Efficacy and Temporal Stability of Reduced Safety Margins for Ventricular Defibrillation
Primary Results From the Low Energy Safety Study (LESS)

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Background—Traditionally, a safety margin of at least 10 J between the maximum output of the pulse generator and the energy needed for ventricular defibrillation has been used because lower safety margins were associated with unacceptably high rates of failed defibrillation and sudden cardiac death. The Low Energy Safety Study (LESS) was a prospective, randomized assessment of the safety margin requirements for modern implantable cardioverter-defibrillator (ICD) systems.

Methods and Results—A total of 636 patients undergoing initial ICD implantation with a dual-coil lead and active pulse generator were evaluated. The defibrillation threshold (DFT) and enhanced DFT (DFT+/H11001 and DFT+/H11001/H11001) were measured using a modified step-down protocol. Conversion testing of induced ventricular fibrillation before discharge, at 3 months, and at 12 months was performed in all 392 patients, as was randomization to chronic programming at either 2 steps above DFT+/H11001/H11001 or maximal output in all patients. The induced ventricular fibrillation data had conversion success rates of 91.4%, 97.9%, 99.1%, 99.6%, and 99.8% for safety margins of 0, 1, 2, 3, and 4 steps above the DFT+/H11001/H11001, respectively. A margin of 4 to 6 J was adequate to maintain high conversion success over time (98.9% before discharge versus 99.2% at 12 months; P=NS). Over a mean follow-up of 24±13 months, conversion of spontaneously occurring ventricular tachyarrhythmias >200 bpm was identical (97.3%), despite a safety margin difference of 5.2±1.1 J for the 2-step group versus 20.8±4.2 J for maximal output.

Conclusions—With a rigorous implantation algorithm, a safety margin of about 5 J is adequate for safe implantation of modern ICD systems. (Circulation. 2002;105:2043-2048.)

Key Words: defibrillation ■ tachyarrhythmias ■ defibrillators, implantable ■ safety

Ventricular defibrillation testing is routinely performed at the time of implantable cardioverter-defibrillator (ICD) placement. One of the primary functions of such testing is to confirm an adequate safety margin for defibrillation. Traditionally, a safety margin of at least 10 J between the maximum output of the pulse generator and the energy needed for defibrillation has been used because early studies indicated that lower safety margins were associated with unacceptably high rates of failed defibrillation and sudden cardiac death.1–3 Subsequently, it was shown that defibrillation thresholds (DFTs) tend to increase over time with transvenous lead systems, further reinforcing the need for large defibrillation safety margins at implantation.4–7 However, these studies were performed in an era when abdominal pulse generators and monophasic waveforms were used. The downsizing of pulse generators permitted the routine pectoral implantation of devices. This led to the development of ICDs in which the pulse generator shell was part of the shocking pathway. Such active pectoral pulse generators, in combination with biphasic waveforms, result in marked reductions in DFTs and more stable thresholds long-term.8–11 Thus, the need for a large defibrillation safety margin at implantation with modern ICD systems is unclear.

Lower shock strengths when treating ventricular arrhythmias have been observed to decrease postshock arrhythmias.12,13 Additionally, shorter time to therapy for detected
ventricular fibrillation (VF) and lower energy delivery have the potential for decreasing the risk of syncope and prolonging battery life. Accordingly, the Low Energy Safety Study (LESS) was designed as a multicenter, randomized study to assess the safety and efficacy of lower safety margins on defibrillation effectiveness.

Methods

A total of 702 patients were enrolled at 32 investigational sites between April 1997 and December 1999. Written, informed consent was obtained from all patients, and the study was approved by the Institutional Review Board of each participating center. At ICD implant, 636 patients completed all testing required by the LESS protocol and were randomized into the study. Details of the study design and patient enrollment were described previously.14

The study was designed to be unblinded to the initial ICD implantation with a standard indication for such therapy. All patients received a dual-coil defibrillation lead (ENDOTAK), and an active can pectoral pulse generator was implanted in 99% of the cases. Both single and dual-chamber ICD systems in the VENTAK Mini or AV families were implanted. All leads and pulse generators were manufactured by Guidant Corporation (St Paul, Minn.).

