Clinical cardiac electrophysiology has evolved rapidly over the past several decades, allowing wide-ranging therapeutics to improve the lives of millions of patients. The progression from physiology-based investigations to large, randomized trials of new drugs and devices has allowed clinicians to treat patients with greater confidence and an increasing sense that interventions are evidence-based. Approaches to national health care reform have applauded this trend and the increasing authority and rigor of national treatment guidelines, with many leaders calling for greater adherence to evidence and guidelines alike.

However, the nuances of the published literature may be lost in translation to patient care or obscured by formal recommendations, which become rapidly ingrained in current practice and the training of new clinicians. Trainees, in particular, may never question the genesis of these recommendations, and thus fail to appreciate the underpinnings of some of the most closely held views in clinical medicine. This article examines the hazards of this phenomenon in clinical arrhythmia management. We ask 3 questions, considered by many to be already settled by the existing evidence and forceful recommendations. We propose that considering these questions more closely illustrates areas in need of further debate and investigation and the importance of preserving critical thinking and clinical judgment.

Three Questions in Clinical Arrhythmia Management

1. Are Class IC Antiarrhythmics Contraindicated for Patients With Structural Heart Disease or Coronary Artery Disease?

This restriction is well known to cardiologists, internists, and medical students. The American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2006 guidelines for managing atrial fibrillation warn against using any class IC agent in patients with “ischemic heart disease or left ventricular dysfunction due to the high risk of proarrhythmia effects.” Use of these therapies in patients “who have well-defined risk factors for proarrhythmia with that agent” has a class III, Level of Evidence A recommendation—“evidence and/or general agreement that a procedure/therapy is not useful or effective and in some cases may be harmful.” “Structural heart disease” is repeatedly listed as a factor predisposing to drug-induced proarrhythmia but not clearly defined. Nevertheless, these proscriptions are based in part on a broad extrapolation from the Cardiac Arrhythmia Suppression Trial (CAST)—which ironically has been noted as the paradigm of rigorous evidence changing established clinical practice, insofar as it proved the inadequacy of PVC suppression as a surrogate end point for reducing arrhythmic mortality.

However, the actual CAST study population was only a very narrow slice of all those patients who might be deemed to have “structural heart disease” or “coronary artery disease” (both quite broad and heterogeneous categories that are inconsistently defined). The inclusion criteria for CAST were more specific: Patients were eligible 6 days to 2 years after myocardial infarction if they also had (1) an average of 6 or more PVCs/h on ambulatory monitoring of at least 18 hours duration, without runs of ventricular tachycardia of 15 or more beats at a rate ≥120 bpm; and (2) left ventricular ejection fraction ≤55% if recruiting within 90 days of the myocardial infarction or ≤40% if recruiting 90 days or more from the MI. Additionally, during the open-label titration period, patients needed to demonstrate ≥80% suppression of PVC burden and ≥90% suppression of longer runs of ventricular tachycardia. Only then were patients randomly assigned to ongoing therapy or placebo. CAST randomly assigned nearly 1500 highly selected patients after a run-in period, 432 to encaïnide and 323 to flecaïnide, with a hazard ratio of 2.64 (95% confidence interval [CI], 1.60 to 4.36; P=0.0001) for death or cardiac arrest.

Importantly, the actual study population was reported as having a mean left ventricular ejection fraction of just over 30% along with established chronic coronary artery disease and a history of myocardial infarction. Low use of β-blockers (<30% in both active and placebo groups) despite what is now considered a class IA indication for that therapy further challenges continued application of these data to modern patients. Warnings about structural heart disease are included in the labeling mandated by the Food and Drug Administration, such as in the label for flecaïnide. This labeling restricts the indications for flecaïnide for supraventricular tachycardia to “patients without structural heart disease,” though this is again not clearly defined—and for all indications warns against its use in patients with recent myocardial infarction. It is, however, rather more circumspect.
about extrapolation—noting that “applicability of the CAST results to other populations … is uncertain.”

It is now considered at best bold and at worst malpractice to use any IC agent in patients with coronary artery disease (of any type) or with structural heart disease (variously interpreted). However, class IC agents remain a highly effective option for acute cardioversion of atrial fibrillation as well as maintenance of sinus rhythm.15–22 Although other studies have also suggested identified potential risks of IC agents in selected populations,23,24 such as survivors of documented myocardial infarction, this may or may not be relevant to patients who (for example) merely have established epicardial stenoses without infarction or those who have a preserved ejection fraction.48 There is less specific evidence of harm for propafenone in particular.

