST had a prior myocardial infarction (MI), and nearly half had a left ventricular ejection fraction (LVEF) of <40%. In contrast, the patient described in the scenario has a low risk of ischemia and thus does not require stress testing prior to initiation of a class 1C AAD. For patients at risk for CAD, stress testing or an anatomic evaluation for CAD (eg, coronary computed tomography or invasive angiography) is recommended to exclude ischemia if a class 1C AAD is to be considered. The stress test should be done before the drug is initiated, given that mortality can occur early during drug titration, as was the case in the moricizine arm of the CAST, in which deaths occurred within the first 14 days.[15] Notably, even if CAD is present but subclinical, in the absence of symptoms or ischemia, observational data show that there is no class 1C AAD-associated mortality increase compared with matched patients not taking a class 1C AAD.[16,17]

Monitoring for ischemia or evidence of new conduction delay during class 1C AAD use

Scenario

In patients on chronic stable treatment with a class 1C AAD, is periodic stress testing required in the absence of symptoms concerning ischemia?

Recommendations

1. In patients taking a class 1C AAD without conduction delay or symptoms concerning ischemia, routine exercise stress testing is not required.
2. In patients taking a class 1C AAD who develop new QRS widening of $\leq$40 ms above baseline and a QRS duration of $\leq$120 ms, exercise stress testing may be considered.
3. In patients taking a class 1C AAD who develop new QRS widening of >40 ms above baseline and QRS duration of >120 ms, dose reduction or discontinuation of the 1C AAD is recommended.

Discussion

Class 1C AADs, such as flecainide and propafenone, demonstrate use-dependent sodium channel blockade, with a potential for conduction delay with widening QRS at faster heart rates, as well as proarrhythmia, including ventricular tachycardia (VT) and atrial flutter (AFL) with 1:1 atrioventricular (AV) conduction.[18–21] Propafenone has intrinsic beta-blocker properties (especially in patients who are poor metabolizers), which may limit heart rate increase.[22,23] Nevertheless, it retains use-dependence and at high rates can produce clinically significant widening of the QRS. In patients without conduction delay or symptoms concerning for ischemia, routine stress testing does not enhance management.[24,25] A resting electrocardiogram (ECG) at routine visits is sufficient to monitor for new conduction abnormalities.[8]

In patients who develop new moderate QRS widening (ie, $\leq$40 ms above baseline) at rest because of class 1C AAD use, exercise stress testing may help to identify patients at higher risk for proarrhythmia.[26] Evaluating the

degree of change in QRS may guide the decision to discontinue or reduce the dose of the class 1C AAD to mitigate proarrhythmic risk, as supported in retrospective studies.[27,28] A >40 ms increase in QRS duration from baseline during treatment indicates excessive use-dependent sodium channel blockade and warrants dose reduction or discontinuation of the class 1C AAD.[6,29] If the baseline QRS is >120 ms because of conduction disease (especially left bundle branch block), class 1C AADs should be avoided. If a class 1C agent is deemed the most appropriate therapy despite QRS widening, an evaluation of risk-benefit relationships should be undertaken.

Use of 1C AADs in patients with known nonobstructive CAD

Scenario

Can a class 1C AAD be used by patients without a prior MI but with asymptomatic nonobstructive CAD (eg, seen on invasive angiogram or coronary calcium on screening computed tomography or quantitative positron emission tomography) who desire antiarrhythmic suppression of AF or premature ventricular complexes (PVCs)? What if they have had revascularization (percutaneous coronary intervention or coronary artery bypass graft)? For patients on chronic class 1C AAD therapy who develop symptoms suggestive of coronary ischemia, should the drug be stopped?

Recommendations

1. In patients with CAD, class 1C AADs may be used with caution, and only if ischemia is proven to be absent.
2. In patients with revascularized obstructive CAD, class 1C AADs are not recommended as a first-line maintenance drug because of the ongoing relatively high risk of developing ischemia.
3. For patients receiving a class 1C AAD who develop symptoms suggestive of ischemia, the drug should be stopped and resumed only if myocardial ischemia and infarction have been ruled out.

Discussion

The use of class 1C AADs in the presence of CAD can be a complex issue in part because the flecainide and propafenone package inserts issue warnings regarding using these agents in patients who have had an MI.[30,31] The flecainide warning states that it is of uncertain applicability to other populations, specifically those without prior MI. Thus, if CAD is present but there is no evidence for ischemia or infarct on a stress test, a class 1C AAD could potentially be used. In this scenario, careful education, discussion, and documentation are required. Many considerations may be operative during this decision-making: for example, the desire to avoid amiodarone and its organ toxicities, especially in a young person. Any signal suggestive of ischemia represents a risk for life-threatening ventricular arrhythmia, and the class 1C AAD should be stopped. In the absence of symptoms or ischemia, there is no increased mortality compared with matched patients not taking a class 1C AAD.[16,32]

Patients who have revascularized CAD have demonstrated a propensity toward significantly obstructive atherosclerosis. Their likelihood of having an undiagnosed MI, or of developing ischemia in the future, is high. Thus, for patients with known prior MI, class 1C AADs are not recommended as a first-line drug because of the ongoing relatively high risk of developing ischemia even if a stress test is negative. Although this is an understudied area, any of these conditions may lead to higher proarrhythmic risk in the setting of class 1C AAD use.[12,14,33] However, the European Rythmol Atrial Fibrillation Trial included patients with a LVEF of >35% who were at least 1 year post-infarction and had no angina or ischemia on a stress test, and those patients did not experience an increased incidence of ventricular arrhythmias or mortality despite medium- to high-dose treatment with propafenone.[32,34] In most patients with revascularized CAD, other effective AADs are available. It is the opinion of this writing committee that only in selected cases should class 1C AAD use be considered in patients with established, albeit "revascularized" CAD. Such exceptions could include when all other drugs are contraindicated, the chance of developing ischemia is minimized, and surveillance for ischemia is assured. Furthermore, given the likely ischemia-mediated proarrhythmic effects of class 1C AADs, these drugs should be discontinued if there is clinical suspicion that ischemia is present.

Use of class 1C AADs in PVC-mediated cardiomyopathy

Scenario

In patients with suspected PVC-induced nonischemic cardiomyopathy, can a class 1C AAD be used to suppress PVCs?

