Journal of the American College of Cardiology
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Published by Elsevier Science Inc.

Vol. 36, No. 3, 2000
ISSN 0735-1097/00/$20.00
PII S0735-1097(00)00806-8

EDITORIAL COMMENT

Prevention of Recurrent Life-Threatening Arrhythmias: Will Lipid-Lowering Therapy Make a Difference?*

Stefan H. Hohnloser, MD, FACC, FESC
Frankfurt, Germany

There is a strong, positive, independent, continuous, graded relation between hypercholesterolemia and the risk for coronary heart disease (CAD). In clinical trials, it has been shown that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors or statins inhibit HMG-CoA reductase competitively, reduce LDL levels more than other cholesterol-lowering drugs and lower triglyceride levels in hypertriglyceridemic patients (1,2). Prospective, controlled trials have demonstrated beyond doubt that statins reduce the relative risk of major coronary events by ~30%. This has been shown in trials involving patients with and without CAD and with and without hypercholesterolemia (3–7). Accordingly, lipid lowering by means of statin therapy is now widely applied in clinical practice.

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Coronary artery disease is the underlying structural heart disease in >80% of victims of life-threatening ventricular tachyarrhythmias such as syncopal ventricular tachycardia (VT) or ventricular fibrillation (VF) (8). Therefore, one could speculate that treatment of hypercholesterolemia would result not only in a reduction of major ischemic events, but ultimately also in a reduction of arrhythmic episodes in high risk patients with coronary disease. Unfortunately, at present, this hypothesis has not been proven beyond doubt in the large primary and secondary prevention trials (3–7). However, two secondary prevention trials have provided some evidence in support of this hypothesis. In the Scandinavian Simvastatin Survival Study (4S) (3), the primary study end point was total mortality. However, data on instantaneous death and death within 1 h—both most likely due to VT or VF—are provided; in the placebo group, this accounted for 63 of 189 coronary deaths, as compared with 37 of 111 coronary deaths in the simvastatin group. This reduction in presumably arrhythmic death was comparable to the reduction of death due to definite acute myocardial infarction (63 vs. 30 deaths). The level of significance, however, for instantaneous death alone was not provided (3). The second trial providing at least some evidence for this hypothesis is the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study (5). This trial used death from coronary heart disease as its primary end point (5). Among the 4,502 patients in the placebo group, 211 deaths were classified by the Events Committee as sudden death, as compared with 182 such deaths in the 4,512 pravastatin-treated patients. Again, no separate statistical analysis of this mode of death was reported, but this observation supports a beneficial effect of statins on the incidence of arrhythmia-related death in patients with coronary events.

Mechanisms of statin-associated benefits in CAD. An important observation made in secondary and primary prevention trials was that the statin-associated beneficial effects occurred relatively early. Accordingly, retardation of plaque development due to cholesterol lowering could not be the sole reason for the beneficial treatment effects. It is now well appreciated that statins have beneficial effects above and beyond their hypercholesterolemia-lowering capability (1,2). For instance, statins improve endothelial function (9–11) by lowering cholesterol levels and thereby reducing oxidative stress within the vascular wall (12,13). However, statins also have direct effects on vascular biology—independent of their lipid-lowering properties—such as activation of the atheroprotective enzyme nitric oxidase synthase (14), and probably they influence the mevalonate pathway (15). Thus, in addition to reducing oxidative stress, statins counteract the inflammatory process in atherosclerotic plaques and interfere with vascular wall proliferation processes (1,2,16). Accordingly, besides reducing the lipid pool within the plaque, cholesterol lowering with statins may help to stabilize the atherosclerotic plaque and prevent cardiovascular events. Hypercholesterolemia is also associated with hypercoagulability and enhanced platelet reactivity at sites of acute vascular damage (2). There is accumulating evidence that statins may favorably affect thrombus formation, erythrocyte deformability and levels of plasminogen activator inhibitor-1 and fibrinogen (1,2). It has been suggested that the last three effects associated with statin therapy improve hemorheologic characteristics early in the course of therapy (2). In accordance with this hypothesis, both lovastatin and pravastatin significantly reduce the frequency and intensity of ischemic episodes detected by Holter monitoring after as little as 16 weeks of therapy (17,18).

Lipid-lowering therapy and ventricular tachyarrhythmias. In this issue of the *Journal*, De Sutter et al. (19) report their results of 78 patients with CAD and a history of life-threatening arrhythmias. All of these patients were fitted with an implantable cardioverter defibrillator (ICD), a therapy that has been shown to be superior to antiarrhythmic drug therapy for prevention of recurrent sudden death

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Division of Cardiology, J. W. Goethe University, Frankfurt, Germany.

