REVIEW

Statins and clinical outcomes in heart failure

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ABSTRACT

HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors (statins) are well-established therapies in the prevention and treatment of cardiovascular disease, reducing all-cause mortality and cardiovascular events in many disease states. Studies have also suggested that statins given to patients after myocardial infarction improve event-free survival even in short time frames; however, evidence for the benefit of statins in established HF (heart failure) has not been demonstrated with the same rigour of a randomized clinical trial setting. In fact, clinical data examining the effect of statins in HF have been limited by the retrospective or observational nature of these analyses, examination of incompletely validated surrogate end points, small prospective studies in subgroups of HF subjects, and non-uniform doses and different statins being used. In this review, we examine the evidence for the effect of statins on mortality in HF, taking into account theoretical arguments, appropriateness of surrogate markers, animal data and analysis of the predominantly retrospective clinical data that is currently available.

INTRODUCTION

HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors (statins) are well-established therapies in the prevention and treatment of atherosclerotic cardiovascular disease and diabetes [1,2]. These agents reduce all-cause mortality and cardiovascular events in patients with stable coronary artery disease when given over a period of 5 years. Retrospective and observational studies have also suggested that statins given to patients after MI (myocardial infarction) improves event-free survival over a shorter period [3–5]. In addition, these agents have been shown to reduce mortality in a number of other settings, including post-PCI (percutaneous coronary intervention), post-carotid endarterectomy, sepsis and in haemodialysis subjects [6–8].

However, evidence for their benefit in the setting of established HF (heart failure) has not been demonstrated with the same level of clinical trial data, exacerbated by the fact that patients with HF have been systematically excluded from most large cardiovascular outcome studies of statins. In addition, subsequent clinical data examining the effect of statins in HF have been limited by the retrospective nature of these analyses, examination of incompletely validated surrogate end points, small prospective studies in subgroups of HF subjects, and non-uniform doses and different statins being used. Although there are a number of other reviews of statins in this condition [9–13], none of these have been able to elucidate whether the difference in effect is related to dose, potency, lipophilicity or an as yet unmeasured effect (e.g. degree of inhibition of protein prenylation). In this review, we examine the evidence for the effect of statins on mortality in HF, taking into account theoretical arguments, appropriateness of surrogate markers, animal data and analysis of the small amount of clinical data that

Key words: clinical trial, heart failure, 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), infarction, mortality, remodelling, statin.

Abbreviations: AngII, angiotensin II; CI, confidence interval; EF, ejection fraction; HF, heart failure; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HR, hazards ratio; LDL, low-density lipoprotein; LPS, lipopolysaccharide; LV, left ventricular; MI, myocardial infarction; NF-κB, nuclear factor κB; NOS, nitric oxide synthase; PCI, percutaneous coronary intervention; UNIVERSE, RosUvastatin Impact on VEntricular Remodeling, LipidS, and CytokinEs; Val-HeFT, Valsartan HF Trial.

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is currently available. We await results of large prospective randomized studies on HF that are appropriately powered to assess the impact of statins on mortality.

THEORETICAL CONSIDERATIONS

Although there is now well-validated data regarding statins in the treatment of patients with and at high risk of coronary heart disease, there remains a dearth of knowledge about whether these data extend to treatment of HF patients. In general we still do not know whether it is (i) safe and (ii) beneficial to commence and continue statins in subjects who have HF. Specifically, it would be clinically helpful to know if there is a difference in treatment efficacy, depending on HF aetiology, and to have guidance on dose relativity for each statin. Can we rely on surrogates that are useful in cardiovascular disease, such as LDL (low-density lipoprotein), to guide therapy, or do we use surrogates of cardiac remodelling, a known pathophysiological process in HF, in making these decisions? These are all important questions, some of which may be answered by prospective randomized studies, but some of which may not.