Recommendation

1. In patients with suspected PVC-induced nonischemic cardiomyopathy, class 1C AADs may be used for PVC suppression.

Discussion

Published literature has demonstrated the safety of class 1C AADs to suppress PVCs in patients with nonischemic cardiomyopathy.[35,36] The operative safety issue is the absence of ischemia, because ischemia is believed to be the major driver of mortality in class 1C AAD use.[12,14,34] It is imperative that ischemia be excluded if a class 1C AAD is to be used in individuals who are at risk of having CAD. Although the studies referenced here carefully excluded ischemia, some patients did have evidence of scar (ie, MRI-detected late gadolinium enhancement [LGE]), although in each patient the scar burden was <5%, and it was not reported whether scar had any correlation with arrhythmia. In the setting of significant LGE, the evidence may be less robust. The presence of an implantable cardioverter-defibrillator (ICD) could add additional safety during treatment. As class

1C AADs are negative inotropes, monitoring for HF symptoms should take place, and the drug should be stopped if such symptoms arise.

AV nodal blocking agents during use of class 1C AADs

Scenario

In patients with AF that is well controlled on a class 1C AAD, with a well-controlled ventricular rate when in AF but significant bradycardia when in sinus rhythm, can a class 1C AAD be used without an AV nodal blocking drug?

Recommendations

1. In patients with AF who are treated with a class 1C AAD, a negative dromotropic drug (ie, beta-blocker or nondihydropyridine calcium channel blocker) should be used to prevent AFL with 1:1 AV conduction.
2. In patients with AF who are treated with a class 1C AAD but who are unable to take concomitant AV nodal blockade, a discussion with the patient regarding the associated risks and benefits is recommended.

Discussion

Irrespective of the ventricular response during AF, if at all possible, class 1C AADs should be used with a drug that provides some AV nodal blockade to protect against dangerous ventricular rates due to AFL with 1:1 AV conduction. Because the same drugs that cause AV nodal blockade can cause sinus bradycardia, when there is concern about symptomatic bradycardia, the drug should be initiated at a low dose. Whether to continue a class 1C AAD without an AV nodal blocker requires shared decision-making with the patient.

Scenario

In patients with idiopathic PVCs, can class 1C AADs be used without a concomitant AV nodal blocking drug (eg, beta-blocker, nondihydropyridine calcium channel blocker, digoxin)?

Recommendations

1. In patients for whom PVC suppression is desired and who do not have a history of AF, a class 1C AAD may be used without concomitant AV nodal blockade, given that the risk of AFL with 1:1 AV conduction is far less than if a history of AF were present.
2. In patients for whom class 1C AAD-based PVC suppression is desired and who have a history of AF, AV nodal blockade should be used to slow AV nodal conduction during AF and to reduce the risk of AFL with 1:1 AV conduction.
3. In patients with nonischemic cardiomyopathy for whom class 1C AAD-based PVC suppression is desired, concomitant beta-blockade should be used as part of guideline-directed medical therapy for HF.

Discussion

When suppressing PVCs with class 1C AADs in the absence of cardiomyopathy, beta-blockade is not absolutely required (although it could potentiate PVC suppression and/or improve symptoms). For patients with a history of AF, AV nodal blockade is indicated to decrease the risk of 1:1 AV conduction if AFL were to occur. For patients with cardiomyopathy, irrespective of whether there is a history of AF, published HF guidelines recommend beta-blocker therapy.[37] In a report using class 1C AADs to suppress PVCs in patients with nonischemic cardiomyopathy, beta-blockers were used in 97% of patients, and there was no signal of harm.[35] Although beta-blockers may be favored, digoxin would be another option for AV nodal blockade in the setting of HF. Nondihydropyridine calcium channel blockers, such as diltiazem or verapamil, should not be used in the presence of a depressed LVEF.

Class 1C AADs in congenital heart disease

Scenario

In patients with congenital heart disease (CHD), can class 1C AADs be used?

Recommendations

1. In patients with CHD, class 1C AADs can be considered for long-term management of arrhythmias. If there is concern regarding coronary artery anatomy and perfusion, testing should be performed to rule out ischemia prior to use of a class 1C AAD.
2. In patients with CHD with no myocardial ischemia and without severe ventricular dysfunction, class 1C AADs may be used for acute conversion of supraventricular arrhythmias.

Discussion

Initial concerns regarding flecainide in patients with CHD were perhaps improperly extrapolated from the CAST study, which excluded patients with CHD.[38] A CAST-contemporary multicenter retrospective survey of pediatric cardiac electrophysiologists reported a higher incidence of cardiac arrest and death in children with CHD and supraventricular tachycardia (SVT) treated with encainide or flecainide compared with children with normal hearts (cardiac arrest 8.3% vs 0.3% and death 6.8% vs 0.3%; $P < .001$ for both).[39] Of note, both cardiac arrest and death were over 3 times more common with encainide compared with flecainide.[39,40] These findings led to limited use of class 1C AADs in patients with CHD.[40]

Emerging data support the use of class 1C AADs in CHD. One multicenter database showed an increase in flecainide use in patients with CHD (4.6% in 2004 to 8.7% in 2011).[41] Adverse events in patients with CHD are no different when treated with flecainide compared with other AADs.[41,42] Two other studies found no CHD-based difference in efficacy or safety, with dose reduction or discontinuation in <10%,

and no cardiac arrests or drug-related deaths in children taking flecainide.[43,44]

Two studies including patients with CHD examined the use of class 1C AADs for acute conversion of AF or AFL/intra-atrial reentrant tachycardia (AFL-IART).[45,46] One showed that flecainide had higher efficacy in normal hearts and was more effective for conversion of AF compared with AFL-IART, whereas the other showed there was no CHD-based difference in efficacy. One study found that flecainide was more effective than propafenone.[45] No serious adverse effects were reported.

AAD choices in patients with AF and HF

Scenario

In patients with symptomatic heart failure with preserved ejection fraction (HFpEF) and AF, can dronedarone be used?

Recommendation

1. In patients with HFpEF and paroxysmal or persistent AF, dronedarone appears to be safe for patients with New York Heart Association (NYHA) class I or II HF without an HF decompensation in the prior month.

Discussion

ATHENA (A Trial With Dronedarone to Prevent Hospitalization or Death in Patients With Atrial Fibrillation) was a randomized controlled study of dronedarone vs placebo among 4628 patients with AF or AFL.[47] Post hoc analyses stratified the ATHENA population by LVEF and the presence or absence of HF. Overall, dronedarone reduced the risk of death or cardiovascular hospitalization (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.69–0.84), regardless of HF status and with statistical consistency across the range of LVEF, including among those with HFpEF or HF with mildly reduced ejection fraction (LVEF of >40%, n = 534).[48] Similarly, among ATHENA patients with NYHA class II or III symptoms and LVEF <40%, dronedarone was associated with improved outcomes compared with placebo.[49]

In contrast, European Trial of Dronedarone in Moderate to Severe Congestive Heart Failure (ANDROMEDA) was a randomized study of dronedarone among hospitalized patients with new or worsening HF, all of whom had heart failure with reduced ejection fraction (HFrEF) (LVEF of ≤35%) and an episode of NYHA class III or IV symptoms or paroxysmal nocturnal dyspnea in the month before admission.[50] That study was stopped early due to a signal of excess mortality from dronedarone, leading to the recommendation that the drug should be avoided in patients with unstable HF or in those who are within 1 month of an acute decompensation.

