EDITORIAL COMMENT
Lipid-Lowering Therapy for Prevention of Ventricular Tachyarrhythmias*
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In this issue of the Journal, Mitchell et al. (1) report that lipid-lowering therapy (LLT) was associated with a 36% relative risk reduction (RRR) in all-cause mortality in patients with ischemic heart disease (IHD) enrolled in the Antiarrhythmics Versus Implantable Defibrillator (AVID) trial. This rivals the benefit observed for implantable cardioverter defibrillators (ICDs) over amiodarone therapy (RRR 38%) (2) and is greater than the effect of LLT observed in patients with IHD in the Scandinavian Simvastatin Survival Study (4S) (RRR 30%) and in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial (RRR 22%) (3,4). This striking effect could be

dismissed for a number of reasons. The fact that LLT was not randomized and outcome assessment was not a pre-planned analysis raises the likelihood of a statistically significant association due to chance or selection bias. Another possibility is that the severity of disease and comorbid conditions in AVID trial patients magnified the mortality benefit of LLT. Moreover, any advantage of LLT could be considered moot because application of current guidelines for LLT mandate treatment of most if not all patients with IHD similar to those enrolled in the AVID study.

Although all-cause mortality is all-important, the finding that LLT has antiarrhythmic activity would make LLT distinctive if not unique among other available treatments. No conventional antiarrhythmic drug has been shown unequivocally to reduce mortality, with the possible exception of amiodarone, which has been shown to lower mortality modestly (RRR 13%) (5). Beta-blockers dramatically reduce all-cause and sudden death in heart failure and after myocardial infarction (MI) (5) but were not associated with a reduction in death or recurrent arrhythmia in patients treated with ICDs or amiodarone in the AVID trial (6).

An effective, safe, well-tolerated antiarrhythmic therapy could have substantial clinical impact. Implantable cardioverter defibrillators can prevent sudden cardiac death (SCD), but patients with recurrent ventricular tachyar-
because if LLT possesses an antiarrhythmic effect independent of ischemia, it might benefit patients with nonischemic arrhythmia mechanisms. At present, however, reduction of ischemia can be neither accepted nor excluded as the mechanism for the antiarrhythmic effects of LLT.

Increased sympathetic activity is likely to participate in the spontaneous initiation of sustained VTA in some patients prone to recurrent episodes (10). Sympathetic activity can stimulate several processes that can be arrhythmogenic including ischemia (16). Therefore, the report that LLT and improves autonomic function indicates another mechanism by which LLT could reduce VTA events (17).

Lipid-lowering therapy could exert antiarrhythmic effects by altering ionic currents across the myocyte cell membrane. Individual lipid-lowering drugs might interact directly with ion channel proteins by mechanisms similar to conventional antiarrhythmic drugs, but it is unlikely that the diverse group of drugs that have lipid-lowering properties would have a uniform effect on ion channel function. A more plausible possibility is that LLT alters channel protein function by changing the lipid environment of the cell or organelle membranes. It was once assumed that the bilayer phospholipid structure of membranes served only to separate and electrically insulate individual cells and organelles and to provide structural support for the membrane proteins that were responsible for the regulation of transmembrane functions. However, it was demonstrated several years ago that the phospholipid composition of membranes was not static but could change according to the dietary distribution of fatty acids. Moreover, it was shown that membrane functions can be perturbed by changes in dietary fatty acids (18). Alterations in protein channel function mediated by a change in cell membrane phospholipid composition has been proposed to be the mechanism by which n-3 (also called omega-3) polyunsaturated fatty acids (PUFA) reduce the risk of sudden death (19). Recently, for instance, Honen and Saint (20) showed that diets supplemented by lard, canola oil, or fish oil altered duration of calcium sparks in rat atrial myocytes. The investigators speculated that the change in calcium kinetics observed with the fish-oil diet reduces the propensity for the class of arrhythmias related to “calcium overload.” A credible antiarrhythmic effect should have a proarhythmic counterpart. In other words, if a change in membrane phospholipid composition can be antiarrhythmic, an opposing change should be proarrhythmic. This has been proposed as the mechanism by which trans-fatty acids increase the risk of primary cardiac arrest (21).

Recurrent VTA in patients with IHD are believed to result, in part, from remodeling associated with progressive electrophysiologic changes due to the formation of anatomic barriers, regions of slow conduction, and prolonged and heterogeneous repolarization. An MI often initiates the process, but inflammation, ischemia, neuroendocrine stimulation, and other factors continue for years. The importance of remodeling to the arrhythmogenic process in IHD is suggested by the long delay between MI and the first episode of VTA (5.7 years in the Electrophysiologic Study Versus Electrocardiographic Monitoring trial) (15). Inhibition of remodeling has been demonstrated for some lipid-lowering agents. Fluvastatin attenuated myocardial hypertrophy and fibrosis and reduced death due to heart failure and arrhythmias in a mouse model of MI (22). In a nonischemic model, simvastatin resulted in improvement of cardiac function in association with regression of hypertrophy and fibrosis in rabbits with hypertrophic cardiomyopathy (23). Probucol, a drug that lowers lipids by a mechanism different from that of pravastatin and simvastatin, inhibited remodeling and prevented worsening left ventricular function in a nonischemic canine model of remodeling and heart failure produced by rapid pacing (24). In each of these studies the observed effects on cardiac remodeling appeared to be independent of lipid-lowering.