POTENTIAL ADVERSE EFFECTS FROM STATINS

Lowering cholesterol with statins compared with innately low cholesterol

A clear distinction needs to be made with respect to the adverse effects of lowering cholesterol itself and lowering cholesterol with statins. Regarding the former, the ‘lipoprotein-endotoxin theory’ described by Rachhaus et al. [14] suggests that higher concentrations of total cholesterol are beneficial in patients with chronic HF who have increased pro-inflammatory cytokine activation, possibly related to LPS (lipopolysaccharide) ‘leaking’ from the gut wall. Circulating lipoproteins ‘mop’ up the pro-inflammatory cytokines as well as LPS, both of which are likely to play an important role in the pathophysiological processes underlying HF. Lowering lipoprotein fractions may thus lead to increased pro-inflammatory cytokine and LPS concentrations, effects which are known to be detrimental to cardiac function in the HF setting.

In addition, there is some co-relational evidence that high cholesterol levels are beneficial in many disease states, even when coronary artery disease co-exists. For example, in a re-analysis of the Framingham data, Kronmal [15] has shown that the association between cholesterol and mortality was negative over the age of 80, an age when over 20 % of the population may have HF [16]. Similarly cholesterol has been shown to be inversely related to hospital mortality in patients that are acutely ill [17], regardless of malnutrition and other comorbidities. Importantly in HF, higher cholesterol levels have been associated with reduced mortality, regardless of the underlying cause of the HF [18]. For example, taking a baseline cholesterol of 4.9 mmol/l, this relationship demonstrates a reduced survival for each 25 % further reduction in total cholesterol. Care is important when interpreting these data as not only is it observational and post hoc, but more importantly it does not eliminate the possibility that low cholesterol (and low LDL) may be a marker for more severe HF or other confounders, such as cardiac cachexia and cytokine activation [19]. Somewhat confusingly, a recent retrospective study in 24598 adults with HF has shown that there is an association between initiation of statin therapy and risks of death and hospitalization even after adjustment for cholesterol level [20]. Additionally, the point regarding whether there is a difference in outcome from innately low LDL compared with the outcome in lowering LDL from a statin has still not been addressed.

This point becomes important when the data for dose and potency of statin and effect on cardiac remodelling and mortality are considered.

Lowering ubiquinone

The ‘ubiquinone (coenzyme Q10) hypothesis’ also raises concerns over the lowering of cholesterol in HF (see Figure 1 for an explanation of the cholesterol pathway). As mevalonate concentrations fall with inhibition of HMG-CoA reductase, decreases in ubiquinone concentrations occur. Ubiquinone plays an important
antioxidant and membrane-stabilizing role and is also involved in mitochondrial functioning, important for high ATP-utilizing tissues such as the heart. Similarly, a decrease in mevalonate reduces selenoprotein concentrations that are necessary for cell transcription and repair, processes important in cardiac cell functioning.

Other adverse effects
Lastly, there is a large body of knowledge on the adverse effects of statins, effects that were not well demonstrated in the large statin studies due to the relatively young age and absence of comorbidities in these subjects. Regulatory authorities are now aware of the role of dose and concentration on myopathy, an effect which is known to effect the skeletal muscle because of its ease of access to clinical examination and biopsy, but which is possibly just as likely to effect cardiac muscle. Various theories have been proposed to explain the relationship between cholesterol lowering and myopathy, most referring to the reduction in cholesterol concentration and altered membrane potential in the phospholipid bilayer of the muscle cell ([21], but see [21a], [22]).

POTENTIAL BENEFICIAL EFFECTS

General
There are many potential and well-documented mechanisms underlying the beneficial effects of statins on clinical outcomes. Most of these are associated with the effect of statins on remodelling and arrhythmia, both surrogates for mortality in HF [23]. For example, HF is associated with autonomic dysfunction, which in turn is related to HF severity and increased mortality [24] and which has been attenuated with statins [25–27]. In states of abnormal cardiac remodelling, such as post-MI, statins have additional beneficial effects [28], via a number of mechanisms, including inhibition of extracellular matrix deposition [29], anticytokine actions [30], mobilization of endothelial progenitor cells [31] and interactions with the renin–angiotensin system [32]. More specifically, statins are known to directly inhibit AngII (angiotensin II)-induced cardiac myocyte hypertrophy [33,34] and prevent apoptosis of cardiomyocytes [35], a potential cause of HF [36]. Statins up-regulate eNOS [endothelial NOS (nitric oxide synthase)] expression [37–39], stimulate endothelial NO production [40] and increase the supply of the NO substrate l-arginine [41], important in cardiac function. In an animal study using MRI (magnetic resonance imaging) post-MI to assess remodelling, the effect of cerivastatin on attenuating hypertrophy after MI was completely abrogated by NOS inhibition [42]. Statins are also known to inhibit MAPK (mitogen-activated protein kinase) [43], and to interfere with cellular proliferation [44,45], the integrity of the actin cytoskeleton [46] and the induction of matrix proteins [47], all important in the development of HF [48–50].