Because there was minimal overlap between ATHENA and ANDROMEDA (ie, <5% of ATHENA patients had LVEF of <35%), it is not possible to differentiate between the impact of severe left ventricular dysfunction and the impact of recent HF decompensation as the instrumental factor that led to increased mortality in ANDROMEDA. Similarly, because ANDROMEDA enrolled only those with LVEF of ≤35%, it is unknown whether patients with HFpEF and a recent HF exacerbation would experience net benefit or net harm when treated with dronedarone. Taken together, at present, the evidence supports dronedarone use in HFpEF patients only during clinical stability and nonpermanent AF.

It is conceivable that a patient with stable NYHA class III HF symptoms without a recent hospitalization could be treated with dronedarone. However, these patients were excluded from the recommendation because of their high risk of decompensation leading to hospitalization. Approximately half of deaths in the dronedarone arm of the ANDROMEDA study were arrhythmic, so the presence or absence of an ICD has uncertain impact on this recommendation.

Scenario

In patients with HF and AF, can sotalol be used as a first-line treatment?

Recommendation

1. In patients with AF and HF, sotalol should not be used as a first-line treatment.

Discussion

Sotalol is not a first-line therapy for the treatment of AF, in part because of the finding of increased mortality associated with its use.[8,51,52] Among patients with HF, concerns related to sotalol are amplified in HFrEF due to more severe QTc prolongation among patients with HFrEF vs HFpEF.[53–55] Of note, this trend is also observed with dofetilide.[55] An observational study showed that sotalol use in patients with HF was associated with increased risk of VT but not sudden cardiac arrest.[56] In a small subset of another observational study, serious side effects of sotalol were not reported, but there was frequent discontinuation for fatigue, bradycardia, and hypotension.[57] Other AADs appear to have a more favorable effectiveness and safety profile.[52,58]

Scenario

In patients with symptomatic HFpEF and AF, can class 1C AADs be used?

Recommendation

1. In patients with HFpEF and AF, flecainide or propafenone may be used.

Discussion

EAST-AFNET 4 (the Early Treatment of Atrial Fibrillation for Stroke Prevention Trial randomized patients with a new diagnosis of AF to early rhythm control or standard of care.[59,60] Among the 1395 patients randomized to early rhythm control, 136 had stable HFpEF and received flecainide or propafenone therapy.[61] None of these patients experienced serious drug-related side effects, including progression of HF. In another substudy, 14 patients with HFpEF enrolled

in the RACE 3 (Routine Versus Aggressive Upstream Rhythm Control for Prevention of Early Persistent Atrial Fibrillation in Heart Failure) trial received flecainide for management of AF; no serious side effects were reported.[57] Propafenone was compared with amiodarone in a Taiwanese population-based study among patients with HF as defined by diagnosis codes; left ventricular function was not reported, but only 2% were described as having "cardiomyopathy," suggesting that the large majority of the HF population likely had HFpEF.[62] Compared with amiodarone, patients treated with propafenone had a lower risk of proarrhythmia, death, or worsening HF. Although reassuring, causality cannot be assessed in this observational study.

Scenario

In patients with symptomatic HFrEF and AF, can class 1C AADs be used? Does the presence of an ICD affect the recommendation?

Recommendation

1. In patients with symptomatic and irreversible HFrEF, treatment of AF with class 1C AADs is not recommended because of the drugs' negative inotropic effects.

Discussion

Flecainide and propafenone have negative inotropic effects, which can be amplified in HFrEF.[63] In an older series of patients with LVEF of <30%, new and worsening HF was seen when these drugs were used.[64] More contemporary observational studies suggest that these drugs can be used safely with careful monitoring for evidence of progressive HF along with contemporary HF treatment, but the available data are limited.[57,65] Because the primary concern related to flecainide and propafenone in patients with HFrEF is related to negative inotropy (ie, not arrhythmia), the presence or absence of an ICD does not impact this recommendation.

Scenario

In patients with hypertrophic cardiomyopathy (HCM) with significant left ventricular hypertrophy and AF, can sotalol or dofetilide be used?

Recommendation

1. In patients with HCM, either sotalol or dofetilide may be used for the treatment of AF.

Discussion

AF is a common arrhythmia among patients with HCM. For these patients who desire an AAD for rhythm control, limited data are available regarding the safety and effectiveness of sotalol and dofetilide. In a small cohort of patients with HCM, dofetilide load was attempted in 25 patients.[66] Of these, 21 were discharged following successful loading, whereas use of dofetilide failed in the other 4 owing to QTc prolongation (n = 3) or ineffectiveness (n = 1). Approximately 1 year later, 11 of these 21 (52%) patients were still taking dofetilide. None of the 10 who discontinued dofetilide did so owing to side effects. In a separate single-center case series, 20 patients with HCM and AF were treated with dofetilide, with relatively frequent discontinuation for ineffectiveness, and side effects were no more common in the HCM group than in other populations.[67] In the same series, there were 45 patients treated with sotalol. This group also had relatively frequent discontinuation for ineffectiveness (similar to other series), and again there were no more side effects than reported for other populations.[68] Among HCM experts, sotalol is generally accepted as a reasonable rhythm control strategy for AF in patients with HCM.[69]

Missed doses of dofetilide or sotalol

Scenario

For patients who are on a chronically stable dose of dofetilide or sotalol, with no known or suspected change in renal function and no relevant changes in other drug treatments, who have missed some doses of dofetilide or sotalol (including interruption peri-ablation), is hospital admission required for drug re-initiation? Do these recommendations change if an ICD or pacemaker is present?

Recommendations

1. In patients taking dofetilide or sotalol who miss any doses, it is reasonable to resume the drug without inpatient monitoring within 7 days of being off the drug, as long as there is no indication that renal function, exposure to other QT-prolonging drugs, or electrolyte homeostasis have changed, and as long as stroke risk is mitigated.
2. In patients taking dofetilide or sotalol, if more than 1 dose of dofetilide or sotalol is missed and renal function or electrolyte homeostasis are suspected to have changed, admission for reloading and monitoring is recommended.
3. The presence of a pacemaker or ICD does not change the recommendations regarding monitoring during dofetilide or sotalol initiation or re-initiation.

Discussion

Doses of dofetilide or sotalol may be missed inadvertently, held for a procedure such as ablation, or held in the context of complicating medical problems in which renal function and electrolyte status are potentially altered. Although there has been a tradition in some practices to hospitalize for reloading patients who have missed more than 2 doses of dofetilide, there are no data showing the necessity for this practice.

