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EDITOR'S FORUM

Subject of the year: Who are we missing, who are we overtreating, and who is best served? Refining the prescription of implantable cardioverter-defibrillator therapy

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The National Heart, Lung and Blood Institute (NHLBI) and the American Heart Association report that although the overall death rate from cardiovascular disease (CVD) has fallen, heart disease continues to remain as the major killer of Americans. In 2005, the overall death rate due to CVD was 278.9 per 100,000: 324.7 per 100,000 for white males, 438.4 per 100,000 for black males, 230.4 per 100,000 for white females, and 319.7 per 100,000 for black females. From 1995 to 2005, death rates from CVD declined 26.4%. Data for 2006 show that CVD accounted for 34.2% (829,072) of all 2,425,900 deaths in 2006, or one of every 2.9 deaths in the USA. About 2,400 Americans die of CVD each day, an average of one death every 37 s. More than 150,000 Americans dying as a result of CVD were ≥65 years of age, and 32% of these deaths occurred before age 75 years, well before the average life expectancy of 77.9 years. In 2005, one in eight death certificates (292,214 deaths) in the USA mentioned heart failure (HF) [1].

Sudden cardiac death (SCD) is often unexpected and affects individuals in the prime of their lives. According to the National Center for Health Statistics, approximately 60% of unexpected cardiac deaths are treated by emergency medical services, 27% of patients receive out-of-hospital bystander cardiopulmonary resuscitation, and only 2% of patients receive defibrillation by lay responders, although the latter has been increasing [1]. In the last 50 years, the rate of deaths due to coronary heart disease has decreased by over 60%, but the SCD rate has only fallen 49% [1].

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Systolic HF incidence approaches ten per 1,000 population after 65 years of age, and 75% have antecedent hypertension. At 40 years of age, the lifetime risk of HF occurring without antecedent MI is one in nine for men and one in six for women. The annual rates per 1,000 population of new HF events for white men are 15.2 for those 65–74 years of age, 31.7 for those 75–84 years of age, and 65.2 for those ≥85 years of age. For white women in the same age groups, the rates are 8.2, 19.8, and 45.6, respectively. For black men, the rates are 16.9, 25.5, and 50.6, and for black women, the estimated rates are 14.2, 25.5, and 44.0, respectively [1].

Many strategies have been employed to decrease the occurrence of SCD with implantable cardioverter-defibrillators (ICDs) becoming first-line therapy for primary and secondary prevention indications. Similarly, cardiac resynchronization therapy (CRT) either with (CRT-D) or without (CRT-P) ICD capabilities have been shown to improve clinical outcomes in chronic HF. However, as in the natural history of any new therapy, the limitations and imperfections of ICD therapy have been increasingly recognized. Furthermore, these devices have been studied primarily in the context of carefully managed randomized controlled trials, and it is not clear how they compare with standard medical therapy in routine clinical practice and among certain patient subsets such as women, the elderly, and minorities who have been consistently underrepresented in clinical investigations. It also appears that these groups may be underserved in "real world" clinical care. And when therapies migrate from randomized controlled clinical trials to the general community, benefits may be attenuated [2, 3].

The limitations of published randomized clinical trials have been the subject of passionate editorials [4, 5]. In my

opinion, a pivotal area that will be the subject of research and debate regards the prescription of ICD and CRT therapy in women, the elderly, and minorities and how to identify patients who will benefit from device implantation. Indeed, recognizing the knowledge gap in these areas, the NHLBI issued a challenge grant in the context of President Obama's stimulus package. The challenge reads: "Implantable cardioverter defibrillators and cardiac resynchronization therapy have been shown to improve clinical outcome in chronic HF, but they are expensive technologies and have been studied primarily in the context of carefully managed randomized controlled trials. It is not clear how they compare with standard medical therapy in routine clinical practice and among certain patient subsets, such as women, the elderly, and minorities [6]".