Previous studies. Reduction in SCD is expected of any therapy that reduces the incidence and progression of IHD. The 4S investigators enrolled patients with IHD and high cholesterol levels and followed them for a mean of 5.4 years (3). Simvastatin treatment reduced all-cause and IHD mortality by 30% and 42%, respectively. Instantaneous deaths in the absence of confirmed MI were less common in the statin group than in the placebo group (29 vs. 39 patients) as were unwatched events (13 vs. 23). The only cardiac arrest occurred in a patient treated with simvastatin. Crude all-cause, IHD, and sudden (instantaneous) death rates (calculated from the tabulated data) were 11.5%, 8.5%, and 1.8% in the placebo group and 8.2%, 5.0%, and 1.3% in the simvastatin group, respectively. The point estimate of crude reduction in sudden death was 26%. A reduction of SCD that is proportional to the reduction in IHD deaths is anticipated for an intervention that affects SCD and non-sudden deaths equally. Instead, the effect of LLT on SCD was less than the effect on all IHD deaths (26% vs. 42%). A related observation is that the percentage of SCD with respect to IHD deaths was lower in the placebo group (21%) than in the simvastatin group (26%). The LIPID trial included patients with IHD and a broad range of cholesterol levels (4). A 24% RRR for IHD deaths was observed. The SCD mortality (defined differently than in 4S) in the LIPID trial was 4.7% (n = 211) in the placebo group and 4.0% in the treatment group (n = 182). This represents a crude reduction of SCD of only 14%. All-cause and IHD mortality in the placebo group was 14.1% (n = 633) and 8.3% (n = 373), respectively, and 11.0% (n = 498) and 6.4% (n = 287), respectively in the LTT group. As observed in the 4S, the percentage of SCD to all IHD deaths in the LIPID study was smaller in the placebo group (57%) than in the treatment group (63%). In contrast, the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico (GISSI)-Prevenzione investigators reported that dietary supplementation with n-3 PUFA reduced all-cause mortality by 20%, cardiovascular deaths by 30%, and SCD by 45% (25). Thus, although LLT clearly reduces SCD, the effect
does not appear to be selective. None of the major randomized trials of LLT have reported a statistically significant effect on VTA or SCD incidence, whereas the effects of n-3 PUFA appear relatively consistent (26). On the other hand, none of the trials of LLT had adequate statistical power to evaluate SCD as an end point. Therefore, the effect of LLT on SCD remains unresolved.

The absence of a preferential effect of LLT on primary prevention of SCD should not be overemphasized in the assessment of a possible salutary effect in patients with recurrent VTA. In a retrospective study of patients comparable to those enrolled in the AVID trial, De Sutter et al. (27) analyzed 78 patients with ICDs and IHD. Patients with VTA in the setting of acute MI were excluded, as were patients in whom VTA could not be induced at electrophysiologic study after revascularization. During a mean follow-up of 490 ± 319 days, the 27 patients receiving LLT demonstrated a lower incidence of VTA recurrence (22%) compared with controls (57%, p = 0.004). A multivariate analysis demonstrated that use of LLT was an independent predictor of freedom from VTA recurrence.

**Uncertainties.** The drugs used for LLT have different mechanisms of actions, potencies, and effects beyond lipid-lowering. In the study of Mitchell et al., LLT ascertainment was based on the response to a yes/no question on hospital discharge and follow-up forms. The agent administered for LLT was not known for the majority of patients. Detailed information from a sample of 237 patients (23% of the 1,016 enrolled AVID patients) showed that 26% of the patients received LLT, 79% of whom received statins, 19% fibric acid derivatives, and 3% bile acid resins. This raises the possibility that the observed beneficial effects were due to a single class of drugs (i.e., statins). De Sutter et al. (27), however, did not report a differential effect of statins (used in 59% of the LLT patients) compared with those receiving fibrates (41%).

The temporal relationship between the initiation of LLT and the outcome variables also raises challenging questions about the mechanisms. Only 20% of the LLT patients in the ICD group studied by Mitchell et al. were started within six months of the index hospitalization. The remaining 80% were receiving LLT before, during, and after the index VTA event. This pattern was also observed in the report of De Sutter et al. (27) in which 89% of the treated patients were receiving LLT at the time of presentation. Therefore, LLT did not prevent the index VTA event in either study. It is not known if LLT begun after the index VTA will provide the same protective effect. Neither study definitely supports nor excludes an immediate-type effect similar to conventional antiarrhythmic drugs, which are believed to exert their effects only in the presence of adequate concentrations at the effector sites. Conventional antiarrhythmic drugs may reduce the frequency of arrhythmia recurrence but rarely provide full protection (28). However, the observed temporal relationship is also compatible with a long-term effect. It is conceivable that LLT therapy exerted salutary effects months or years before the index event by inhibition of remodeling or improving myocardial perfusion. Although the index VTA was not prevented, it is possible that the frequency of subsequent events was reduced sufficiently to result in a favorable outcome in patients receiving LLT.