Considerable variation in practice has been reported. In a 2017 multinational survey of cardiologists, reloading procedures ranged from never admitting patients for reloading (19%) to always admitting them (21%).[70] Substantial heterogeneity was also observed in the duration of time off drug that triggered readmission, the timing and frequency of QTc reassessment, and the use of laboratory testing. In some writing committee members' institutions, longstanding

practice has been to require inpatient reloading only after the dofetilide interruption exceeds 1 week. There exists a single published manuscript indicating that when dofetilide was restarted after a drug hiatus, 31.9% of patients required dose adjustment or discontinuation, indicating a potential safety hazard.[71] However, in this sole available published series examining re-initiation of dofetilide after a hiatus, the time off drug was 660 ± 701 days (median 114 days), weakening its relevance to drug holidays that are short and characterized by clinical stability. It also should be recognized that hospitalization for observation is not necessarily without consequence: for example, inpatient monitoring carries risks, such as hospital-acquired infection, and imposes high financial cost to patients and the healthcare system.

Although dofetilide, as mandated by the package insert, is consistently initiated in the hospital with telemetry monitoring, some clinicians habitually initiate sotalol in the outpatient setting, and it is perhaps even more commonly re-initiated on an outpatient basis when patients have been previously exposed and have done well without QT concerns. However, the sotalol package insert contains a black box warning: "To minimize the risk of induced arrhythmia, patients initiated or re-initiated [on sotalol] should be placed for a minimum of 3 days (on their maintenance dose) in a facility that can provide cardiac resuscitation, continuous electrocardiographic monitoring and calculations of creatinine clearance."[72] For safety considerations, the writing committee agrees that both dofetilide and sotalol should be initiated only with inpatient telemetry monitoring. Intravenous sotalol is now available in the United States and some other countries, and protocols exist to allow initiation with a truncated stay, but this still must be done in a monitored setting.[73,74]

Based on clinical experience and balancing pragmatism with safety concerns, when doses of dofetilide or sotalol are missed and there is no suspicion of altered renal function or a change in other pharmacologic therapy that can affect the QTc, the writing committee chose 7 days as the recommended maximum interval off dofetilide or sotalol to allow resumption of the drug without admission (or extension of an admission) for drug reloading. This recommendation also applies for pediatric patients undergoing a sotalol "wean": 7 days since the last dose would be the maximum interval off sotalol to allow resumption of the drug without admission. However, when there is any concern for altered renal function or drug metabolism, electrolyte status, or the interim addition of a QT-altering drug, in-hospital telemetric monitoring and ECG observation are indicated. Further research in this area would be welcomed. Of course, whether or not hospital monitoring is applied, resumption or initiation of any AAD for patients with AF requires an appropriate background of anticoagulation or structural stroke reduction (eg, left atrial appendage occlusion/exclusion/resection).[8]

Finally, even if an ICD is implanted, these guidelines should be followed given the risk of incessant or repetitive ventricular tachyarrhythmia (VT) or ventricular fibrillation. Regarding pacemakers, although they might prevent bradycardia and thus decrease the risk for torsades de pointes (TdP) VT, they are not a perfect prophylaxis because they cannot defibrillate.

Transition and discontinuation

Transitioning between AADs

Scenario

For patients on long-term antiarrhythmic therapy for whom a change to another AAD is desired, how long should the first drug wash out before initiation of the replacement drug? Does this differ for amiodarone, given its very long half-life?

Recommendation

1. In patients who are changing from 1 AAD to another, waiting at least 3 half-lives for drug washout is reasonable before initiating a new AAD, to minimize the risk of proarrhythmia and other adverse drug effects. Clinical judgment should be used in the setting of transitioning from amiodarone to another AAD.

Discussion

The pharmacokinetic principles of steady state and washout are based on an individual medication's elimination half-life ($t_{1/2}$), with each typically achieved after 3–5 half-lives.[1] Consideration must also be given to active metabolites (and their respective $t_{1/2}$), pharmacodynamic properties (eg, QT prolongation), renal and hepatic function, and drug interactions.[75] The ability to wait for a full washout is dependent on the type of arrhythmia and the clinical stability of the patient. In the case of AF, most patients will tolerate a full washout of all AADs, which lasts a few days, except in the case of amiodarone. However, in patients with VT, this may not be appropriate or possible. Inpatient observation during transitions may be warranted. Thus, clinical judgment is required, but the goal should be to wait at least 3 half-lives (Table 1).

In clinical trials, dofetilide was initiated in patients previously treated with amiodarone only if serum amiodarone concentrations were below 0.3 mg/L or amiodarone had been withdrawn for at least 3 months.[76] Guidelines generally recommend waiting several months before initiating a new AAD after amiodarone discontinuation, but clinicians should exercise clinical judgment and shared decision-making.[8] Recent observational data suggest that dofetilide can be initiated 7 days after amiodarone discontinuation in patients with an ICD.[77]

Adding new medications in patients taking chronic AADs

Scenario

For patients taking dofetilide or sotalol who begin taking a new drug with QT-prolonging potential, what precautions should be taken?

Recommendation

1. In patients taking dofetilide or sotalol, the use of other QT-prolonging drugs may be considered with monitoring of the QT interval.

Discussion

Concomitant administration of 2 or more QT-prolonging drugs increases the risk for QT prolongation and TdP.[78,79] The labeling for dofetilide and sotalol states that these drugs' use in conjunction with other drugs that prolong the QT interval has not been studied and is not recommended.[76,80] However, this limitation greatly impacts the number of patients that qualify for these AADs, given the common use of drugs that may have an effect on the QT interval (eg, selective serotonin receptor inhibitors, atypical antipsychotics, some antibiotics). One potential strategy involves consideration of pharmacokinetic principles. If a patient has been maintained on a QT-prolonging drug without recent or anticipated dosage adjustments, their QT interval should already reflect any prolongation from that drug. The required inpatient initiation of dofetilide or sotalol allows for close monitoring of any additional AAD-induced QT prolongation. If the load is completed successfully, the patient can be monitored as an outpatient with strict instructions to alert if the original QT-prolonging drug's dose is adjusted. The opposite sequence (ie, initiating a QT-prolonging drug when the patient is already on dofetilide or sotalol) is more challenging because inpatient monitoring in this scenario is logistically challenging and is without guidance. However, if such a combination is desired, it may be reasonable to obtain a baseline ECG, initiate the new drug, and repeat ECG monitoring at an interval based on the new drug's pharmacokinetics. Mobile outpatient cardiac telemetry would also be a reasonable option.

Using AAD combinations

Scenario

In patients with ventricular arrhythmias refractory to amiodarone therapy and catheter ablation, what add-on AADs can be used? If multiple AADs are used, how should treatment be monitored and managed?