For example, consider an actual patient from our institution whose paroxysmal atrial fibrillation was well controlled on flecainide for several years. He had no abnormalities on echocardiography and did well until presenting with chest pain that eventually led to a cardiac catheterization demonstrating severe left anterior descending and left circumflex stenoses, which were both stented. Conventional wisdom would suggest that he should not remain on flecainide, and indeed he was switched first to dronedarone and then dofetilide, neither of which controlled his arrhythmia symptoms. This patient had a pulmonary vein isolation—itself hardly a risk-free enterprise—but arguably this patient could have remained on flecainide, as he has never had an infarction and has a normal echocardiogram despite being labeled as with the vague distinction of “structural heart disease” or “coronary artery disease.” Similarly, patients with implantable cardioverter-defibrillators (ICDs) (not a practical option at the time of CAST) regardless of the underlying substrate might plausibly be safely treated with IC agents because they would be protected from deleterious proarrhythmia and more easily maintained on β-blockers.

Pulmonary vein isolation is the subject of ongoing investigation in patients with structural heart disease with reported risks of major complications including stroke or tamponade of 5% and mortality rates of 1 in 1000.25–27 Surgical therapy such as the MAZE or mini-MAZE procedure has also emerged as a potential therapy for both lone complex atrial fibrillation, with risks including those associated with any cardiac surgery and particularly the need for permanent pacemaker placement. Yet, it would be almost inconceivable to imagine a clinical trial for pulmonary vein isolation or mini-MAZE including a treatment arm of class IC agents, even for those who would not have met inclusion criteria for CAST. Only dronedarone has been approved for control of atrial fibrillation in the past decade—and its approval was not actually for control of arrhythmia specifically—and yet a contemporary reassessment of IC agents in the context of more robust use of β-blockers and better imaging modalities to more precisely characterize categories of “structural heart disease” would be nearly impossible to design in the face of the established revulsion to this therapy in all but lone AF.

**Summary**

This example illustrates the way in which a broad extrapolation can lose subtlety progressively from original data to guidelines, clinical practice, and teaching of trainees. Successive reinforcement of conclusions without recognition and careful definition of the underlying population studied restricts therapeutic options for potentially eligible patients who have not been shown to be harmed by this therapy. Indeed, some patients may be subjected to invasive interventions (such as ablation or surgery) that may be more dangerous than a therapy that may be avoided unnecessarily.

**2. Do Patients With Symptomatic Systolic Heart Failure and a QRS >120 ms Benefit From Cardiac Resynchronization Therapy?**

Many might consider this matter closed with the publication of several large, randomized, controlled trials demonstrating clinical benefits to this population. However, applying clinical trial results to a given patient requires assessment not only of the predefined inclusion and exclusion criteria but also at the population of patients actually enrolled and randomly assigned in the trial. It is widely recognized that cardiac resynchronization therapy (CRT) is not effective in all patients who receive device implants, even in clinical trial settings.28 Attempts to refine patient selection have been difficult.29 As such, adherence to guidelines has been emphasized to ensure at least that patients who receive CRT are similar to those who would have been included in the relevant trials demonstrating their effectiveness.30,31

QRS duration is just one of these characteristics, though in the absence of any firmly established alternatives it serves as a marker of interventional and intraventricular dysynchrony, with a cutoff of 120 ms from CARE-HF and COMPANION reflected in the current guidelines.32,33 However, the mean QRS in CARE-HF and COMPANION was closer to 150 to 160 ms, and subgroup analyses of narrower QRS populations showed no benefit, consistent with the findings from the largest study of CRT in patients with a narrow QRS.9,34

How compelling, then, is the QRS cutoff of 120 ms? Should guidelines reflect the entry criteria or the actual patient population that was studied?35 Although clinical trial interpretation certainly begins with evaluation of the inclusion criteria, appropriate extrapolation to real-world patients requires consideration of the actual patients studied. Hence, the “Table 1” is a crucial feature of nearly every published study, describing the characteristics of study patients in great detail as well as the effectiveness of the randomization protocol. This is all the more true when there are sound physiological reasons or other evidence to suggest that discrepancies between entry and exit criteria may be clinically important.

At the very least, then, the substantial discrepancy between entry and exit QRS duration might give committees pause in the strength of a recommendation based solely on the former. With the strongest (class 1A) recommendation already appended to patients with QRS ≥120 ms, there is little incentive for industry (who fund nearly all clinical studies in clinical electrophysiology) to explore the hypotheses suggested by these subgroup analyses.35 Indeed, to investigators and institutional review boards, it may seem wholly unethical to randomly assign patients away from a therapy as that is as
strongly endorsed as aspirin in acute coronary syndromes and angiotensin-converting enzyme inhibitors and β-blockers for heart failure.13,36,37

Although the primary purpose of these recommendations is to provide guidance to the clinical community, their influence outside of this specific role is hard to ignore. Guidelines strongly affect the ways that medical interventions are marketed, with advertisements commonly quoting guidelines directly. Similarly, guidelines affect payors by defining a standard of care and providing patients and physicians with expert opinion to be used in support of expanding insurance coverage. Industry-sponsored research necessarily is driven not only by clinical questions but also by business considerations. There is an undeniable cascade of effects, then, when complex and costly therapies such as CRT acquire the strongest recommendation possible.

