The state-of-the-art review by Tung and colleagues provides a thoughtful perspective on balancing the benefits and risks of implantable cardioverter-defibrillator (ICD) therapy addressing the concerns of many caring physicians. It also provides the opportunity to emphasize the imperative of practicing evidence-based medicine, the importance of balance in the interpretation of clinical trial results, and how updates in the new Device-Based Therapy Guidelines for the implantation of ICDs and pacemakers advance these goals (2).

Tung et al. (1) suggest that: 1) the clinical benefit of ICD therapy has been overestimated in clinical trials; 2) the adverse effects on morbidity, quality of life, and the potential for proarhythmic effects has been underestimated; and 3) unfavorable cost-effectiveness of ICD therapy is understated. In this response these issues will be addressed using the evidence base resulting from controlled clinical trials and rigorously developed evidence-based practice guidelines (Fig. 1).

Has the Clinical Benefit of ICD Therapy Been Overestimated?

The design of clinical trials in arrhythmia therapy has undergone revolutionary change in the last 2 decades. The CAST (Cardiac Arrhythmia Suppression Trial) study highlighted the pitfalls of not only surrogate end points (e.g., premature ventricular contractions [PVCs]), but also of active control groups (3). Although PVCs were suppressed, mortality was increased by antiarrhythmic drug therapy. Furthermore, since the 1-year mortality was generally considered to be about 10% in patients with PVCs at the time the CAST trial was done, the 5% mortality rate in the CAST trial patients treated with antiarrhythmic drugs could have been judged to indicate a dramatic beneficial effect had there not been a randomized, blinded control group. Thus, the admonition by Tung et al. (1) regarding problems with “control” arms is well taken. Indeed, all primary prevention trials should incorporate a placebo control. In the 2 trials of ICD therapy that incorporated “placebo” control groups, the fact that antiarrhythmic therapy performed worse than optimized medical therapy may be considered disappointing, but not necessarily unexpected. That “no formal comparison was commented upon” does not detract from these studies’ overall findings. As elegantly shown by Myerburg et al. (4), without a placebo control as a point of reference, when 2 active interventions are compared, it is impossible to know whether either is worse, the same, or better than no intervention at all!

In their discussion regarding beta-blocker utilization, Tung et al. (1) allege that because patients randomized to ICD therapy were disproportionately treated with beta-blockers, the benefit of ICD therapy was accentuated. Nevertheless, to overstate this point and suggest that the use of beta-blocker therapy accounts for the difference in survival is inaccurate because the negative trials in Figure 1...
suffered from other issues. The CABG-Patch (Coronary Artery Bypass Graft-Patch) trial, as discussed by the authors, was performed in the era of epicardial ICD implantation, and patients were revascularized (5). Both the CAT (Canadian Amiodarone Therapy) trial (6) and the AMIOVIRT (Amiodarone versus Implantable Cardioverter-Defibrillator Trial) study (7) were small and had event rates less than anticipated. Similarly, in the DEFINITE (Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation) trial, event rates were also lower than expected (8). However, the high rate of beta-blocker use is to be commended, and, indeed, the low event rate in the DEFINITE trial may be due to the fact that all patients enrolled had nonischemic cardiomyopathies, rather than an ischemic basis. Patients in the DINAMIT (Defibrillators in Acute Myocardial Infarction Trial) study also enjoyed high rates of beta-blocker use, as is appropriate in the post-infarction population (9). The CIDS (Canadian Implantable Defibrillator Study) trial was troubled by low rates of beta-blocker administration (10), but was terminated early after the results of the AVID (Antiarrhythmics Versus Implantable Defibrillators) trial were released (11). Finally, the CASH (Cardiac Arrest Study-Hamburg) trial was designed to use beta-blockers in only 1 arm, and suffered from other problems such as interim looks at outcomes and termination of 1 of the 4 arms prematurely (12).