Recommendations

1. In patients taking amiodarone who have refractory ventricular arrhythmias, mexiletine is a safe adjunct therapy, with no significant pharmacokinetic interactions.
2. In patients taking AADs for refractory ventricular arrhythmias, the addition of quinidine may be useful, with monitoring of the QT interval.
3. In patients with refractory VT, quinidine may be used in combination with mexiletine, but in general, combining quinidine with other QT-prolonging agents, such as amiodarone or sotalol, should be avoided.

Discussion

In patients on chronic amiodarone, addition of mexiletine may reduce ventricular arrhythmia events and appropriate ICD therapies.[81] In a retrospective study of 37 patients, adding mexiletine to amiodarone had no significant effect on QRS width, QTc interval, or PR interval and was associated with a significant decrease in the total number of ICD shocks.[82] The addition of mexiletine can also allow reduction in amiodarone dosage during follow-up. The combination of amiodarone and mexiletine can significantly prolong both the ventricular refractory period and the tachycardia cycle length.[83] As such, when combination drugs are used, ICD tachycardia detection settings should be adjusted accordingly. Pharmacokinetic studies have shown no significant interactions when amiodarone and mexiletine are used in combination.[84]

Quinidine also can serve as an add-on AAD in the management of refractory ventricular arrhythmias. The combination of mexiletine and quinidine results in synergistic antiarrhythmic effects and allows lower individual drug doses, with improved tolerability.[85] In contrast, the addition of quinidine to amiodarone can be associated with significant prolongation of QTc.[1,86]

Table 1 Typical elimination half-lives of commonly used oral antiarrhythmic medications

Antiarrhythmic	Half-life	Minimum wash-out period
Amiodarone	53 d (mean)	3 mo*
Dofetilide	~10 h	36 h
Dronedarone	13–19 h	48 h
Flecainide	12–30 h	72 h
Propafenone	Extensive metabolizers, 2–10 h; poor metabolizers, 10–32 h†	48 h
Sotalol	12 h	36 h

*An alternate antiarrhythmic drug may be initiated earlier than 3 months after stopping amiodarone, based on clinical scenario and symptom severity.
†Highly dependent on CYP2D6 activity, with the prevalence of poor metabolizers ranging from 5%–10% among White patients, to 2%–5% among Black patients, to less than 1% among some populations of Asian descent.

AAD management in renal insufficiency

Scenario

In patients on long-term therapy with a renally excreted AAD (dofetilide, sotalol, or flecainide) who develop acute kidney injury (AKI), should the dose be adjusted, or should the drug be held? How can resumption of the AAD be managed?

Recommendations

1. In patients taking dofetilide or sotalol who develop significant AKI, the drug should be discontinued and held until recovery. Re-initiation should be performed following the standard protocol for new initiation.
2. In patients taking flecainide who develop significant AKI, drug discontinuation or dose reduction should be considered, depending on the clinical scenario.

Discussion

Dofetilide and sotalol rely heavily on renal elimination, and accumulation can occur quickly in AKI, increasing the risk of QT prolongation and TdP.[76,80] The instability of renal function during AKI makes accurate calculation of creatinine

clearance difficult. Re-initiation should occur following the standard protocol for new initiation.[8] The presence of an ICD does not alter this recommendation, because these devices do not prevent TdP.

Flecainide is mostly metabolized by the liver (70%) but is also partially renally eliminated (30%). No dosage adjustment is required until creatinine clearance is $\leq$35 mL/min.[30] In the setting of AKI, flecainide may be dose-reduced or held based on an individualized risk-benefit assessment (eg, if the patient is in AF or has very symptomatic AF that is usually suppressible with flecainide). Patients should be monitored for toxicity, with a low threshold to hold flecainide. Serum trough flecainide concentration may be monitored but is not readily available at all locations, or may take too long to result to provide actionable guidance.[87,88]

QT measurement and surveillance

Scenario

Patients with AF who are treated with certain AADs (eg, dofetilide, sotalol) require QT monitoring. How should the QT (and QTc) be measured before drug initiation? Should cardioversion be performed before or after initiation of AAD?

Recommendations

1. In patients with AF, the QT interval should be averaged over multiple beats and corrected for heart rate using a non-Bazett's correction formula such as Fridericia or Hodges.
2. In patients with AF who are initiating dofetilide or sotalol, it is reasonable to delay electrical cardioversion until after dose 3 or 4 so that rhythm and QTc can be monitored thereafter for at least 12 hours.

Discussion

Both tachycardia and heart rate irregularity can affect QTc measurement in AF. Although it is the most commonly used correction method, multiple studies have shown that Bazett's formula yields inaccurate results in AF, whereas other formulas give results that more closely match the QTc measured in sinus rhythm.[89–91] The Fridericia correction, $QTc = QT/(RR^{1/3})$, has the advantage of simplicity and accessibility. The Hodges correction ($QTc = QT + 0.00175[HR-60]$) is also useful. Of note, free apps for smartphones and computers, or web-based calculators, may facilitate these calculations. Accuracy can be improved by averaging multiple beats (at least 3–5 beats).[89–96] A strong argument can be made for initiating antiarrhythmic drug therapy before cardioversion, because pharmacologic conversion may occur in over 40% of patients with persistent AF treated with dofetilide.[97] Whether dofetilide or sotalol is started before or after restoration of sinus rhythm does not impact dose at discharge. Importantly, QTc is higher immediately after cardioversion than it is during follow-up, making it desirable to continue QTc and telemetry monitoring for some time after sinus rhythm is achieved (at least 12 hours).[98,99]

Scenario

In patients receiving ibutilide for chemical cardioversion of AF, should magnesium be given empirically, either before or after administration? If the patient has a pacemaker in place at the time of chemical cardioversion with ibutilide, should the pacemaker be reprogrammed in a particular way? How long should the patient be monitored after ibutilide dosing?

Recommendations

1. In patients with AF undergoing chemical cardioversion with ibutilide, it is advisable to administer 2–4 g of intravenous magnesium (aiming for serum concentration of $\geq$3.8 mg/dL) before or during infusion.
2. In patients with AF and a pacemaker who are undergoing chemical cardioversion with ibutilide, increasing the pacing rate to 80–100 beats per minute to reduce risk of pause-dependent TdP may be useful.
3. After administration of ibutilide for chemical cardioversion of AF, patients should be monitored for at least 4 hours.