JACC Vol. 36, No. 3, 2000
September 2000:773–5

(20–22). Twenty-seven of these patients were receiving lipid-lowering therapy, and 51 were not. After an average follow-up period of 490 days, device activation occurred significantly more often in patients without versus with lipid-lowering therapy. In fact, absence of lipid-lowering therapy was independently associated with recurrent VT or VF on multivariate analysis, even after correcting for other treatment imbalances, particularly the use of antiadrenergic therapy. Although the results of this study appear to support the aforementioned benefits of lipid-lowering treatments, some words of caution are appropriate.

The major limitations of this study are its retrospective, observational design and the relatively small patient group, as stated by the authors. Accordingly, a finding by chance is considerable. Moreover, there are some imbalances regarding pharmacologic therapy of both patient groups, aside from the use of lipid-lowering agents. Beta-blockers were administered in 65% of patients without subsequent ICD interventions, as compared with only 34% of those with device therapy during follow-up ($p = 0.012$). Beta-blockers are well known to suppress life-threatening arrhythmias (23). Accordingly, this is of concern despite the fact that subgroup analysis of individuals on beta-blockers (yielding very small sample sizes) indicates that lipid-lowering drugs continued to be associated with fewer ICD activations.

Only one of the three secondary ICD prevention trials has reported data on the use of lipid-lowering therapy (24). In the Antiarrhythmics Versus Implantable Defibrillators trial (AVID), 132 of 1,016 patients received such treatment. In contrast to the results of the present study (19), there was no difference regarding the primary study end point of total mortality between patients with and without lipid-lowering drugs (24). This finding was consistent in patients treated with the ICD or antiarrhythmic drug therapy.

Myocardial ischemia and sudden death due to VT or VF. It is tempting to speculate on the mechanism(s) by which lipid-lowering therapy could influence the likelihood of recurrent VT or VF in high risk patients. At least 80% of patients who experience sudden death have coronary disease as the underlying anatomic substrate (8). Autopsy studies have found recent occlusive coronary thrombus in 15% to 64% of victims of sudden cardiac death (8,25). Accordingly, sudden cardiac death may be divided into instantaneous death that appears to be caused by primary arrhythmic events, and death occurring several hours after the onset of symptoms that are thought to be related to arrhythmias that arose in the setting of acute myocardial ischemia or infarction (26). The hearts of victims of instantaneous death had fewer coronary lesions but more extensive scarring and old coronary artery occlusions as compared with the hearts of those who did not die instantaneously (26). In patients without a history of heart disease, acute myocardial ischemia may be more often responsible for sudden death. Alternatively, in patients with impaired left ventricular function and scars from a previous infarction, acute ischemia is usually less important. Of note, the patients enrolled in the study of De Sutter et al. (19) had markedly reduced left ventricular ejection fractions, indicating that they may belong to the latter group of sudden death victims. This is in accordance with other recent findings, for instance, those reported by the AVID investigators (24). In the AVID study, the causes of death in 1,016 patients enrolled in this secondary prevention trial were analyzed. It was found that only 4 of 79 arrhythmic deaths were associated with markers of ischemia (24). The authors therefore concluded that the majority of events were unrelated to measurable ischemia. This notion is supported by numerous previous small trials (27,28). Accordingly, in the context of the potential benefits of lipid-lowering therapy for reduction of arrhythmic events, it is reasonable to assume that the potential antiarrhythmic effects of statins should be linked to their ability to reduce the ischemic burden of the myocardium, but there is much less reason why these agents should act on the arrhythmic substrate.

Clinical implications. There is sound evidence that lipid-lowering therapy, particularly statins, reduce cardiovascular mortality and morbidity in patients with CAD. That statins exert part of this beneficial effect by reducing the likelihood of arrhythmia-related sudden cardiac death is a tempting hypothesis that has not been proven yet. The study of De Sutter et al. (19) should trigger further careful examination of this hypothesis. Their conclusion that prospective, well-designed, randomized trials are needed to confirm this hypothesis is valid. Such trials would also be potentially helpful in defining the role of acute myocardial ischemia as a trigger for sudden cardiac death in more detail. Apart from this, survivors of VT or VF need to be carefully and repeatedly screened for hypercholesterolemia to promptly institute statin therapy where appropriate.

Acknowledgments

I express my gratitude to Volker Schächinger, MD, for his careful review of the manuscript, and to Sabine Zach-Lampson for her editorial assistance.

Reprint requests and correspondence: Dr. Stefan H. Hohnloser, Department of Medicine, Division of Cardiology, J. W. Goethe University, Theodor Stern Kai 7, 60590 Frankfurt, Germany. E-mail: hohnloser@em.uni-frankfurt.de.

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