Screening patients for primary prophylaxis implantable cardioverter defibrillators: Insights into current practices

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Randomized clinical trials have established that the prophylactic use of implantable cardioverter defibrillators (ICDs) prolongs survival in patients with left ventricular (LV) systolic dysfunction secondary to previous myocardial infarction (1) or associated with heart failure from any cause (2).

The Multicenter Automated Defibrillator Implantation Trial II (MADIT II) (1) recruited patients who suffered a myocardial infarction more than a month previously, and had a LV ejection fraction (LVEF) of 30% or less, and subsequently randomized them to receive an implantable defibrillator or no device. MADIT II found a dramatic 34% reduction in hazard ratio of all-cause mortality in the ICD arm. The results were so clear that the study ended with an average follow-up of 20 months, before 20% of patients without defibrillators had died. A reduction in absolute mortality of 5.6% (from 19.8% to 14.2%) was recorded at study end (1).

Another pivotal trial, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) (2), compared ICD therapy or amiodarone with placebo in 2521 patients with symptomatic heart failure due to ischemic or nonischemic LV dysfunction. Among patients who had an ICD, there was a RR reduction of 23% and an absolute reduction in mortality of 7.2% over five years, compared with the control group. The ICD represents a powerful tool to reduce the risk of sudden death, although at a significant cost. The annual number needed to treat per life saved ranged from 10 to 13 in the two largest clinical trials at three to five years (1-3).

Clinical trials that led to the guidelines for primary prevention ICD insertion used various techniques for LVEF assessment, including echocardiography and equilibrium radionuclide angiography (RNA), as used in the study by Lane et al (4). Given the results of these trials, the American College of Cardiology/American Heart Association/Heart Rhythm Society (5) currently recommend that the clinician use the LVEF determination method believed to be the most clinically accurate and appropriate in their respective institution. In view of the fact that LVEF is a central criterion with respect to prophylactic ICDs, the Canadian Heart Rhythm Society (CHRS) guidelines (6) advocate that quantitative LVEF measurement must be performed. No preferred method is mentioned, again reflecting the assortment of techniques used in MADIT II (1) and SCD-HeFT (2). Nevertheless, the CHRS position paper (6) clearly describes qualitative echocardiographic estimates as insufficient to assess the suitability for ICD implantation.

Assessing patients for prophylactic ICD insertion involves several factors beyond LVEF measurement. Medical therapy should be optimized and coronary revascularization performed if indicated. Hence, the standard of practice is to incorporate clinician discretion along with medical and social factors during the risk assessment for sudden cardiac death, as portrayed in the CHRS guidelines.

Regardless, optimizing our strategy to screen potential candidates for ICD is indeed a desirable goal. In this context, the study by Lane et al (4) in the present issue of *The Canadian Journal of Cardiology* is extremely welcomed. The authors conducted a 'real-world' prospective cohort study on screening practices for ICD implantation in southern Ontario.

Current semiquantitative echocardiogram (SQE) techniques showed significant overlap between grades and poor overall positive predictive values compared with ejection fraction measurements on RNA. This finding was particularly pronounced with grades 2 or 3 LV systolic function. As a screening tool evaluation, it is granted that specificity is not as important as sensitivity. Although the sensitivity of a grade 3 or worse SQE for predicting an RNA of less than 30% was 92.8%, the specificity was only 30%. The setback was that the majority of patients had either grade 3 or worse LV function, and only 53.2% of those had an RNA LVEF of less than 30%. This translates into a significant limitation at this cut-off value because one-half of the individuals referred would require further testing. When results were in the lower extreme (ie, LVEF grade 4), SQE showed a positive predictive value of 93% for an LVEF of less than 35%. However, only one-third of patients had a grade 4 echocardiogram, and SQE was therefore useful in only a relatively small number of patients.

Because SQE techniques did not provide a single cut-off value, the authors evaluated data from 102 patients with available quantitative echocardiogram and RNA results. Nonetheless, results were not very encouraging. Inspecting the positive likelihood ratios revealed values between 1 and 2, only altering probability to a small (and seldom important) degree (7).

Recent guidelines have focused on ejection fraction cut-off values to determine eligibility for primary prevention ICDs. There are now a number of modalities available for the determination of LVEF, including two-dimensional (2D), contrast or three-dimensional (3D) echocardiography, RNA (planar and single-photon emission computed tomography [SPECT]), gated perfusion imaging (SPECT or positron emission tomography), contrast LV angiography, cardiovascular magnetic resonance imaging and computed tomography. It should be kept in mind that the determination of LVEF lacks a true 'gold standard' and that there may be variation among the commonly used clinical techniques of LVEF determination. Many studies comparing the accuracy and variability of different techniques are dated. Also, a number of studies report high coefficients of correlation but do not necessarily report good agreement. For example, if two methods of calculating ejection fraction were consistently 20% apart, they would exhibit high correlation but poor agreement (8).