Discussion

Across dose-response analyses, the reported rate of conversion to sinus rhythm after ibutilide dosing ranges from 40% to 70% for AF and approximately 80% for AFL, usually within 30–45 minutes.[100–102] The main limitation is the risk of TdP, seen in 1%–4% of cases during the first hour after administration, especially in patients with bradycardia and low ejection fraction.[101,103] Based on this timeline, we recommend monitoring the patient for at least 4 hours following ibutilide infusion.[104,105] Intravenous magnesium mitigates the risk of TdP by attenuating QT prolongation and lessening early afterdepolarizations, while increasing conversion success by 10%–20% in some studies.[106–109] Another study in patients with rheumatic AF or AFL highlighted that serum magnesium of $\geq$3.8 mg/dL is predictive of an optimal response (with sensitivity 96% and specificity 63%).[104,110]

In patients with a dual-chamber pacemaker, overdrive pacing at 90 beats per minute effectively prevents pause-dependent QT prolongation and TdP.[111]

AAD therapy for inappropriate sinus tachycardia

Scenario

In a patient with inappropriate sinus tachycardia (IST) who is still symptomatic after being treated with beta-blockers, what other medical therapy may be useful or recommended?

Recommendation

1. In patients with symptomatic IST with an incomplete response to beta-blockers, ivabradine can be considered. Verapamil or diltiazem may also be used, although they are generally less effective than ivabradine. In rare cases, clonidine or amiodarone may be used if other agents are ineffective.

Discussion

For patients with symptomatic IST, beta-blockers are first-line therapy, but high doses are often required and may not be well tolerated. Beta-blockers are more effective when high sympathetic tone is present.[112] Some studies have demonstrated that the "funny current" (I_f) blocker ivabradine results in significant improvement in both heart rate control and symptom burden in patients with IST, either as monotherapy or combined with beta-blockers.[113–115] However, it may be best to avoid ivabradine in patients with paroxysmal AF or in those who are at high risk for AF.[116] Despite possibly promoting lower ventricular rates in AF, ivabradine increases AF risk by 15% in patients in sinus rhythm and has been associated with higher risk for HF hospitalization and all-cause death when used in patients with AF.[117]

The non-dihydropyridine calcium channel blockers (ie, verapamil and diltiazem) may be considered when beta-blockers are ineffective or poorly tolerated, although their efficacy is limited. Calcium channel blockers may modestly reduce symptoms of IST, particularly in mild cases or when beta-blockers are contraindicated or not well tolerated.

In refractory cases in which symptoms are debilitating and other treatments have failed, amiodarone or clonidine may offer some benefit. However, their use may be limited by side effects.

AAD interactions with oral anticoagulants and cardiac implanted electronic devices

Antiarrhythmics and oral anticoagulants

Scenario

In patients requiring both oral anticoagulation and AAD therapy, what particular interactions should be considered?

Recommendation

1. In patients on oral anticoagulation and AADs, attention to drug–drug interactions is recommended, given the potential for heightened bleeding risk.

Discussion

Drug–drug interactions between AADs and oral anticoagulants (OACs) are important considerations in the management of arrhythmias, especially because rhythm control strategies for AF are increasingly combined with long-term anticoagulation.[8,118–121] As shown in Table 2, many AADs can alter anticoagulant exposure through inhibition of cytochrome P450 pathways or P-glycoprotein transport, resulting in potentially higher OAC plasma concentrations and an increased risk of bleeding. As a result, certain combinations may require closer monitoring, dose adjustment, or even complete avoidance in specific patients. The following table highlights the most clinically relevant interactions and provides concise, practical guidance to support safer prescriptions in routine practice.

Drug–device interactions

Scenario

In a patient with a history of ventricular tachyarrhythmia and an ICD for whom amiodarone is initiated, is noninvasive programmed stimulation (NIPS) or defibrillation threshold (DFT) testing recommended? Should the VT detection rate be lowered?

Recommendations

1. In patients with ICDs who are initiating amiodarone, routine DFT assessment is of unclear benefit.
2. In patients suspected of having a marginal DFT who are started on long-term amiodarone, DFT assessment is reasonable after completion of drug loading.
3. In patients with a history of sustained monomorphic VT who are initiated on amiodarone and/or mexiletine, NIPS is reasonable to assess tachycardia cycle length and the response to antitachycardia pacing (ATP). Empiric lowering of the VT detection zone is also reasonable.

Discussion

AADs can affect the DFT, the lowest delivered energy that will convert VT or ventricular fibrillation to a supraventricular rhythm. A substudy from the OPTIC (Optimal Pharmacological Therapy In Implantable Defibrillator Patients) trial demonstrated that beta-blockers or sotalol resulted in a slight reduction in DFT. In contrast, oral amiodarone and its metabolite desethylamiodarone can raise the DFT with chronic use.[122,123] As such, in patients with a secondary prevention ICD and a marginal DFT, DFT assessment could be considered during chronic amiodarone use.[124] Of note, dofetilide can lower the DFT.[125]

Amiodarone can prolong the VT cycle length by as much as 20% because of its class 1 properties; mexiletine can have a similar effect.[126–128] Consequently, subsequent episodes of slower clinical VT can fall below programmed rate detection parameters, failing to detect VT and increasing the risk of hemodynamic compromise. In patients who have had sustained monomorphic VT and who are started on amiodarone or mexiletine, performing NIPS can be useful to assess the rate of inducible VT and its response to ATP. If NIPS testing is not or cannot be performed, the VT detection zone may be empirically lowered to capture VT that may be slower because of drug effect.

Scenario

In patients with an ICD and failed defibrillation or a marginal DFT, what is the role of AADs in reducing the DFT, and should this be measured or assessed?

Recommendations

1. In patients with a marginal DFT, sotalol, beta-blockers, or dofetilide can be considered to reduce the DFT.

Table 2 Clinically relevant interactions between antiarrhythmic drugs and oral anticoagulants

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Clinical comment/ recommendation
Amiodarone	↑ INR (CYP2C9 inhibition) ⚠	↑ (P-gp inhibition) ⚠	↑ (P-gp/CYP3A4 inhibition) ⚠	↑ (P-gp/CYP3A4 inhibition) ⚠	↑ (P-gp inhibition) ⚠	Monitor INR; use DOACs with caution.
Dronedarone	↑ INR (CYP2C9 inhibition) ⚠	↑ (P-gp inhibition) – Contraindicated ✗	↑ (P-gp/CYP3A4 inhibition) ⚠	↑ (P-gp/CYP3A4 inhibition) ⚠	↑ (P-gp inhibition) ⚠	Avoid with dabigatran; caution with other DOACs.
Sotalol	None ☑	None ☑	None ☑	None ☑	None ☑	Renally excreted; does not inhibit CYP enzymes and does not change P-gp activity; interaction unlikely.
Flecainide	No interaction ☑	None ☑	None ☑	None ☑	None ☑	No clinically meaningful interaction with OACs.
Propafenone	↑ INR (CYP2C9 inhibition) ⚠	↑ (P-gp inhibition) ⚠	↑ (CYP3A4 inhibition) ⚠	↑ (CYP3A4 inhibition) ⚠	↑ (P-gp inhibition) ⚠	Monitor INR; observe for bleeding on DOACs.
Quinidine	↑ INR (CYP2C9 inhibition) ⚠	↑ (P-gp inhibition) – Avoid ✗	↑ (P-gp/CYP3A4 inhibition) ⚠	↑ (P-gp/CYP3A4 inhibition) ⚠	↑ (P-gp inhibition) – ⚠	Avoid with dabigatran. Caution with other OACs.
Disopyramide	None ☑	None ☑	None ☑	None ☑	None ☑	No clinically meaningful interaction.
Lidocaine/mexiletine	None ☑	None ☑	None ☑	None ☑	None ☑	Considered safe.
Dofetilide	None ☑	None ☑	None ☑	None ☑	None ☑	Renally eliminated; no clinically relevant interaction with OACs.