Interest in the allocation of ICDs to the elderly is not new [7–15]. As increasing age is associated with increased mortality, the benefit afforded by ICDs might be expected to be especially great in the elderly. However, as age increases, so too do comorbid conditions which may dilute the salutary effects of ICD therapy. Some studies [7, 8] reported retrospective observations that ICDs are effective treatments for life-threatening ventricular arrhythmias in both elderly and younger patients, and that age should not be a contraindication to implantation [14]. However, the elderly have worse outcomes than do younger patients [11, 14, 16]. Of 204 (16.6%) patients aged ≥75 years in the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), 121 were randomized to ICD therapy [17]. The hazard ratio for mortality in the older patients assigned to ICD therapy compared to those in the conventional therapy group was 0.56, similar to the 0.63 value seen in younger patients indicating to the authors that ICD therapy in the elderly was associated with an equivalent reduction of mortality compared to younger patients. In SCD-HeFT, the benefits of ICD therapy were attenuated in patients aged 65 years or older relative to younger patients [18]. For patients with secondary prevention ICD indications in CIDS, CASH, and AVID, those over 75 years did not derive a significant survival benefit from device therapy [14]. Finally, with regard to the elderly, we recently reported the contemporary ICD prescription patterns, ages, indications, and implanted ICD and CRT-D type of patients enrolled in the St. Jude Medical Advancements in ICD Therapy Registry [16]. Although at 2 years overall mortality in patients aged ≥70 years was greater than in younger patients (incrementally increasing from 5.8% to 17.8% as age increased from age 18–39 to 0 ≥80 years, respectively), noncardiac death was more common in older than in younger patients. Sudden and non-sudden cardiac death rates were similar, and trends for changes as a function of age were absent. Of patients ≥80 years receiving a CRT-D, 78% had a QRS duration and NYHA Class that met accepted implantation criteria with similar findings in the National Cardiovascular Data Registry (NCDR). Overall, over 40% of new ICDs and CRT-Ds are implanted for patients >70, and over 10% for patients ≥80 years of age. A significant proportion of those receiving a CRT-D did not fulfill accepted criteria for implantation [16].

Our data and those from the NCDR raise important questions. Older patients may have different wishes and needs compared to younger patients. Lunney et al. found that, compared to functional patients, those who were frail were eight times more likely than the former to be dependent on caregivers to support activities of daily living in the month before death [19]. These observations highlight the importance of differentiating expected outcomes and needs in the elderly and that it may be helpful to tailor treatment strategies and care plans specific to specific patient wishes and status. Thus, studies that assess anticipated benefits of device therapy for the elderly are needed.

Curtis et al. [20] and Hernandez et al. [21] published companion papers highlighting gender differences in ICD use. In the first, a 5% sample of Medicare beneficiaries from 1999–2005 was analyzed, and the authors showed that among male Medicare beneficiaries in 2005 who met criteria for primary prevention, 32.3/1,000 received an ICD within 1 year of diagnosis, but among female beneficiaries ICDs were implanted in only 8.6/1,000. An accompanying editorial pointed out that although the Centers for Medicare & Medicaid Services met its stated goal of 25,000 ICD implantations in the first year after expanding coverage, these were performed mostly in men [22]. The second paper by Hernandez et al. used data from the "Get with the Guidelines" Heart Failure database from 2005–2007 and found that 35.4% of patients eligible for ICD therapy received one by hospital discharge. Both women and minorities were less likely to have an ICD implanted than were white men. It is conceivable that rather than women having been underserved, men were and are being over treated [21].

As for women, racial and ethnic minorities have been underrepresented in clinical trials, so they have been the recipients of contemporary therapy less often than their non-minority counterparts. For example, in the Hernandez paper discussed above, compared with white men, black men were 73% as likely to receive an ICD, whereas white women and black women were only 62% and 56% as likely to receive an ICD, respectively [21]. In an analysis of the NCDR data base, Farmer et al. found that African-American and Hispanic patients who were eligible for CRT-D were less likely to receive therapy than were white patients. Interestingly, black and Hispanic patients receiving CRT-Ds were more likely to have met established criteria for implantation. These findings suggest important racial/

ethnic differences in the treatment of patients with advanced HF [23].

The above discussion supports the NHLBI's challenge for studies to address the needs of populations not represented in the clinical trials published to date. In addition, risk stratification algorithms are needed to determine which patients can be expected to not only benefit but also not benefit from device implantation [24, 25]. Some of the questions that await answers include, but are not limited to, the following questions:

1. Given comorbidities in the elderly, to what degrees are clinical and cost effectiveness attenuated by those comorbidities?
2. Since 80% of devices are implanted for primary prevention of SCD, since only a single chamber ICD is needed for resuscitation, and since 2/3 of elderly patients receive either a dual chamber or CRT ICD, would they do just as well with a single chamber less expensive device associated with fewer complications? Are outcomes affected by type of device implanted?
3. What are the barriers to prescription of ICD and CRT therapy to women and minorities with appropriate indications for device therapy?
4. Given that women are known to experience a greater number of complications related to device implantation, are there predictors of adverse events that are modifiable?
5. Do the elderly, women and minorities have more sinus node dysfunction, AV conduction disturbances, and bundle branch blocks to explain the small use of single chamber ICDs for primary prevention?
6. Is it possible to risk stratify and identify patients expected to benefit and not benefit from treatment? Is there a role for electrophysiologic study for this indication in contemporary practice?

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