Defibrillation testing was performed via the implanted ICD system. At implantation, the DFT was measured using a modified step-down protocol starting at 14 J (stored energy). VF was most often induced with either a train of pulses at 30-ms intervals (Fib High, 66% of patients) or a low-energy shock timed to occur on the upslope of the T-wave (T-shock, 26% of patients). If the first shock successfully terminated VF, then the energy was decreased on subsequent trials to 11, 9, 7, 5, and 2 J until a failure occurred. If the initial 14 J shock was unsuccessful, then energy was increased to 17 and 21 J on subsequent trials until successful. The DFT was defined as the lowest energy to terminate VF. After the DFT measurement, additional defibrillation trials starting at the DFT energy were required. If either of the next 2 trials failed, the energy was increased to the next step and testing continued. The DFT+ and DFT++ were defined as the lowest energy requiring termination VF on 2 or 3 consecutive trials, respectively. With this protocol, the DFT≤DFT++≤DFT+++. The DFT++ was used as a conservative estimate of the energy required for consistently high conversion success, thereby allowing the testing of small safety margins in this study. Patients with a DFT++ >21 J were excluded because they did not meet clinically accepted implant criteria.

A detailed assessment of the effect of safety margin on defibrillation margin was assessed using induced VF episodes before discharge, at 3 months, and at 12 months in 392 patients (LESS Phase 1). Phase 1 patients were assigned to have the first 2 shocks programmed to 0, 1, 2, 3, or 4 energy steps above the implant DFT+. Step size ranged from 1 to 6 J but was 2 to 3 J in ~75% of cases, depending on the DFT+ energy and the energy levels programmable in the pulse generator. Three VF induction/defibrillation trials were performed on each patient at each follow-up visit (total of 9 trials per patient). Successful conversion was defined as the restoration of baseline rhythm with either of the first 2 shocks. The same energy, as determined via the DFT+, at implant and randomization, was used for all trials at all follow-up visits, regardless of the results from previous trials. The efficacy of a low energy safety margin for the treatment of spontaneous ventricular tachyarrhythmias >200 bpm was also assessed. Patients in Phase 1 underwent a second randomization to have the first 2 shocks in the VF zone chronically programmed to either 2 steps above the DFT+ (low energy) or to maximal output (high energy). To increase the number of spontaneous arrhythmias evaluated, a second series of 244 patients (LESS Phase 2) was also randomized to chronic programming at either 2 steps above DFT+ or maximum output, but they did not undergo the serial testing of induced episodes. Therefore, the effect of programmed energy on spontaneous episodes was assessed in all 636 subjects, whereas the effect of energy on induced episodes was measured in 392 subjects.

Statistical Analysis

Continuous variables were expressed as mean±SD. Defibrillation conversion success rates were expressed as a percentage, and differences between randomized groups were determined with Fisher’s exact test. P<0.05 was considered statistically significant. The results of 3 prospectively defined end points are presented here.

End point 1 was an assessment of safety margin on induced VF conversion efficacy, which was determined by comparing the 0, 1, 2, and 3 steps above DFT+ groups to the 4 steps above DFT++ group. A minimum of 224 defibrillation/conversion trials in each of the 5 groups was calculated to assure an 80% power to detect a 4% reduction in defibrillation efficacy from an expected control rate of 99% using a one-sided test (based on data from the Low-Energy Endotak Trial [LEET] study15). Data from each of the 3 follow-up periods was pooled to achieve adequate power for this end point.

End point 2 was an evaluation of temporal changes in conversion efficacy, which were assessed by comparing the induced VF conversion data at 3 months and 12 months to that before discharge. To achieve the predetermined sample size of 285 episodes per group per time period (based on an 80% power to detect a 4% change with a 2-sided test), data from the 1 and 2 steps above DFT groups were pooled into a “low” safety margin group and data from the 3 and 4 steps above DFT++ groups were pooled into a “high” safety margin group. Data from the 0 safety margin group were not analyzed for this end point.