↑ = increased activity/effect on the anticoagulant; ✗ = not safe; ⚠ = caution; ☑ = safe; CYP = cytochrome P450; DOAC = direct oral anticoagulant; INR = international normalized ratio; OAC = oral anticoagulant.

2. In patients with failed shocks who are newly treated with AADs to reduce the DFT, reassessment of the DFT is reasonable.

Discussion

In a substudy of the OPTIC trial, patients on beta-blockers or sotalol had a slight reduction in the DFT, and in contrast, a slight DFT increase was seen with amiodarone.[129] Beta-blockers, sotalol, and dofetilide may be appropriate agents in selected patients with marginal defibrillation safety margins, although the increased risk of TdP must be considered in the case of sotalol or dofetilide.[130]

Scenario

In pacemaker-dependent patients in whom a class 1C AAD is initiated, are there any recommendations regarding monitoring of capture threshold?

Recommendations

1. In patients with cardiac implantable electronic devices who take class 1C AADs, routine reassessment of pacing thresholds is recommended. Class 1C AADs should be stopped if the safety margin of the pacing threshold is inadequate, and ATP outputs should be reassessed.

Discussion

Flecainide, propafenone, and amiodarone all increase ventricular pacing thresholds.[131] Class 1C AADs exhibit use-dependence, and rate-dependent elevations in the pacing threshold (that may already be higher) may be magnified such that ATP might be ineffective. Therefore, in patients with VT who are initiated on AADs that can increase the capture threshold, the device's ATP output should be programmed to the highest available energy to provide a wide safety margin.[127,130]

AAD in pregnancy and lactation

Scenario

In patients who are pregnant or lactating and who desire antiarrhythmic medical therapy, which AADs are recommended? Does this vary by trimester?

Recommendations (chronic management)

1. In pregnant or lactating patients with atrial arrhythmias or other SVTs, metoprolol or propranolol and digoxin are recommended for chronic management, and verapamil may be considered as a second-line agent. Among the dedicated antiarrhythmic medications, flecainide is preferred for recurrent atrial arrhythmias/SVT.
2. In pregnant or lactating patients with ventricular tachyarrhythmias, medical therapy with metoprolol or propranolol, verapamil, flecainide, or sotalol is reasonable (but sotalol should be avoided during the first trimester and lactation if possible).

Recommendations (acute management)

1. In pregnant or lactating patients who require acute treatment for atrial arrhythmias/SVT, adenosine and metoprolol or propranolol are recommended. Flecainide or propafenone may also be useful.
2. In pregnant or lactating patients who require acute treatment for hemodynamically stable idiopathic VT, metoprolol or a class 1C AAD (ie, propafenone or flecainide) are recommended.

Discussion

Recommendations regarding AAD use during pregnancy and lactation are summarized in Table 3. Pregnancy trimesters represent clinical reference points rather than strict pharmacologic boundaries throughout gestation. Atrial and ventricular arrhythmias are less common in the first trimester because the hemodynamic, autonomic, and hormonal changes that increase arrhythmogenicity typically occur later in pregnancy.[132,133] Metoprolol and propranolol remain the safest treatments, independent of trimesters and lactation status. Sotalol should be avoided during the first trimester and during lactation. Sotalol may be used during the second and third trimesters, with monitoring of QTc, whereas nadolol should be avoided during pregnancy and lactation, except perhaps in the presence of long QT syndrome (LQTS) or catecholaminergic polymorphic ventricular tachycardia (CPVT) if the benefit outweighs risk.[134] For SVT involving an accessory AV pathway, propafenone may be used after the first trimester.[135] Few data are available regarding mexiletine during pregnancy or lactation, so it should be reserved for when no alternatives exist.[136] Similarly, amiodarone should be used only for life-threatening ventricular tachyarrhythmias refractory to other treatments, owing to its well-documented effects on fetal thyroid function and neural development.[137] Generally, AAD use should be minimized during the first trimester, reserving treatment for maternal or fetal benefit only when it outweighs the risk of teratogenicity.[5]

Scenario

What is the appropriate management for newborns exposed to transplacental AADs used for treatment of maternal arrhythmias?

Recommendation

1. In newborns exposed to AADs, a 12-lead ECG should be obtained. If there has been exposure to beta-blockers during pregnancy, monitoring for neonatal bradycardia and hypoglycemia should occur for the first 24 hours of life.
2. In infants with an abnormal ECG, clinical manifestations of toxicity, or fetal hydrops, continued telemetry and early echocardiography are recommended.

Discussion

Fetal and neonatal arrhythmia management following exposure to maternal AADs is well delineated in the HRS expert

Table 3 Antiarrhythmic medications during pregnancy and lactation

Class	Medication	First Trimester	Second Trimester	Third Trimester	Lactation
Class 1 (Na+ channel blockers)	Flecainide	☑	☑	☑	☑
	Propafenone	⚠	☑	☑	⚠
	Procainamide	☑ acute use only	☑	☑	⚠ short courses
	Quinidine	⚠	⚠	⚠	⚠
	Lidocaine (IV)	☑	☑	☑	☑
	Mexiletine	⚠ case-level data	⚠	⚠	⚠ limited data
Class 2 (Beta-blockers)	Metoprolol/ propranolol	☑ preferred	☑	☑	☑
	Atenolol	✗ avoid	✗ avoid	✗ avoid	✗ avoid
	Nadolol*	⚠ only if indicated for LQTS, CPVT	⚠ only if indicated for LQTS, CPVT	⚠ only if indicated for LQTS, CPVT	⚠ only if indicated for LQTS, CPVT; monitor infant
Class 3 (K+ channel blockers)	Sotalol	✗ Avoid	☑ monitor QT	☑ monitor QT	⚠ monitor infant
	Dofetilide	✗	✗	✗	✗
	Amiodarone†	✗	✗	✗	✗
	Dronedarone	✗	✗	✗	✗
Class 4 (Ca2+ channel blockers)	Verapamil	☑ second-line for SVT after metoprolol/ propranolol	☑	☑	☑
	Diltiazem	⚠	⚠	⚠	⚠
Other	Digoxin	☑	☑	☑	☑
	Adenosine	☑	☑	☑	☑

