EDITORIAL COMMENT

Atrial Fibrillation or Sinus Rhythm?
Controversy and Contradiction in Quality of Life Outcomes*
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Attempts to improve quality of life by restoring sinus rhythm will usually be unsuccessful.
—The AFFIRM Trial Investigators (1)

Restoration and maintenance of sinus rhythm was associated with significant increases in a number of quality of life measurements.
—The SAFE-T Study Investigators (2)

Assessment of disease impact on quality of life can be measured by a number of scales, of which the most commonly used in cardiology is probably the generic health survey Short Form-36 (3). There have been several studies in which the effect of atrial fibrillation (AF) on quality of life has been measured, and patients with this arrhythmia, whether paroxysmal or persistent, are consistently found to have significant impairment on a number of aspects of physical and mental functioning (4). The impaired quality of life in AF is similar in magnitude to that found in patients who have had a myocardial infarction (5), and quality of life measures correlate poorly with the severity of underlying disease (6). This suggests that it is the arrhythmia rather than the associated pathology that causes the bulk of impairment. Rather surprisingly, even “asymptomatic” patients with AF have been found to have an impaired quality of life (7); perhaps this is related to the knowledge that they have a cardiac illness.

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Any therapy that improves quality of life must do so by improving some aspect of patient well-being. The SAFE-T (Sotalol Amiodarone Atrial Fibrillation Efficacy Trial) substudy reported in this issue of the Journal (2), demonstrated a modest improvement in treadmill exercise tolerance if sinus rhythm could be restored, a finding that confirms previous data from a number of smaller studies (8–12) and which was also noticed, to a modest degree, in the AFFIRM (Atrial Fibrillation Follow-Up Investigation of Rhythm Management) trial (13). The authors also report that restoration of sinus rhythm in patients with persistent AF was associated with an improvement in quality of life compared to those remaining in AF. This is particularly intriguing in light of recent studies showing that restoration of sinus rhythm in AF patients has no effect on mortality or on major physical end points, which therefore implies no benefit in attempted restoration of sinus rhythm if survival or complications alone is the reason for such therapy (14,15).

The cardiology community is no stranger to controversy and contradiction, and both abound in the management of AF. The SAFE-T study quality of life findings are similar to those reported from the Canadian Trial of Atrial Fibrillation (CTAF) (16), a drug efficacy study similar in design to the SAFE-T study (17). However, data from other studies, foremost among them the AFFIRM (14) and RACE (Rate Control Versus Electrical Cardioversion for Persistent Atrial Fibrillation) (15) studies, found no improvement in quality of life in a group undergoing attempted restoration of sinus rhythm compared with patients randomized to a strategy of heart rate control (1,18). When clinical trials come to opposing conclusions, particularly when such conclusions may have significant clinical impact, a careful evaluation is mandatory to determine whether these apparent contradictions can be reconciled and, if so, what is the likely lesson. This editorial will examine some of the arguments involved, concentrating on an analysis of the SAFE-T and AFFIRM trial conclusions.

The quality of life results in both the AFFIRM and SAFE-T trials were both based on a secondary analysis and thus their interpretation requires a degree of caution. However, both were prospectively planned and used similar (but not identical) well-validated quality of life instruments in a reasonable number of patients, rendering the results robust. The answer as to which conclusion is correct may therefore lie in differences in the trials themselves. The AFFIRM investigators required a much tighter rate control strategy than that required in the SAFE-T study, perhaps suggesting that poorer rate control might account for the difference in quality of life. However, this is an unlikely explanation, because analyses of the AFFIRM trial data based on quartiles of achieved heart rate in the AF arm showed no difference in any measured outcome, including quality of life (19).