For end point 3, differences in spontaneous conversion efficacy were compared between patients programmed to 2 steps above DFT+ versus those programmed to maximum energy. Because the conversion success rates for spontaneous episodes were expected to be lower than those required to induce VF, a second sample size of 367 episodes per group was computed based on 80% power to detect a 4% reduction in conversion from an expected control rate of 97% (based on data from the LEET study15). Assuming an episode occurrence rate of 1.6 episodes per patient per 2-year follow-up period and an expected attrition rate of 15% per year, a minimum of 638 patients were required for enrollment.

Results

Patient Population

The population in this study was typical of patients undergoing ICD implantation. The 636 randomized patients were 78% male, with a mean age of 66±12 years. There was a history of coronary artery disease in 74% of patients, and 36% had undergone previous coronary artery bypass surgery. The mean left ventricular ejection fraction was 35±14%, and 69% of subjects had clinical congestive heart failure (New York Heart Association class II to IV). We used 337 (53%) single-chamber pulse generators and 299 (47%) dual-chamber pulse generators in this study.

As expected, patients frequently received antiarrhythmic drugs. At hospital discharge from implantation, 33% of subjects were receiving class I or III antiarrhythmic drugs, including amiodarone in 21%. At the 12-month follow-up visit, 31% of subjects were receiving antiarrhythmic drugs, including amiodarone in 20%. The use of amiodarone, sotalol, and β-blockers did not change significantly over the 3-year enrollment period of the trial.

Conversion Efficacy for Induced VF

The mean DFT for this cohort was 7.9±3.7 J, the DFT+ was 8.7±3.7 J, and the DFT++ was 9.1±3.8 J. Previously reported analyses demonstrated that DFTs were not influenced by the mode of induction,16 but male sex, lower ejection fraction, and use of amiodarone were each independently associated with higher DFTs.17 A summary of the
induced episode testing is presented in the Table. At the evaluation before discharge, 94.4% of VF inductions were terminated with either the first or second shock programmed to the DFT+ energy (ie, no safety margin). The proportion of successful trials increased with increasing safety margins such that the conversion efficacy was at least 99% at all energies 2 steps or greater than the DFT+.

The results of induced testing at the other time intervals are also shown in the Table. Combining the data from all 3 follow-up periods (last column), as prospectively defined by end point 1, confirmed the significant effect of programmed energy on defibrillation efficacy. Compared with the highest output group programmed to 4 steps above the DFT+, conversion efficacy was only significantly lower for shocks programmed at the DFT+ (P<0.0001) and those at 1 step above the DFT+ (P<0.01).

Although not shown in the Table, a second shock was needed for 16.2%, 6.4%, 3.6%, 2.2%, and 1.6% of episodes in the 0, 1, 2, 3, and 4 step groups, respectively. Only the 0 and 1 step groups had higher second shock usage than the 4 step group (P<0.0001 and P=0.0003, respectively). Further analysis demonstrated that shock failures were proportionally distributed across the range of DFT+ values (for example, 14% of failures occurred among patients with a DFT+ ≥17 J, which represents 16% of the population tested.) Higher DFT+ did not lead to a higher rate of failures during follow-up. Thus, a safety margin of 2 steps above DFT+ was adequate to achieve very high conversion success (96.4% after 1 shock and 99.1% after 2 shocks) among all patients throughout the study.

The data from the Table indicate that a small decrease in defibrillation efficacy at the 12-month follow-up may have occurred in some of the energy step groups. Pooling the data from 1 and 2 steps above DFT+ into a low safety margin group, as defined by end point 2, showed a small but statistically significant reduction in conversion success at 12 months (96.4%) compared with both the before discharge (99.0%, P=0.01) and 3 month (99.7%) follow-up periods. The data in the Table suggest that the group programmed to 1 step above DFT+ had a greater reduction in efficacy at 12 months. However, such a subanalysis is underpowered because of the low number of episodes at 12 months, and there was some overlap in the actual energy margins across groups because of the limitation of programmable shock energies.