Not surprisingly, more recent studies of CRT in patients with milder symptoms have mimicked previous designs.38 The QRS entry criteria for REVERSE was ≥120 ms and ≥130 ms for MADIT-CRT.39–41 However, the actual mean QRS in REVERSE was 153 ms; in MADIT-CRT it was not reported, but ≈65% of subjects in both arms had a QRS ≥150 ms. Evidently there is little incentive and perhaps no accepted ethical approach under current guidelines for future studies to better refine a population that would more reliably benefit from an expensive and invasive therapy.39,42

A similar point has been made about the treatment of ejection fraction in MADIT-II—the entry ejection fraction was 30%, but the mean was closer to 20%, with the former chosen as the standard for the guidelines.9 Again, subgroup analyses have offered reasonable hypotheses that those with an ejection fraction >25 may not benefit—but there seems to be little enthusiasm for testing this prospectively and potentially sparing tens of thousands of patients from unnecessary procedures and the health care system the attendant costs.

The same problem is seen with regard to age in MADIT-II and SCD-HeFT—the most common indications for primary-prevention ICD placement. Both trials had minimum ages (18 and 21, respectively) but no maximum age. In MADIT-II, the mean age was 64 years, and subgroup analyses showed markedly more benefit in patients <60 years. Of the >1200 patients randomly assigned in the study, only 204 were ≥75 years, and no benefit was seen in this group.42 In SCD-HeFT, the mean age was 60 years, and no benefit was seen for patients in the subgroup >65 years of age. Although ICD guidelines do carefully emphasize the importance of considering a patient’s medium- and long-term prognosis in determining eligibility, there is no randomized evidence supporting the widespread practice of ICD implantation in much older individuals than those clearly shown to benefit.45 A similar argument can be made with regard to decreased renal function, which also has been shown to markedly attenuate the benefits of ICD therapy.46 These subgroup analyses generate important hypotheses—mere hypotheses, but compelling and plausible—that are unlikely to be investigated prospectively, to the detriment of patients and the clinical community.

In general, subgroups must be interpreted with caution, but not all subgroups are the same.47,48 Analyses that are pre-specified rest on a sound physiological basis and demonstrate marked treatment differences are relatively noteworthy.48 Indeed, this reasoning has informed significant policy decisions in the past. The Food and Drug Administration advisory panel recommendations on expanding CRT to New York Heart Association class I and II congestive heart failure patients considered subgroups based on the presence of left bundle-branch block; CMS limited reimbursement to those patients with a wide QRS complex after initial publication of the MADIT-II study, based on similar reasoning. In the case of CRT, we suggest that the intended population is so vast and heterogeneous that, in fact, public health considerations mandate further inquiry into suggestive subgroup analyses, particularly insofar as “public health” includes concerns about the costs of an expensive therapy with a suboptimal response rate even in clinical trial conditions.

Notably, the current device guidelines state that “it is inevitable that the indications for device therapy will be refined with respect to both expanded use and the identification of patients expected to benefit the most from these therapies.”35 However, the latter goal is directly challenged by interpretations of pivotal clinical trials that fail to reserve judgment on patients who may have been eligible for those studies but were not well represented by the study subjects.

Summary

The CRT case and subsequent examples demonstrate that strong recommendations emphasizing only entry rather than exit characteristics of trial subjects create the appearance of certainty in an area greatly in need of further research, limiting both the incentives and perhaps the ethical avenues for pursuing those studies and testing provocative hypotheses. This is all the more troublesome for interventions such as CRT, where even in trial conditions many patients fail to respond to therapy. Although subgroup analysis is fraught with difficulty and potential for bias, there is an important role for prespecified, carefully defined, and biologically compelling subgroups identifying marked treatment differences to promote further investigation and shape clinical recommendations.