Lane et al evaluated echocardiography, frequently the first test used because of the absence of ionizing radiation and the ease of accessibility, portability and relatively low cost compared with other imaging techniques. Many echocardiography laboratories rely on visual 'eyeball' estimates of LVEF. However, these may not always be accurate (9). Quantitative methods involve using M-mode measurements or linear dimensions derived from the 2D image. The Teichholz method for calculating LVEF from LV linear dimensions may result in inaccuracies because of geometric assumptions required to convert a linear measurement to a 3D value. A potential disadvantage of M-mode dimensions is that overestimation will occur if the beam is oblique with respect to the long or short axis of the ventricle. On the other hand, underestimation can occur if the M-line is not centred in the

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ventricular chamber. With nonsymmetric disease processes (eg, ischemic heart disease) or with alterations in LV shape (eg, dilated cardiomyopathy), M-mode measurements at the base may not be representative of overall LV dimensions or function.

Therefore, the American Society of Echocardiography (10) recommends quantification using a Simpson's rule in the presence of distorted LV geometry and when a more accurate determination of LVEF is necessary. For a good quantitative value, nonoblique standard image planes, inclusion of the apex of the LV, adequate endocardial definition and accurate identification of endocardial borders are needed. The drawback to routine quantitative determination of LVEF is that it is a time-consuming process. Reproducibility of ejection fraction on echocardiography using the Simpson's method can be as good as plus or minus 7% (11). However, in 10% to 20% of patients, LVEF cannot be accurately determined due to suboptimal endocardial definition (12). The accuracy of quantitative methods diminishes rapidly in cases in which more than two wall segments cannot be adequately visualized. In these cases, the use of intravenous contrast agents can improve endocardial border definition and reader confidence in the assessment of wall motion. Contrast echocardiography has been proven to improve the estimates of LVEF substantially (12,13). For example, Hundley et al (13) calculated the LVEF in 40 patients using both non-contrast and contrast echocardiography, and compared the results with those obtained using same-day magnetic resonance imaging. The percentage of patients who were correctly classified as having normal, mildly to moderately depressed or severely reduced LVEF improved significantly from 71% before contrast to 94% after contrast ($P<0.03$). Why is contrast not used more routinely in echocardiography laboratories? Previous concerns regarding risk in patients with heart failure appear to be largely overstated (14). However, use of contrast does require placement of an intravenous catheter and the availability of a physician to order contrast unless it has been done prospectively. This results in delays in laboratory work flow and imposes an additional burden on already busy echocardiography laboratories.

Finally, 3D echocardiography has recently been introduced clinically and, in theory, should lead to improved quantification of LV volumes and LVEF. Disadvantages include significant postacquisition reconstruction times, and the need for 3D echocardiographic equipment and appropriate expertise (10). Further studies need to be performed to validate this emerging modality.

Determination of LVEF using RNA has several advantages, including high accuracy and reproducibility (15-17). Wackers et al (15) recommend that "to be attributed to nonrandom physiologic alterations, the absolute change in ejection fraction should be $\geq 10\%$ in normal patients and $\geq 5\%$ in abnormal patients". Using planar RNA, radioactive counts from the ventricular cavity at end diastole and end systole are used to calculate LVEF. Therefore, the calculation is mainly independent of the need to define the endocardium accurately. In addition, the measurements do not rely on geometric assumptions regarding the shape of the LV and the technique can be used for accurate volumetric measurements. This method is not limited by the patient's body habitus, is not time consuming and is easy to perform.

Three important limitations of RNA need to be considered. First is the associated radiation exposure, which at approximately 5.7 mSv, is just under twice the average amount of natural environmental radiation the average person receives in North America (18). Second, errors in measurement can be introduced by improper operator selection of the optimum projection for separation of the right ventricle and left ventricle, and separation of the left ventricle and left atrium on planar imaging. However, as a technique, it is generally regarded as being more independent of both operator experience and subjective assessment than echocardiography. SPECT RNA overcomes potential cavity separation issues by using automatic or semiautomatic programs that are volumetric, whereby the LV is considered as a 3D structure (19). However, these methods tend to yield ejection fractions that are 7% to 10% higher than planar RNA and must be used with caution given that most guidelines were established using planar RNA values

(19,20). For this reason, many centres using SPECT RNA will continue to acquire and report LVEF using planar RNA. Finally, in the current environment of radioisotope shortage imposed by ailing nuclear reactors, there is limited availability of technetium 99m, the isotope used to label red blood cells for RNA studies.

In a direct comparison between the two techniques, van Royen et al (16) performed both RNA and 2D echocardiograms on 73 clinically stable patients within a four-day period. LVEF by both techniques was compared after blinded analysis by three echocardiographers and three nuclear technologists. Reproducibility was assessed by blinded repeat analysis after a one-week interval. The mean intraobserver variability was 2% for RNA and 15.3% for 2D echocardiography. Similarly, the mean interobserver variability was 3.8% for RNA and 18.1% for 2D echocardiography. More importantly, clinically relevant differences did not occur on repeat processing of RNA, whereas potentially clinically relevant differences occurred in 8% to 26% of studies on repeat analysis of echocardiography. However, the echocardiography analysis used visual estimates of ejection fraction, once again highlighting the limitations of a nonquantitative ejection fraction determination.