✗ = not safe; ⚠ = caution; ☑ = safe; CPVT = catecholaminergic polymorphic ventricular tachycardia; IV = intravenous; LQTS = long QT syndrome; SVT = supraventricular tachycardia.
*Propranolol or nadolol may be used in LQTS/CPVT patients. In the absence of LQTS/CPVT, propranolol or metoprolol are safer alternatives. Nadolol's nonselective properties, long half-life, and high breast-milk transfer warrant caution, particularly in newborn or preterm infants.
†Reserve amiodarone for only life-threatening maternal/fetal arrhythmias and refractory ventricular tachycardia/cardiac arrest.

consensus document and American Heart Association scientific statement.[132,138] Some considerations to note are that many antiarrhythmic agents cross the placenta and that some actually achieve higher concentrations in the umbilical cord blood than in the maternal plasma.[135] The neonatal ECG is often normal despite detectable antiarrhythmic plasma concentrations, but can serve as a simple screening tool for drug toxicity.[139] Because clinically meaningful toxicity is uncommon in neonates who have had exposure to maternal AADs, a targeted approach is recommended, including ECG screening, short-term monitoring if clinically warranted, and selective echocardiography for structural concerns or fetal hydrops. Ideal management includes multidisciplinary collaboration between neonatology, maternal-fetal medicine, high-risk obstetrics, and electrophysiology.

Gaps in knowledge and future directions

In this scientific statement, the writing group focused on scenarios that practicing clinicians in electrophysiology commonly face but for which limited data exist. Our approach acknowledged that we often have limited clinical trial data for commercially available AADs and that there is a lack of clear incentives for future large, randomized studies of these drugs. Indeed, it is expected that future evidence regarding AAD use will largely come from real-world and pragmatic studies as these research techniques evolve to embrace a wider range of data sources, including electronic medical record systems, registries, and administrative sources. Although those data are nonrandomized, this approach to investigation allows for assessment of therapies in complex clinical scenarios as well as in understudied populations including pregnant and lactating patients, children, and adult patients with congenital heart disease, for whom the existing clinical data are challenging to apply directly.

Even with expectations for accumulating observational data, there still is a critical need for novel AADs with less toxicity and better effectiveness. Of note, there has been increasing interest in the development of atrial-specific AADs, which are of paramount importance for the growing epidemic of AF. Optimal use of existing AADs should also be investigated, including safe and effective dosing of drugs with QT-prolonging potential in the setting of a wide native QRS or during ventricular pacing. In parallel, the antiarrhythmic effects of existing anti-inflammatory medications are an area of ongoing and renewed investigation.

The development of new AADs will require innovation from scientists and investment by the pharmaceutical industry to identify new molecular targets, explore genetically tailored drug therapy, and develop novel models to efficiently assess drug toxicity. Partnership with regulators can also help to expedite the development process.

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Appendix 1 Writing committee member disclosure of relationships with industry and other entities

Writing committee member	Employment	Honoraria/ speaking/consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/ partnership/ principal/ majority stockholder	Stock or stock options	Intellectual property/ royalties	Other
Daniel P. Morin, MD, MPH, FHRS (Chair)	American College of Physicians	Abbott	Zoll Medical Corporation	Zoll, Inc.	None	None	None	None	None
Elizabeth S. Kaufman, MD, FHRS (Vice Chair)	None	None	None	Janssen Pharmaceuticals	Biosense Webster, Inc.; Medtronic, Inc.	None	None	None	None
Kirsten Bova Campbell, PharmD, FHRS	None	Wolvers Kluver	None	None	None	None	None	None	None
Andrew E. Epstein, MD, FHRS	None	Mediasphere Medical; Abbott; Zoll Medical Corporation; Medtronic PLC	None	None	Abbott Medical; Medtronic, Inc.; Boston Scientific	None	None	None	American Heart Association
Zachary D. Goldberger, MD, FHRS	None	None	None	None	None	None	None	Elsevier	None
Bülent Görenek, MD	None	None	None	None	None	None	None	None	None
Jeroen M. L. Hendriks, PhD, RN	None	Biotronik; Medtronic, Inc	None	None	None	None	None	None	None
Prince J. Kannankeril, MD, MS, FHRS	None	None	None	National Institutes of Health	None	None	None	None	None
Naga Venkata K. Pothineni, MD (SDC Liaison)	None	Biosense Webster, Inc.; Boston Scientific	Medtronic, Inc.	None	None	None	None	None	None
Kamala P. Tamirisa, MD, FHRS	None	None	None	None	None	None	None	None	None
Santiago O. Valdés, MD	None	None	None	Milestone Pharmaceuticals	Medtronic, Inc.	None	None	None	None
Emily P. Zeitler, MD, MHS, FHRS	None	Medtronic, Inc.; Boston Scientific; Sanofi; V-Wave	None	None	None	None	None	None	Biosense Webster, Inc.; Sanofi

This table is a comprehensive list of the relationships with industry and other entities (RWI) disclosed by each writing committee member for the 12 months before the initial meeting of the writing committee and up through the completion of the document. The table does not necessarily reflect the RWIs of the writing committee members at the time of publication. Please refer to the HRS Code of Ethics and Professionalism for definitions of disclosure categories or additional information about the HRS policy on the disclosure of relationships with industry and other entities.

*Research and fellowship support are classed as programmatic support. Sources of programmatic support are disclosed but are not regarded as a relevant relationship with industry for writing group members or reviewers.

Appendix 2 Reviewer disclosure of relationships with industry and other entities

Peer Reviewer	Employment	Honoraria/speaking/ consulting	Speakers' bureau	Research*	Fellowship support*	Ownership/ partnership/ principal/ majority stockholder	Stock or stock options	Intellectual property/ royalties	Other
James Coromilas, MDCM, FHRS	None	None	None	None	None	None	None	None	None
Christopher M. Janson, MD	None	None	None	None	None	None	None	None	None
Christina Miyake, MD, MPH, MS	None	Boston Scientific	None	None	None	None	None	None	None
James E. Tisdale, PharmD	None	University of Texas; Texas Society of Health-System Pharmacists	None	NIH/NHLBI; Indiana CTSI; American Heart Association	None	None	None	None	Arizona Center for Education and Research on Therapeutics; Pharmacotherapy Publications Inc.; American College of Clinical Pharmacy Foundation, Inc.

This table is a comprehensive list of the relationships with industry and other entities (RWIs) disclosed by the reviewers at the time the document was under review. The table does not necessarily reflect the RWIs of the reviewers at the time of publication. Please refer to the HRS Code of Ethics and Professionalism for definitions of disclosure categories or additional information about the HRS policy on the disclosure of relationships with industry and other entities.

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