Fibrosis
The antifibrotic effects of statins are likely to be very important in the beneficial effects on mortality post-MI. CTGF (connective tissue growth factor; also known as CCN2) is a profibrotic inducer of matrix proteins [51] activated by the profibrotic factors TGF-β (transforming growth factor-β) and AngII [52]. This has been shown to be reduced with statins [29]. Similarly, a recent study in a rodent model of HF induced by MI has shown that a marked reduction in mortality with atorvastatin was likely to have been due, at least partly, to a significant reduction in interstitial fibrosis in the non-infarcted myocardium [53]. Rats that received atorvastatin also had reduced LV (left ventricular) systolic dysfunction and reduced chamber dilation, with haemodynamically measured decreases in end-diastolic pressure and improved Tei index, similar to that previously demonstrated with cerivastatin [28].

Nuclear transcription factor NF-κB (nuclear factor κB)
A major effect of statins on fibrosis is via its effect on the expression of the nuclear transcription factor NF-κB, a controller of genes encoding cytokines, chemokines, interferons, MHC proteins, growth factors, cell adhesion molecules and viruses, and which is activated by hypoxia and hyperglycaemia [54–56]. These factors are all known to be detrimental in cardiac remodelling and in overall survival in HF [57].

Endothelial effects
Lastly, the pro-angiogenic properties of statins and their effects on re-endothelialization following vessel injury are many, and statins have been shown [37] to induce new blood vessel growth in ischaemic limbs in a manner similar to VEGF (vascular endothelial growth factor), an important effect in cardiac disease post-ischaemia.

CLINICAL DATA (Table 1)

Remodelling and cytokine data
There have been somewhat conflicting reports on the clinical benefit of statin therapy depending on whether the surrogate of cardiac remodelling or the more relevant outcome of morbidity and mortality is examined. There are a number of recent reports on the effects of statins on cardiac remodelling and markers of cardiac function in HF. Although the prospective and randomized UNIVERSE (RosUvastatiN Impact on VEntricular Remodeling, LipidS, and CytokinEs) study [58] and another randomized study [59] reported no benefit of statins on remodelling or remodelling markers in HF, other studies
### Table 1  Observational and interventional studies investigating the efficacy of statin treatment in HF