3. Do Patients With Nonischemic Cardiomyopathy, Systolic Dysfunction, and Symptomatic Heart Failure Benefit From ICDs?

The first 2 examples demonstrate the consequences of an imperfect evidence base, including the possible loss of therapeutic options and decreased feasibility and incentives for important studies. The latter in particular is seen again in the recommendation in favor of ICD therapy for patients with nonischemic cardiomyopathy who meet the inclusion criteria for the SCD-HeFT study. In contrast to the use of QRS width, left ventricular ejection fraction, or age (continuous variables treated as categorical) described previously, the difficulty in this case arises from grouping patients with ischemic and nonischemic etiologies of their heart failure.

The substrate for sudden cardiac death is markedly different in these populations,49–53 and previous studies suggested...
that these populations respond differently to ICD therapy. Though no single study has demonstrated a benefit in the nonischemic group alone, the current ACC/AHA/HRS guidelines support ICD implantation for primary prevention in nonischemic cardiomyopathy patients in New York Heart Association class II or III with a left ventricular ejection fraction <35% with a class IB recommendation—indicating that treatment should be offered based on evidence from a single randomized trial or high-quality nonrandomized studies.60

The DEFINITE study, the largest specifically targeting this population alone, randomly assigned 458 patients with nonischemic cardiomyopathy to optimal medical therapy with or without an ICD. These patients had a mean ejection fraction of 21%, predominantly New York Heart Association class II–III heart failure, and two thirds had nonsustained ventricular tachycardia and frequent PVCs (at least 1 of which was a requirement for entry, though ventricular ectopy is not included as a requirement in the guidelines). There was a strong trend but no statistically significant difference in the primary end point of all-cause mortality, for which the study was underpowered because of a relatively low event rate. Similar problems prevented the CAT and AMIOVIRT studies from providing definitive support for ICDs.54,55 An 1800-patient meta-analysis of available studies described a benefit in primary prevention (none was seen in secondary prevention), but this was derived from heterogeneous studies that included some treatment arms with CRT-D.43,56–58 This study claimed a 31% relative risk reduction versus an absolute risk reduction estimated to be only 2%.

In SCD-HeFT, the actual event rates were much lower in the nonischemic than the ischemic population (5-year event rates of 0.432 and 0.359 for ischemic placebo and ICD groups, respectively, versus 0.279 and 0.214 for nonischemic placebo and ICD groups). Lower event rates in the nonischemic group were also noted in an etiology-specific analysis of the CARE-HF trial.59 The overall study was positive in SCD-HeFT, but more than 1200 randomly assigned subjects could not provide sufficient power to demonstrate a statistically significant benefit in the nonischemic population. Although the study’s primary findings may be the most defensible estimate of the treatment effect even for the nonischemic patients, the larger picture give us pause. Specifically, progressively larger and more rigorous evaluations of a similar specific population continue to lack statistical significance while confirming comparatively low event rates and therefore lower absolute benefits.60

Therefore, although both ischemic and nonischemic patients are clearly at heightened risk for SCD, the question of treating the latter with ICDs remains, in our view, incompletely resolved. Indeed, the most recent NICE guidelines excluding nonischemic patients from coverage for primary-prevention ICDs suggest that some experts remain unconvinced.61 Allowing debatable evidence to support a robust recommendation may limit future studies to better refine the population that actually benefits or to study patients with nonischemic cardiomyopathy independently in a properly powered study. There remains no single study examining just this population demonstrating a significant benefit of ICD therapy, and yet there is a class IB indication for implantation. As with the example of CRT, it may be deemed unethical to randomly assign an “SCD-HeFT” patient to medical therapy alone with the clinical question considered to be settled. Again, it now becomes very difficult to select an important population for prospective investigation, and industry has no incentive to do so as long as recommendations (and payors’ behavior) remain strong and unchanged.

Summary
This case reinforces the power of strong recommendations to limit important and necessary research, in this case driven by an uncertain pooling of heterogeneous populations into a single trial whose subgroups then suggest different treatment effects.

Conclusions
We have asked these 3 questions in the hopes of illustrating the challenges of practicing evidence-based clinical electrophysiology. These challenges include preserving the subtlety of study populations from published results through to practice, exploring important subgroups prospectively, and cautiously framing recommendations to allow for future refinement of the risks and benefits of complex interventions. Considering these questions “answered” by the current data may limit physician and patient choices and diminish the incentives and ethical options for future studies. Clinicians and the public may be misled by unrealistic expectations of benefits or harms based on blunt description of study subjects’ characteristics, a mistake that generally favors treating more patients with increasingly costly interventions. A more subtle approach to the evidence in clinical arrhythmia management, mindful of the hazards outlined here, will benefit patients, providers, and public health.

Disclosures
Dr Kramer is a consultant to the Circulatory Systems Advisory Panel of the Center for Devices and Radiologic Health, Food and Drug Administration. Dr Josephson reports receiving consulting fees from Biosense Webster.

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