Threats, opportunities, and statins in the modern management of heart failure

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This editorial refers to ‘Prognostic significance of serum cholesterol levels in patients with idiopathic dilated cardiomyopathy’† by M. Christ et al., on page 691

Effective management of heart failure is becoming increasingly complex. Polytherapy, both pharmacological and device-based, should now be the standard practice for the management of most patients with heart failure.1 This requires considerable medical expertise, training, and organization of care. Unfortunately, although heart failure is a highly malignant and treatable condition, its management is poorly resourced and organized compared with cancer.2,3

Further developments in the provision of care for patients with heart failure carry threats and opportunities. One important threat is that the complex polypharmacy could lead to more confusion, more adverse drug effects, and more drug interactions. For instance, even though spironolactone has been shown to be effective in clinical trials, and to save lives, its use without proper monitoring may increase mortality. Another threat is the perception among some health care providers and research sponsors that new treatments are unlikely to improve much on the existing therapy for heart failure. Despite the success of properly managed treatment, the prognosis of heart failure remains poor. Twenty years ago, the 2-year mortality of heart failure with relatively mild symptoms was about 35% and for patients with relatively severe symptoms about 70%.1 Modern treatment has reduced these figures, respectively, to about 10 and 20% (Figure 1A–C).

The success of treatment so far is only partial. Further progress could take at least three forms. First, new treatments may be identified to add to the effect of existing ones. Secondly, treatments that are harmful or redundant should be removed from clinical practice. Thirdly, new, more effective treatments might replace one or more components of the existing therapy. In terms of life-saving advances in cardiology, restriction of the use of class I antiarrhythmic drugs is one of the greatest. Treatments inherited from our predecessors may not be safe or effective in modern practice. For example, aspirin reduces the benefits of ACE-inhibitors and possibly beta-blockers in patients with heart failure, and increases the risk of heart failure hospitalization by about a third but, despite the evidence, is still widely used.4

Many patients with heart failure, especially those with coronary disease, are prescribed statins although there is no evidence that they are either safe or effective in this setting. Many physicians argue that statins could not be harmful, and must surely be beneficial in patients with heart failure because of coronary disease. Coronary artery disease is common in patients with heart failure, but treatments including aspirin4 and revascularization,5 directed at this target have yet to be shown to be safe and effective. Statins reduce vascular events in the setting of both primary and secondary prevention, but have not been shown to be effective for tertiary prevention (that is, in heart failure).6 The relative benefits of statin therapy are substantial (about a 35% reduction in major cardiovascular events) but the absolute gain, <1% per year for mortality and 1–2% per year for morbidity, is modest. Older patients at greater risk of heart failure may derive less benefit, and statins do not seem to prevent the development of heart failure in this population. Randomized controlled trials are required to determine whether the relative or absolute gains observed in other settings apply in heart failure. Given the high rate of events in patients with heart failure there is an opportunity for statins to provide benefit but there is also the risk that a small benefit will be swamped by other factors driving the natural history of the disease, leading to a neutral outcome. Statins could also have an adverse effect on outcome in heart failure.

One important factor that may confuse those without expert knowledge of heart failure is the change in the relationship between cardiovascular risk factors and outcome once heart failure develops. Patients with at least moderately increased blood pressure, raised cholesterol, and who are overweight live longer than patients who have a low-normal blood pressure, low cholesterol or who are below ideal weight.7 This may reflect the fact that blood pressure, cholesterol, and weight decline as heart failure progresses and hence they become the markers of more severe disease. If this is true, then it may still be useful to reduce elevated blood pressure, cholesterol, and weight. However, it is also possible that each of
these 'markers' is part of the mechanism of progression of heart failure, in which case treatment may accelerate the decline.

It is possible that high cholesterol accelerates the development of atheroma but protects the failing myocardium and vascular endothelium. This complex situation can be simplified by studying the relationship between outcome and cholesterol and the effects of statins in patients without overt evidence of atheroma. Christ et al. provide valuable information in this respect for patients with dilated cardiomyopathy, a group of patients who should have a low burden of atheroma and in whom there is no good theoretical or clinical evidence, as yet, that hyperlipidaemia or statin therapy contributes to the progression of disease. They demonstrate that patients with higher serum cholesterol have a slightly better prognosis, as has been shown for other groups of patients with heart failure, but showed that this could be entirely explained by the severity of heart failure. However, the small subgroup of patients on statins had a markedly better prognosis and there was an independent relationship between statin therapy and improved outcome. Small randomized

![Figure 1](A–C) Summary of the effects of pharmacological and device therapy on all-cause 2-year mortality.5
controlled trials also suggest that statins may improve left ventricular function, endothelial dysfunction, and haemostasis in patients with dilated cardiomyopathy. However, these data constitute insufficient evidence to prove that statins are either safe or effective for patients with heart failure. Statins also reduce the endogenous production of the powerful anti-oxidant co-enzyme Q-10. At this time, there is far more evidence to justify the prescription of co-enzyme Q-10 than a statin to patients with heart failure.8

Other pharmaco-epidemiological studies also suggest that statins may improve survival in patients with heart failure. This sort of analysis has been misleading in the past and cannot reliably distinguish between the effect of treatment, of the care-giver, or of the reason for the prescription. Also, analyses failing to show benefit are much less likely to be reported leading to publication bias. Properly designed and executed randomized controlled trials are required, such as GISSI-CHF6 and CORONA.9

However, most treatments investigated for heart failure are not found to reduce morbidity or mortality. Neutral treatments should also be considered harmful for several reasons. Patients will still be exposed to adverse effects and drug interactions. Patients taking multiple medications are likely to have lower adherence to therapy and failure to take life-saving therapy as directed puts the patients at risk. Finally, doctors who prescribe treatments not shown to be effective may, perversely, be less likely to prescribe effective ones to avoid polypharmacy. Therefore, neutral therapies have hidden harm.

In summary, epidemiological studies can provide a rationale for doing a randomized controlled trial but should not be used as proof that a treatment is effective. Once a treatment has been shown to be effective, epidemiological studies become useful in estimating the size of effect that treatment should have in clinical practice.

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References