<table>
<thead>
<tr>
<th>Type of study</th>
<th>Author (date) [reference]</th>
<th>HF criteria</th>
<th>Subjects (n)</th>
<th>Statin (dose)</th>
<th>Duration (months)</th>
<th>Outcome</th>
<th>Summary of main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observational</td>
<td>Sacks et al. (1996) [87]</td>
<td>LVEF 26–40 %</td>
<td>706</td>
<td>Pravastatin (40 mg)</td>
<td>60</td>
<td>Cardiovascular mortality</td>
<td>Positive effect on cardiovascular mortality</td>
</tr>
<tr>
<td></td>
<td>de Looﬀ er et al. (1999) [65]</td>
<td>LVEF &lt; 40 %, and ischaemic</td>
<td>8</td>
<td>Simvastatin (20 mg)</td>
<td>3</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td></td>
<td>Segal et al. (2000) [74]</td>
<td>NYHA Classes II–IV, and LVEF &lt; 40 %</td>
<td>3152</td>
<td>Not specified</td>
<td>18</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td></td>
<td>Stumpf et al. (2003) [80]</td>
<td>LVEF 22 % and 78 % ischaemic</td>
<td>50</td>
<td>Any</td>
<td>0</td>
<td>IL-10</td>
<td>No effect on IL-10</td>
</tr>
<tr>
<td></td>
<td>Hognestad et al. (2004) [67]</td>
<td>Post-MI</td>
<td>5301</td>
<td>Not specified</td>
<td>25</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td></td>
<td>Mozaffarian et al. (2004) [78]</td>
<td>NYHA Class III or IV, and LVEF &lt; 30 %</td>
<td>1153</td>
<td>Lovastatin, pravastatin and simvastatin</td>
<td>16</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td></td>
<td>Joynt et al. (2004) [79]</td>
<td>LVEF &lt; 40 %, and 87 % ischaemic</td>
<td>96</td>
<td>Any</td>
<td>0</td>
<td>CRP</td>
<td>No effect on CRP</td>
</tr>
<tr>
<td></td>
<td>Horwich et al. (2004) [66]</td>
<td>EF &lt; 40 %, and 45 % ischaemic</td>
<td>551</td>
<td>Atorvastatin, simvastatin and pravastatin</td>
<td>12</td>
<td>Mortality/transplantation</td>
<td>Positive effect on mortality and requirement for transplantation</td>
</tr>
<tr>
<td></td>
<td>Ezekowitz et al. (2004) [82]</td>
<td>Clinical HF</td>
<td>6427</td>
<td>Any</td>
<td>12</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td></td>
<td>Ray et al. (2005) [69]</td>
<td>New HF</td>
<td>28 828</td>
<td>Any</td>
<td>96</td>
<td>Mortality/MI/CVA</td>
<td>Positive effect on mortality/MI/CVA</td>
</tr>
<tr>
<td></td>
<td>Rosolova et al. (2005) [81]</td>
<td>55 % ischaemic</td>
<td>607</td>
<td>Any</td>
<td>48</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td></td>
<td>Sola et al. (2005) [68]</td>
<td>EF &lt; 35 %</td>
<td>446</td>
<td>Any</td>
<td>24</td>
<td>Mortality/hospitalizations/ specified surrogate end points</td>
<td>Positive effect on mortality/hospitalizations/ surrogates</td>
</tr>
<tr>
<td></td>
<td>Fukuta et al. (2005) [76]</td>
<td>Normal EF</td>
<td>137</td>
<td>Any</td>
<td>21</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td></td>
<td>Streit et al. (2005) [86]</td>
<td>NYHA Class II or III, and LVEF 40 %</td>
<td>24</td>
<td>Atorvastatin (40 mg)</td>
<td>1</td>
<td>Endothelial function</td>
<td>Positive effect on endothelial function</td>
</tr>
<tr>
<td></td>
<td>Foody et al. (2006) [70]</td>
<td>Hospital admissions for HF</td>
<td>54 960</td>
<td>Any</td>
<td>12</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td></td>
<td>Krum et al. (2006) [72]</td>
<td>NYHA Class III or IV, and LVEF &lt; 35 %</td>
<td>50 10</td>
<td>Any</td>
<td>24</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td></td>
<td>Krum et al. (2006) [73]</td>
<td>NYHA Classes II–IV, and LVEF &lt; 35 %</td>
<td>226</td>
<td>Any</td>
<td>15</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td></td>
<td>Folkeringa et al. (2006) [71]</td>
<td>Hospital admissions for HF</td>
<td>524</td>
<td>Any</td>
<td>31</td>
<td>Mortality</td>
<td>Positive effect on mortality</td>
</tr>
<tr>
<td>Prospective</td>
<td>Node et al. (2003) [60]</td>
<td>LVEF &lt; 40 %, and non-ischaemic</td>
<td>51</td>
<td>Simvastatin (10 mg)</td>
<td>3</td>
<td>NYHA Class</td>
<td>Positive effect on functional class</td>
</tr>
<tr>
<td></td>
<td>Laufs et al. (2004) [61]</td>
<td>Non-ischaemic</td>
<td>15</td>
<td>Cerivastatin (0.4 mg)</td>
<td>5</td>
<td>MLWHF and 6MWT</td>
<td>Positive effect on MLWHF and 6MWT</td>
</tr>
<tr>
<td></td>
<td>Tousoulis et al. (2005) [83]</td>
<td>NYHA Class III or IV, LVEF &lt; 35 %</td>
<td>38</td>
<td>Atorvastatin (10 mg)</td>
<td>10</td>
<td>Blood flow</td>
<td>No effect on blood flow</td>
</tr>
</tbody>
</table>
have shown a benefit of statins on remodelling which co-existed with the improvement in clinical markers of HF severity, such as quality of life indices [60,61].