To evaluate induced VF conversion efficacy in greater detail, further analysis was performed based on absolute energy above the DFT+. These results are shown in Figure 1. A slight reduction of defibrillation efficacy at 12 months...
was observed with safety margins of 0 J, and 1 to 3 J. The 4 to 6 J safety margin group showed no reduction in efficacy at 12 months. Of note, the decrease in conversion efficacy observed with a 7 to 9 J margin at 12 months is difficult to interpret because of the small number of episodes at this data point (n = 101). Finally, Figure 2 presents the conversion success of the first shock alone for safety margins defined in terms of absolute energy. Again, 4 to 6 J above DFT was adequate to maintain consistently high conversion success over the 12 months of follow-up, and higher safety margins, particularly those >10 J, did not offer any additional increase in first-shock conversion success.

Conversion Efficacy for Spontaneously Occurring Tachyarrhythmias
The efficacy of low-energy shocks to terminate spontaneously occurring rapid tachyarrhythmias was assessed by randomizing patients long-term to either the test group, in which the first 2 shocks were programmed at 2 steps above the DFT, or the control group, in which all shocks were programmed at maximal output. This resulted in a range of safety margins for the 2 groups because of the differences in DFT and programmable energies. The distributions of actual safety margins are shown in Figure 3. For the test group programmed at 2 steps above DFT++, the mean safety margin was 5.2 ± 1.1 J, whereas for the control group, the safety margin was 20.8 ± 4.2. Despite this 4-fold difference in safety margins, defibrillation efficacy was essentially identical (97.3% in both groups; P = 1.0), as shown in Figure 4. A second shock was needed for 9.2% of patients in the 2 steps above DFT++ group and in 8% of patients in the 31 J group (P = 0.78). It is noteworthy that in both groups, the ventricular arrhythmias of all “failed” episodes (n = 6) were successfully converted with subsequent shocks from the same therapy sequence, with no short- or long-term clinical sequelae.

Discussion
The major finding of this study is that a safety margin of 2 steps, or 4 to 6 J, above DFT++ is as safe and effective as larger safety margins for the treatment of either induced or spontaneous ventricular tachyarrhythmias. Moreover, efficacy is maintained over at least a 1-year follow-up period. The DFT was ≤17 J in almost 98% of patients, which is consistent with previous reports of the low defibrillation energy requirements with this lead system. In addition, the DFT++ was ≤17 J in ∼93% of patients, so that a pulse generator with a maximal output of 23 J could be safely implanted in these patients using this rigorous implant defibrillation testing algorithm.
Comparison With Previous Studies
Traditionally, a defibrillation safety margin of at least 10 J has been used as an acceptance criteria for ICD implantation. This margin was based on studies that showed failures of induced shocks and higher rates of sudden cardiac death in patients with lower safety margins. There are multiple reasons why a large safety margin may be necessary. First, defibrillation is a probabilistic function of energy. Singer and Lang reported that a step-down defibrillation “threshold” estimates the energy for ∼70% efficacy on average, but may have a range of ∼25% to 95% efficacy in a given patient. Data from the present study (Figure 2) showed that the more rigorous DFT++ estimates the energy for ∼85% success on average. Accordingly, an energy somewhat above the DFT is necessary to ensure consistently high conversion success in all patients, and the minimum energy margin necessary depends on the rigor of the testing (i.e., DFT requires more margin than DFT++). Second, defibrillation testing is performed on a sedated patient in the optimal physiological state, whereas spontaneous arrhythmias are frequently triggered by electrolyte imbalances, heart failure exacerbations, or ischemia. Higher energies may be needed to terminate arrhythmias in these situations. Finally, it was reported that DFTs increase over time with monophasic waveforms and nonthoracotomy lead systems. Therefore, an additional safety margin may be needed to compensate for long-term changes in defibrillation requirements. Fortunately, the long-term rise of DFTs is markedly attenuated or eliminated with modern lead systems.4–7 Therefore, any additional safety margin required for this study was designed to be conservative to allow for long-term changes in DFTs.4–7

Limitations
This study must be interpreted in the face of certain methodological limitations. Only dual-coil leads and a single biphasic waveform were used in this study, so the generality of these findings to other lead systems or waveforms is unknown. However, by using a uniform lead and waveform, any confounding influence of these factors was eliminated. In addition, the use of antiarrhythmic drugs was not controlled in this study. This was part of the study design to help conform more closely to clinical practice. Finally, the rigorous defibrillation testing protocol (DFT++) is not commonly employed clinically. Theoretical calculations indicate that such testing is likely necessary to ensure a high probability of conversion success with low-energy safety margins. Therefore, these results may not be directly applied to simpler implantation testing algorithms.