The SAFE-T study was a drug efficacy study, comparing amiodarone and sotalol with placebo for the maintenance of sinus rhythm in patients who had persistent AF at the time of randomization. The AFFIRM trial recruited patients with either paroxysmal AF or persistent AF, and 52% of the AFFIRM trial patients randomized to rate control were actually in sinus rhythm at the time of randomization (20). Despite this mixture of rhythms, the AFFIRM trial analysis of quality of life was stratified by the assigned group (rate or rhythm control) regardless of the rhythm. Thus, one argument in favor of the SAFE-T study conclusions might be
that the failure of the AFFIRM trial to demonstrate improvement in quality of life with rhythm control reflected the high percentage of patients analyzed under the rubric of “rhythm control” who actually had AF at the time of evaluation and vice versa. In contrast to the AFFIRM trial, the SAFE-T study quality of life analysis stratified patients by the actual rhythm at the time of the questionnaire, which was administered at baseline and 1 month and 1 year into the study. The AFFIRM trial investigators briefly mention that reanalysis by actual rhythm also failed to demonstrate a benefit of sinus rhythm over AF, whereas the other major trial comparing rate with rhythm control, the RACE study, found that an ability to maintenance sinus rhythm was associated with an improvement in quality of life (18).

The AFFIRM and SAFE-T studies, therefore, looked at the question of quality of life in different ways and this may be the key to resolving the apparently contradictory conclusions, because both could be correct in their own way. One might reasonably conclude that assignation to a prospective strategy of AF management (sinus rhythm maintenance versus allowing AF to persist) does not offer a group benefit in quality of life of one strategy over the other. However, for the individual, if sinus rhythm can be achieved and maintained, it may offer a better quality of life than would exist if AF persists or returns. Because patient care is fundamentally about the individual and not the group, this resolution would seem to be an argument in favor of attempting to restore sinus rhythm in a patient with newly diagnosed AF. Unfortunately, this conclusion is probably oversimplistic. The AFFIRM trial quality of life analysis had the strength of being performed in previously randomized groups. In contrast, in the SAFE-T study restoration and maintenance of sinus rhythm was attempted in all patients, and when comparing outcomes the investigators were really comparing a group of patients that was successful in maintaining sinus rhythm with one that was unsuccessful. Thus, a host of undetermined factors other than the rhythm may have differentiated these groups and could account for the differences in quality of life and exercise outcomes in the SAFE-T study.

Let us, nevertheless, assume that the SAFE-T study does provide compelling evidence that sinus rhythm is associated with a better quality of life than persistent AF. Should we rethink the primary neutral conclusions of the AFFIRM trial and (re)adopt a more aggressive approach to pharmacologic maintenance of sinus rhythm? Or is there a downside to this approach? One very important factor to recognize, before adopting such a strategy, is the almost total absence of female patients in the SAFE-T study. Although this is understandable in a Veterans Administration study, men and women respond differently to AF. In the CTAf study, 41% of the participants were women, and their quality of life was significantly more impaired than men, despite comparable disease severity (21). A greater impairment of quality of life in women than men with AF was also found in the RACE trial, and this was not affected by the assigned treatment strategy (22). Furthermore, while the frequency of primary end points did not differ significantly between men and women when rate control and rhythm control strategies were analyzed together, when analyzed separately there was a statistically significant 3-fold higher incidence of end points in women in the rhythm control group compared with those randomized to rate control (22). This was driven primarily by a high incidence of side effects of antiarrhythmic drugs and a need for pacemaker implantation, and no such differences were seen in men. Although antiarrhythmic drug-induced bradycardia was the commonest side effect, torsades de pointes is commoner in women, and this is another reason for exercising caution if considering whether sinus rhythm should be restored in an attempt to improve quality of life.

Data from centers with an extensive experience in catheter-based therapies for AF suggest that nonpharmacologic therapy by ablation of fibrillation to maintain sinus rhythm results in significant improvement in quality of life (23,24). However, these techniques are still relatively new and highly operator dependent, and cardioversion with antiarrhythmic drug use remains, for now, the most common approach to restoration of sinus rhythm. Given this, should the results of the present SAFE-T study analysis cause the clinician to alter his or her approach to treating a patient with newly diagnosed AF? The answer can best be phrased in the words of the SAFE-T investigators in an earlier publication: “The quality of life data...tell us less about the advisability of the initial treatment strategies than about the functional consequences of the outcomes” (17). This is indeed true, but the results of the present analysis should reinforce the importance of incorporating knowledge from clinical trials into clinical practice while, at the same time, remembering that every patient, just like every trial, is different. And every patient (just like almost every trial) is worthy of careful thought before hasty conclusions are drawn about the value or futility of a particular management strategy.

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