# Lipid-Modifying Treatments for Heart Failure: Is Their Use Justified?

John G.F. Cleland, MD, PhD, FRCP, FESC[a,*],
Kate Hutchinson, MBChB[b], Pierpaolo Pellicori, MD[b],
Andrew Clark, MD, MA, FRCP[b]

**KEYWORDS**

• Fibrates • Polyunsaturated fatty acids • Statins • Heart failure

**KEY POINTS**

- Most patients with heart failure have atherosclerotic disease either as a cause of ventricular dysfunction or as a concomitant problem.
- Sudden death may be the most common presentation of myocardial infarction amongst patients with heart failure.
- Meta-analyses of trials of fibrates in cardiovascular disease identified no reduction in all-cause or cardiovascular mortality or heart failure events; there are no large trials of fibrates in patients with heart failure, but what evidence exists suggests no benefit.
- Meta-analyses of trials of polyunsaturated fatty acids in cardiovascular disease failed to show an effect on all-cause mortality but did suggest a small reduction in cardiac deaths (9% reduction in relative risk). There is equivocal evidence of benefit in patients with heart failure.
- Meta-analysis shows that statins reduce all-cause and cardiovascular mortality and heart failure events in patients with or at high risk of cardiovascular disease.

## INTRODUCTION

There are theoretical arguments for and against lipid-modifying therapy for patients with heart failure but little conclusive clinical evidence that it provides substantial benefit or causes significant harm. However, one of the curses of modern therapeutics is polypharmacy. In a bygone era, the pharmacopoeia consisted of agents that were safe and ineffective (placebo) and those that might be effective but with varying degrees of toxicity. Placebo does not prevent spontaneous recovery and may have psychological benefits and therefore often appears effective. The low benefit/risk ratio of interventions in this era gave rise to the old adage, "primum non nocere." Now that we have many more medicines, many of which are safe and effective, primum non nocere is no longer a tenable position, at least for serious diseases such as heart failure that rarely remit, because medicine practiced in this way is, paradoxically, quite likely to cause harm. A patient given too

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[a] National Heart & Lung Institute, Royal Brompton & Harefield Hospitals, Imperial College, London UB9 6JH, UK;
[b] Department of Cardiology, Hull York Medical School, Castle Hill Hospital, Kingston-upon-Hull HU6 5JQ, UK
* Corresponding author. Department of Cardiology, Harefield Hospital, Imperial College, Hill End Road, Harfield, Middlesex UB9 6JH, UK.
*E-mail address:* j.cleland@imperial.ac.uk

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many medicines is likely not to take them all and may experience drug interactions. When faced with a plethora of choices, the motto of modern medicine for serious disease is "primum efficatum." Once an agent is shown to be effective, the penalty in terms of side effects, risk, and harm can be weighed. Of course, the power of placebo and concept of primum non nocere might still apply when the disease is likely to resolve spontaneously or causes little disability or when no effective treatments exist. Some medical disciplines are contaminated by agents upon which the medical community wastes huge amounts of money, for example, aspirin for long-term prophylaxis of cardiovascular disease,[1,2] most hypoglycemic agents for type-2 diabetes,[3] and vitamin and mineral supplements for osteoporosis.[4] The purpose of this report is to explore these issues with respect to lipid-modifying agents in patients with heart failure.

Most patients with heart failure have atherosclerosis, which is often the primary cause of their heart failure. Progression of atherosclerosis, which may impair blood flow to heart, brain, kidney, and skeletal muscle, and plaque rupture, leading to acute coronary and cerebrovascular syndromes, could be important pathways for the progression of heart failure, morbidity, and death.[5] Stabilizing plaque either by reducing its cholesterol content or by reducing inflammatory activity could reduce acute vascular events. Causing plaque to regress could reduce ischemia. Hyperlipidemia can also impair microvascular function that can be improved by lipid-lowering therapies.[6] Some authorities believe that all patients with heart failure due to left ventricular systolic dysfunction, regardless of its etiology, have myocardial ischemia, caused by epicardial coronary artery disease, microvascular dysfunction, elevated ventricular filling pressures, or potentially all three.[7]

Fatty acids are an important energy substrate for the myocardium but may be less efficient than glucose and lactate and may increase proton production, lowering cellular pH and impairing cell function. Diverting the myocardial energy substrate from lipids to carbohydrates might be beneficial.[8] Theoretically, lipid lowering might have beneficial effects on myocardial function. Lipid-modifying therapies may also have ancillary effects on inflammatory systems that might also improve myocardial function, encourage repair, reduce fibrosis, and increase electrical stability. However, higher plasma concentrations of arachidonic acid and some long-chain fatty acids, such as docosahexaenoic acid are associated with a lower incidence of heart failure.[9,10]

On the other hand, cholesterol decreases as heart failure progresses and a low cholesterol level is a bad prognostic sign in heart failure. This decrease may just reflect the metabolic stress of a patient who is in the process of dying from heart failure, but there is some concern that circulating lipid fractions may bind endotoxins absorbed from the gut.[11] Lowering cholesterol might impair this natural defense mechanism, cause cytokine activation, increase inflammation, and accelerate the progression of heart failure.[12] Moreover, statins can interfere with the synthesis of coenzyme Q10, an essential component of the mitochondrial respiratory chain.[13] Recent evidence suggests that coenzyme Q10 supplements may have a beneficial effect on prognosis in patients with heart failure.[14]

Lowering cholesterol might be both beneficial and harmful; in some patients the benefit will outweigh the harm; in others, harm and benefit will be similar, and the patient will derive no benefit. In some, harm may outweigh benefit. This article focuses on treatments designed to modify lipids; fibrates, statins and omega-3 fatty acids.

## FIBRATES

There are no substantial randomized, controlled trials of fibrates in patients with heart failure. Node and colleagues[15] investigated the effects of bezafibrate on amino-terminal probrain natriuretic peptide (NT-proBNP) in 108 patients with New York Heart Association (NYHA) class III heart failure enrolled in the Bezafibrate Infarction Prevention study, a study of secondary prevention after a myocardial infarction. After 2 years of follow-up, plasma concentrations of NT-proBNP were similar in patients assigned to bezafibrate or placebo. In the overall population (with or without heart failure), the study was neutral.

Both the Veterans Affairs study of gemfibrozil[16] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) of fenofibrate[17] suggested fewer heart failure events in the actively managed group but no effect on all-cause or cardiovascular mortality. A meta-analysis of more than 45,000 patients in randomized, controlled trials of fibrates for the primary or secondary prevention of cardiovascular disease suggested no effect on all-cause or cardiovascular mortality or heart failure outcomes but a substantial effect on microvascular complications such as retinopathy among diabetic patients.[18]

There is little evidence to support the use of fibrates in patients with heart failure and insufficient trial evidence to confirm that they are either ineffective or safe.