To belittle the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) study for demonstrating an absolute mortality benefit of (only) 5.6%, in view of the high rate of beta-blocker use and low rate of amiodarone use, is disingenuous (13). One may argue the degree of benefit that makes an intervention not only statistically significant but also clinically significant, but the MADIT II study data speak for themselves. Are we to ignore the results of the MADIT II study because the degree of benefit is not more than we would like? For better or worse, the results of the MADIT II study are the best we

**Figure 1 Major ICD Trials**

Hazard ratios (vertical line) and 95% confidence intervals (horizontal lines) for death from any cause in the implantable cardioverter-defibrillator (ICD) group compared with the non-ICD group. *Includes only ICD and amiodarone patients from CASH. AVID = Antiarrhythmics Versus Implantable Defibrillators trial; CABG = coronary artery bypass graft surgery; CASH = Cardiac Arrest Study Hamburg; CIDS = Canadian Implantable Defibrillator Study; DEFINITE = Defibrillator in Nonischemic Cardiomyopathy Treatment Evaluation trial; DINAMIT = Defibrillator in Acute Myocardial Infarction trial; EP = electrophysiological study; LVD = left ventricular dysfunction; LVEF = left ventricular ejection fraction; MADIT = Multicenter Automatic Defibrillator Implantation Trial; MI = myocardial infarction; NICM = nonischemic cardiomyopathy; NSVT = nonsustained ventricular tachycardia; PVC = premature ventricular complex; SAECG = signal-averaged electrocardiogram; SCD-HeFT = Sudden Cardiac Death in Heart Failure Trial.

**Abbreviations and Acronyms**

- CRT = cardiac resynchronization therapy
- ICD = implantable cardioverter-defibrillator
- LVEF = left ventricular ejection fraction
- PVC = premature ventricular contraction
- SCD = sudden cardiac death
have. Furthermore, to equate a 5% increase in hospitalization as counterbalancing a 5% decrease in mortality ignores the point that if patients live longer and quality of life can be preserved, the “trade” for hospitalization will be accepted by many patients (14).

Tung et al. (1) suggest that while ICDs may not be expected to reduce nonarrhythmic death, they should not increase nonarrhythmic deaths “as a side effect.” One can also easily make the argument that by preventing sudden death, the relative incidence of nonarrhythmic death would necessarily be increased as patients live longer free of arrhythmic mortality. Rather than being seen as a negative aspect of the DINAMIT study, the observation of increased nonarrhythmic death may simply reflect that the deaths in patients enrolled in the DINAMIT study were inevitable irrespective of ICD therapy (9,15). Specifically, that death was “confined only to those that received ICD discharges” seems to indicate that for those destined to die, the final mode of exodus can be either heart failure or arrhythmia. If cardiac arrest occurs first, heart failure death would not have the opportunity to become manifest. Conversely, if heart failure takes a patient’s life, that individual would no longer have the opportunity to have a cardiac arrest. To say that ICD shocks in a DEFINITE substudy “increased risk from nonarrhythmic death” does not take into account that the arrhythmia itself may have simply been a marker for impending death.

While it is true that benefit in patients with nonischemic cardiomyopathies was not significant in a certain subgroup analyses in the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) study (16), it is incorrect to state that “the nonsignificant benefit in nonischemic cardiomyopathy subgroup analysis was implemented into guidelines, and lack of benefit in NYHA functional class III patients was left out” (1). Indeed, the SCD-HeFT study conclusion in aggregate was what was incorporated in the guidelines (i.e., benefit was afforded to all patients who met enrollment criteria). This is in keeping with standard application of clinical trials and not “cherry picking” subgroups for inclusion and exclusion from recommendations.

In trials of secondary prevention, the fact that the CIDS (10) and CASH (12) trials failed to demonstrate significant reductions in mortality by ICD therapy can be explained by some of the reasons addressed in the previous text. Furthermore, the CIDS trial was discontinued early because the AVID trial results were positive, and continuing the trial would have been inappropriate. In view of the AVID trial results (11), the trend in the CIDS trial (10), and the meta-analysis combining the AVID, CIDS, and CASH (17) trials, it is reasonable to conclude that the benefit of ICD therapy in high-risk patients with resuscitated ventricular arrhythmias is consistent, and arguably modest. The evidence supports the use of ICD therapy for secondary prevention (Fig. 1).

Is There Discordance Between Evidence and Guidelines in the Post-Infarction Setting?

Tung et al. (1) are correct that the ventricular arrhythmia guideline invoked a left ventricular ejection fraction (LVEF) cutoff of 0.40 for ICD implantation. The new Device-Based Therapy Guidelines, however, addressed this disconnect between the evidence base and recommendations and adopted a more trial-based approach. Specifically, the guidelines now “...acknowledge that the ‘ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death’ used an LVEF of less than 40% as a critical point to justify ICD implantation for primary prevention of SCD. The LVEF used in clinical trials assessing the ICD for primary prevention of SCD ranged from less than 40% in MUSTT (Multicenter Unsustained Ventricular Tachycardia Trial) to less than 30% in MADIT II (Multicenter Automatic Defibrillator Implantation Trial II). Two trials, MADIT I (Multicenter Automatic Defibrillator Implantation Trial I) and SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), used LVEFs of less than 35% as entry criteria. The present writing committee reached the consensus that it would be best to have ICDs offered to patients with clinical profiles as similar to those included in the trials as possible. Having given careful consideration to the issues related to LVEF for these updated ICD guidelines, we have written these indications for ICDs based on the specific inclusion criteria for LVEF in the trials. Because of this, there may be some variation from previously published guidelines” (2).