Shih et al (21) studied the correlation of LVEF between quantitative echocardiography with harmonic imaging modality and RNA obtained within a 15-day interval. This analysis of 377 consecutive patients showed a correlation coefficient value (r) of 0.84 ($P<0.0001$). The highest agreement (91%) occurred in the group with severely depressed LVEF, followed by the group with normal LVEF. In patients with mild to moderate systolic dysfunction, the agreement between 2D echocardiography and RNA was less than 50%, similar to findings observed by Lane et al (4). Previous work by Yu et al (12) demonstrated that this correlation can be improved ($r=0.95$) with contrast echocardiography.

Ultimately, cost-use analysis should be taken into account when considering a screening strategy. Krahn et al (22) studied the cost of preimplantation cardiac imaging in patients referred for a primary prevention ICD. The authors showed that verification of LVEF with RNA can identify noneligible patients, resulting in substantial overall cost savings of \$6,037 per patient. Costs were calculated from a payer perspective; in this case, the Ministry of Health and Long-Term Care of Ontario. The unit costs (technical plus physician) of the echocardiogram and RNA were evaluated. The total unit cost for transthoracic echocardiography and RNA was US\$209.74 and US\$196.19, respectively. One could hypothesize that patients with known cardiomyopathy in whom LVEF reassessment is necessary for consideration of ICD therapy may benefit from RNA as the first and only test. This strategy reduces the number of investigations required, reducing costs while accelerating the decision-making process. Not all patients would benefit from this approach (eg, patients with recent heart failure diagnosis). The current standard of care for patients presenting with heart failure includes 2D echocardiography with Doppler during initial evaluation of ventricular function, LV size, wall thickness and valve function (23). However, for stable heart failure patients in whom the only question is, 'does my patient qualify for a prophylactic ICD?', an RNA may be more attractive.

Some limitations of the study by Lane et al (4) should be considered. First, echocardiograms were performed at several different centres, by multiple operators, using different techniques. Second, selection bias was present because only patients referred for ICD were included. The authors did not include patients who may have been screened before referral. It is plausible that echocardiography is being appropriately used in a much broader population, but we can only see the tip of the iceberg here. This may falsely exaggerate the measured inaccuracies. Finally, although less likely, the suitable imaging modality that best quantitates LV function and predicts risk may not be RNA as used in the analysis (4). A subanalysis of SCD-HeFT (24) illustrated that among the 2521 patients enrolled in SCD-HeFT, LVEF was measured by RNA in 616 (24%), echocardiography in 1469 (58%) and contrast angiography in 436 (17%). Interestingly, the distribution

of ejection fractions measured by RNA differed from those measured by echocardiography or contrast angiograms, but survival did not vary according to the modality of LVEF assessment.

Our ultimate goal as clinicians is to combine available evidence and clinical judgment to protect high-risk patients with ICD therapy while avoiding inappropriate implantations. We congratulate Lane et al for providing important insights into real-world practices in a southern Ontario community. Such analyses are key to review routine clinical practices in community and tertiary centres. Moreover, it presents valuable data for stakeholders implementing population-based screening strategies. Considering findings from this study and its potential limitations, it may be premature to commit to an ICD implantation based solely on a grade 4 LVEF from a qualitative echocardiogram. In the unlikely scenario of an inaccurate LVEF assessment, the stakes are high because an ICD insertion is an invasive procedure that not only entails significant changes to a patient's life, but is also associated with potential procedure-related complications. Whether a grade 4 LVEF determined on an echocardiogram would be enough to warrant ICD implantation should be further verified in a direct comparison study. As a technique, RNA is less dependent on operator experience and subjective assessment than echocardiography, resulting in reduced intra- and interobserver variability. This may reduce the number of investigations required to confirm eligibility, reducing costs (22) while accelerating the decision-making process. In the future, evaluation of scar using magnetic

resonance imaging or new radiotracers may become useful, but this will require validation in large populations. Therefore, based in part on data from Canadian centres (4,22), patients with known cardiomyopathy requiring LVEF evaluation for consideration of prophylactic ICD insertion may benefit from RNA assessment.

Current CHRS guidelines (6) propose qualitative assessment of LVEF based on the diversity of tests applied in clinical trials (24). Presently, either echocardiography or RNA is accepted in clinical practice. However, the data from the study by Lane et al (4) support the need for standardized screening approaches. Ideally, there need to be clear guidelines dictating standardized approaches for the quantification of LVEF across all imaging modalities. The electrophysiology, imaging and clinical communities must work together to develop and implement such standard approaches, and adapt these approaches to other clinical parameters and emerging noninvasive screening tools that develop. The results will include improved sudden cardiac death risk stratification, optimized use of health care resources and, ultimately, better patient care.

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