Clinical Implications
There are several important clinical implications from these results. First, using a rigorous implantation testing criteria (i.e., DFT++), a safety margin of 2 steps, or ∼4 to 6 J, is as effective as full-output shocks for terminating both induced and spontaneous episodes of ventricular tachyarrhythmias. Second, with a safety margin of at least 4 to 6 J above DFT++, defibrillation efficacy seems stable over at least the first year after implantation. Finally, reducing initial shock strength may prolong battery life, decrease the incidence of postshock arrhythmias, and reduce the incidence of hemodynamically mediated symptoms of arrhythmias, such as syncope or postepilepsy recovery, by decreasing charge time and thus the time to therapy.

Appendix
List of LESS Investigators
The following Principal investigators and institutions participated in the LESS Study. They are listed in order of the number of patients enrolled.

Steven Higgins: Scripps Memorial Hospital, La Jolla, Calif; Michael Gold: University of Maryland Medical System, Baltimore, Md; Richard Klein: University of Utah, Salt Lake City; Roosevelt Gilliam: Chippenham Medical Center, Richmond, Va; Harry Kopelman: Saint Joseph’s Hospital, Atlanta, Ga; Scott Hessen: Hahnemann/MCP, Philadelphia, Pa; John Payne: Baylor College of Medicine, Houston, Tex; Robert Bernstein: Sentara-Norfolk General Hospital, Norfolk, Va; Mark Estes: New England Medical Center, Boston, Mass; Adam Strickberger: University of Michigan, Ann Arbor; Lawrence Rosenthal: University of Massachusetts, Worcester; Hugh Calkins: Johns Hopkins, Baltimore, Md; Kenneth Ellenbogen: Medical College of Virginia, Richmond; Ted Friehling: Fairfax Hospital, Falls Church, Va; David Mann: University Hospital, Denver, Co; Francis Marchlinski: Hospital of the University of Pennsylvania, Philadelphia; Robert Rea: Mayo Clinic, Rochester, Minn; Christopher Fellows: Virginia Mason Medical Center, Seattle, Wash; Kent Volosin: Our Lady of Lourdes Medical Center, Camden, NJ; Koonlawee Nademanee: University of Southern California, Los Angeles; Marye Gleva: Washington University, St Louis, Mo; James McClelland: Sacred Heart Medical Center, Eugene, Ore; Mohammad-Reza Jazayeri: Bellin Memorial Hospital, Milwaukee, Wisc; Claudio Schuger: Henry Ford Hospital, Detroit, Mich; Barry Crevey: Methodist Hospital, Indianapolis, Ind; Michael Rome: Tacoma General Hospital, Tacoma, Wash; Robert Hoyt: Mercy Hospital Medical Center, Detroit, Mich; Joseph Souza: Memorial Mission Medical Center, Ashville, NC; Thomas Deering: Piedmont Hospital, Atlanta, Ga; Douglas E. Kopp: University of Chicago, Chicago, Ill; Jeffrey Rottman: Vanderbilt University, Nashville, Tenn; Gerry Tomassoni: Central Baptist Hospital, Lexington, Ky; Roland Filart: Orlando Regional Hospital, Orlando, Fla; Jasbir Sra: Saint Luke’s Medical Center, Milwaukee, Wisc; Fabio Leonelli: University of Kentucky, Lexington, Ky; Raul Weiss: University of Pittsburgh Medical Center, Pittsburgh, Pa; William Batsford: Yale-New Haven Medical Center, New Haven, Conn.

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