Lipid levels were not measured in the AVID trial so it is not possible to determine to what extent lipid-lowering was achieved and how levels were related to arrhythmia inhibition. A correlation between lipid lowering and the antiarrhythmic effects of LLT would not only strengthen the postulated relationship but also would help to delineate the mechanisms. In the study of De Sutter et al. (27), total cholesterol (TC) and low density lipid-cholesterol (LDL-C) were not significantly different between the LLT group and the non-LLT group at the time of index hospital discharge (TC in LLT group 192 ± 47 mg/dl, non-LLT group 215 ± 50 mg/dl, p = 0.119; LDL-C in LLT group 122 ± 47 mg/dl, non-LLT group 132 ± 37 mg/dl, p = 0.419) despite the fact that 89% of the LLT patients were already receiving LLT. Both TC and LDL-C levels rose significantly in both groups during the follow-up period (end of follow-up TC in the LLT group: 213 ± 25 mg/dl, p < 0.005; non-LLT group 257 ± 47 mg/dl, p < 0.01; end of follow-up LDL-C in the LLT group 139 ± 23 mg/dl, p < 0.016; non-LLT: 172 ± 40 mg/dl, p < 0.01 [p values refer to comparison of beginning and end of follow-up values]). Thus, the observed differences in VTA events occurred as lipid levels rose in both groups. The rise in the non-LLT group was greater than that in the LLT group so that cholesterol levels at the end of the observation period were significantly greater in the non-LLT patients for both total cholesterol (p = 0.004) and LDL-C (p = 0.015). It cannot be assumed that cholesterol levels responded differently in the AVID trial. These observations provide no reassurance that lipid-lowering was responsible for the beneficial effects of LLT in either investigation. On the other hand, measurement of cholesterol levels may not fully reflect alterations in the distribution of lipids during LLT. In addition, the observed antiarrhythmic effects of LLT may be unrelated to lipid lowering.

**Safety of LLT.** The patients studied by Mitchell et al. (1) had poor ventricular function (mean left ventricular ejection fraction 0.31), a high prevalence of congestive heart failure (45%), and several comorbid conditions, such as diabetes (26%) and chronic lung (16%) and renal (8%) disease. These characteristics distinguish the patients analyzed by Mitchell et al. from those in most LLT trials. Subjects were excluded from the 4S if they had an MI within six months, requirement for antiarrhythmic therapy, congestive heart failure, persistent atrial fibrillation, cardiomegaly, valvular heart disease, etc. (3). The LIPID trial excluded patients with MI within less than three months, “a clinically significant medical or surgical event within three months, cardiac failure, renal or hepatic disease” (4). Lipid-lowering therapy has an excellent safety record in trials of patients at low risk.
However, the safety of LLT in high-risk individuals has been challenged by a post hoc observational analysis of the Sibrafiban vs. Aspirin to Yield Maximum Protection From Ischemic Heart Events Post-acute Coronary Syndromes (SYMPHONY) trials. The analysis showed that LLT therapy in patients who presented with ACS with levels of cholesterol below treatment guidelines was associated with higher risks of death and MI (29). Moreover, many of the patients analyzed by Mitchell et al. (1) received amiodarone, which interacts with several lipid-lowering drugs and could exacerbate or inhibit electrophysiologic changes caused by LLT. Therefore, it is noteworthy that neither Mitchell et al. (1) nor De Sutter et al. (27) reported any adverse effects of LLT.

Conclusions. The study of Mitchell et al. raises the intriguing possibility that LLT inhibits VTA recurrence in patients with IHD and AVID trial enrollment criteria (i.e., patients who present with sustained VTA in association with cardiac arrest, syncope, or left ventricular ejection fraction of ≤0.40 and symptoms of hemodynamic compromise in the absence of a transient or reversible cause) (13). Because of its post hoc, nonrandomized design, the results must be considered preliminary. Additional research is needed to address the potential mechanisms of the antiarrhythmic effects and, in particular, the link between lipid-lowering and antiarrhythmic actions. Clinical trials are needed to verify the antiarrhythmic effects. However, trials will be complicated by existing guidelines that mandate LLT in most patients who would be candidates for investigation. However, current guidelines are not based on trial-based evidence for this population of patients in whom neither the safety nor benefit has been adequately evaluated. Furthermore, current guidelines specify lipid-lowering targets, whereas the antiarrhythmic benefits may be independent of this effect and could differ significantly among lipid-lowering agents. The Cholesterol Lowering and Arrhythmias Recurrences After Internal Defibrillator Implantation (CLARIDI) trial will evaluate the effect of atorvastatin versus placebo in patients with ICD, IHD, and normal or borderline cholesterol levels (30). Arrhythmia outcome variables should be evaluated in future trials of LLT that include patients at high risk for both atrial and ventricular arrhythmias (23). In this regard, the study of Mitchell et al. has not only raised the level of awareness of this important potential benefit of LLT but also has provided important reassurance that LLT is safe in this population of patients with severely depressed myocardial function and numerous comorbid conditions.

References