Tung et al. (1) overstate that the findings of the DINAMIT study (9) contradict the inferences from the VALIANT (Valsartan in Acute Myocardial Infarction Trial) study (18). Although the VALIANT study did show a high early post-infarction risk for sudden death, there is no evidence that these patients would have been saved by an ICD. As in the DINAMIT trial, these very patients may have been destined to die irrespective of any (good) therapy provided (15). Conversely, though many patients enrolled in the MADIT II study had their interval index myocardial infarction over 6 years before enrollment, analysis of the data did indicate that survival benefit was durable many years after infarction (19).

Have Adverse Effects on Morbidity, Quality of Life, and Proarrhythmia Been Underestimated?

The fact that ICD therapy is not a surrogate for resuscitation from cardiac arrest is not new information. A 1993 policy conference from the North American Society of Pacing and Electrophysiology concluded that “total mortality” was, in fact, the “appropriate” end point for reporting ICD outcomes (20). While the examples Tung et al. (1) provided regarding the “dark side” of ICD therapy are correct, ICDs can have proarrhythmic effects, negative
effects on quality of life, and malfunction, they do not negate the results of studies that in the aggregate show benefit. Tung et al. (1) emphasized the importance of talking to patients. I could not agree more: more than once I have said that we need to return to treating patients rather than ejection fractions! But to point to the COMPANION (Companion of Medical Therapy, Pacing and Defibrillation in Heart Failure) trial (21) data, which shows a 2% higher incidence of sudden death in the cardiac resynchronization therapy (CRT) arm compared with that in the control arm, ignores the often observed choice of patients to “trade” improved quality of life for sudden death, when given the choice (14). Indeed, it is the experience of many clinicians that when given a choice, patients would much prefer quality of life with earlier death rather than prolonged survival with markedly impaired quality of life (14). Indeed, all CRT trials have, in the aggregate, shown both decreased mortality and improved quality of life, even though the incidence of sudden death may be increased, perhaps because patients have lived longer without heart failure and arrhythmic death has replaced heart failure death. The new guidelines repeatedly advise that “all primary SCD prevention ICD recommendations apply only to patients who are receiving optimal medical therapy and have reasonable expectation of survival with good functional capacity for more than one year” (2). A section that focuses on heart failure after first appropriate ICD therapy concludes that “to maximize the benefit after a sudden death has been prevented, it is crucial that the management team evaluate the heart failure profile, review the medical regimen, and plan for ongoing care” (2).

The ICD’s impact on quality of life is influenced by whether or not shock therapy is delivered. However, Hsu et al. (22) observed that simply having survived a life-threatening ventricular arrhythmia has a negative impact. However, Hsu et al. (22) also found that after therapy, most patients had improvement, indeed possibly more so in those treated with an ICD. In the AVID study, although shocks were associated with decreased quality of life, ICD and antiarrhythmic drug therapy were overall associated with self-perceived quality of life (23). In the CIDS trial, quality of life was better with an ICD than with amiodarone (24). And in the DEFINITE trial, quality of life was not affected by ICD implantation undertaken for primary prevention (25).

Regarding hardware malfunction, there are probably many reasons why the ICD market has flattened. Decreased ICD implantation rates were caused not only by recalls, but possibly also by the vigorous application of ICD therapy to a large reservoir of patients with ICD indications that has been emptied over the last several years. Furthermore, experienced clinicians all know that when a new therapy is released there is a rush to implement it, whether it be a drug or device, followed by a swinging of the pendulum back toward the midline. It is my belief that the reservoir and pendulum issues were just as strong in affecting the ICD market as has been the occurrence of recalls. The new guidelines include a section in ICD follow-up addressing complications, device and lead failures, and management strategies. An entire section is entitled “Impact on Quality of Life (Inappropriate Shocks)” (2).

Has ICD Cost-Effectiveness Been Overstated?

Cost-effectiveness analysis is one of the most difficult aspects of any therapy to assess; indeed, a discipline has evolved to address this need. Since many assumptions are made when undertaking these analyses, the arguments of Tung et al. (1) are well taken. As such, in the 2002 Guidelines (26), the writing committee did not overstate ICD cost-effectiveness. The limitations of mathematical modeling and nonrandomized studies to estimate cost-effectiveness were addressed. We specifically indicated that ICD cost-effectiveness would be greatest in patients at high risk of arrhythmic death and at low risk for other causes of death. We also stated that cost-effectiveness would be improved by lowering the cost of the device and improving reliability and longevity. Indeed, the guidelines anticipated the challenges of advisories recently experienced.

Since those guidelines were published, new data have become available. Although cost per life-year saved is expensive ($235,000 in the MADIT-II study), when the time horizon is extended to 12 years, the cost decreases to $78,600 to $114,000 per life-year saved (27). Others have come to similar conclusions (28,29).

The new guidelines incorporate a section similarly addressing cost-effectiveness (2). It begins by stating, “Long-term follow-up studies have consistently demonstrated that cumulative medical costs are increased substantially among patients receiving an ICD.” It goes on to say that patient selection is necessary for ICD implantation to be cost-effective, and that when restricted in this manner, cost-effectiveness may be similar to other accepted cardiovascular therapies and compare well to the benchmark of renal dialysis ($30,000 to $50,000 per year of life saved). In short, the guidelines recognize that ICD implantation will be more cost-effective when used for patients at high risk of arrhythmic death and at low risk of other causes of death. The cost section concludes with an acknowledgement that for CRT, cost-effectiveness has not been evaluated (2).

Resolution and the Future

Tung et al. (1) treat every negative observation or subgroup comparison in the ICD groups as absolute truth, while on the other side, they criticize or belittle every positive observation or comparison. Although, like all clinical trials, those evaluating ICD therapy have limitations, from the perspective of evidence-based medicine, there are few interventions that in multiple trial settings have consistently over a >10-year period produced a 20% to 30% reduction in total mortality (Fig. 1). ICD therapy has done just that. We need to use this powerful tool in the most appropriate manner
based on the guidelines that resulted from the trials. I have not addressed each point discussed by Tung et al. (1), but would stress that guideline committees do look at and weigh the universe of data. Although we all freely admit that there are problems with ICDs, the weight of evidence supports their use for the indications listed in appropriate patients. Furthermore, if follow-up is adequately funded, the National Cardiovascular Data Registry has the opportunity to provide data and help guide future clinical decisions.

Practice guidelines are developed according to a formal process of review of evidence by multiple experts to provide recommendations regarding therapy, including discussions with patients as well as pharmacologic and device-based therapies. The 2008 Device-Based Therapy Guidelines (2) considered the same evidence base and came up with similar recommendations with a different group of experts weighing all of the clinical evidence (30). The “opinions” Tung et al. (1) present are just that—“opinions” of a small group of individuals. By contrast, the 2008 Device-Based Therapy Guidelines (2), like the 2006 Ventricular Arrhythmia Guidelines (30), represent the results of a robust process of evaluating all evidence by 2 independent groups of experts, formal review by other experts, and final approval by the governing boards of the Heart Rhythm Society, American College of Cardiology, and American Heart Association. This process legitimizes guidelines, and therefore, they carry the full weight of organizational endorsement behind them.

Finally, yes, there is a dark side to ICD therapy. Devices fail, and in unpredictable subsets, especially patients who get inappropriate shocks, quality of life is decreased. Unfortunately, life is not perfect. Thus, the Heart Rhythm Society has taken the opportunity of confronting the “dark side” of ICD therapy, especially in regard to device and lead malfunction, and developed guidance documents on responsible reporting and how industry should handle observations on device function (31).

It is my hope, as indicated in the final section of the 2008 Device-Based Therapy Guidelines, that research will be undertaken to help identify not only patients who would be the most likely to benefit from ICD therapy, but also those expected not to benefit (2). Retrospective analyses have already shown that this may be possible (32,33), and trials are in progress in this regard. Already specific patient populations are now recognized for whom the benefit of ICD therapy outweighs any risks (2). But, until data are available that may reliably allow us to more precisely focus the prescription of ICD therapy to patients who may benefit most and avoid adverse effects on quality of life, we are left with the results of clinical trials that in the aggregate show improved survival in a broad selection of patients with left ventricular dysfunction and either demonstrated or anticipated risk for arrhythmic death. Evidence-based medicine, the rigorous process of guideline writing, review, and approval, and the ethical consideration of offering proven life-prolonging therapies to all patients, provide a compelling rationale for the clinician to carefully consider the guidelines in their clinical decision making.

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