In addition, another randomized and prospective study examining statins in HF has shown that the use of 20 mg of atorvastatin in patients with non-ischaemic HF resulted in a statistically significantly improvement in LVEF (LV ejection fraction) and a reduction in LVEDD (LV end-diastolic diameter) and LVESD (LV end-systolic diameter) over 12 months, as well as a significant reduction in pro-inflammatory cytokine concentrations [62].

Of particular note and with relevance to the possible detrimental effect of low cholesterol on mortality discussed above is that both the UNIVERSE study [58] and the study by Bleske and co-workers [59] used higher doses of very potent statins and investigated predominantly non-ischaemic HF compared with the positive reports above.

Some of the earlier large lipid-lowering studies, such as the CARE (Cholesterol And Recurrent Events) trial, have shown that statin therapy also reduced the risk of developing HF, presumably via improved remodelling [63,64]. Similarly, in a small study of post-MI patients [65], six out of eight subjects with an LVEF < 40 % had an improvement in LVEF compared with baseline after 12 weeks of simvastatin therapy.

**Clinical outcome data**

Although there is evidence from prospective randomized animal studies demonstrating that statins have a major mortality reducing effect on the numbers of deaths due to HF induced by MI [28,50,53], in humans data suggesting that statins reduce mortality in HF (regardless of whether the aetiology is ischaemic or non-ischaemic) have only been retrospective and post-hoc.

A retrospective study examining 551 patients for clinical management/heart transplant evaluation [66] has shown that statin use was associated with improved survival without the necessity of urgent transplantation in both ischaemic and non-ischaemic HF patients [91 compared with 72 % \((P < 0.001)\) and 81 compared with 63 % \((P < 0.001)\) respectively] at 1 year follow-up. Similarly, a retrospective review of the OPTIMAAL (Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan) study [67] has shown that the patient group with HF post-MI receiving either a \(\beta\)-blocker or a statin had improved survival compared with those that received neither (relative risk reduction 55.2 and 46.1 % respectively; \(P < 0.001\) compared with placebo).

Similarly, Sola et al. [68] in a non-randomized, but prospective, study have shown that statin therapy in patients with HF was associated with decreased all-cause mortality at 2 years compared with those not on statin therapy (15 compared with 33 %; \(P < 0.005\)) as well as a reduction in hospitalizations for HF (22 compared with 38 %; \(P = 0.001\)). The lack of prospective randomization
and differing baseline characteristics in the statin and comparator populations makes further interpretation difficult. A second prospective study by the same group [62] was not powered to examine mortality (there were two deaths in each group), so we are left wondering whether the LVEF and remodelling benefits seen with 20 mg of atorvastatin translate into a clinically significant benefit.

Statin use is also associated with a lower risk of death among elderly subjects (66–85 year olds) recently diagnosed with HF (adjusted HR (hazards ratio), 0.67 [95 % CI (confidence interval), 0.57–0.78]) [69] or in elderly patients hospitalized with HF [70], a group otherwise neglected in studies of statins.

Interestingly, examination of survival data from a large CHF (congestive HF) registry [71] has shown that, in Cox multivariate regression analysis, the use of statins remained significantly associated with decreased mortality independent of the cause of HF. Statins were as effective in ischaemic as in non-ischaemic HF and in patients with depressed as well as preserved LVEF [71].

Unfortunately, until recently, none of the large-scale clinical trials with statins in patients with heart disease had prospectively enrolled patients with HF. However, post-hoc analyses of these studies have shown a benefit for HF patients. In addition, post-hoc analyses of some of the large HF trials have also recently been undertaken. For example, in a post-hoc analysis of the Val-HeFT (Valsartan HF Trial) study [72] in patients that were matched for LVEF and ACEi (angiotensin-converting enzyme inhibitor) use, 2 year mortality was 17.9 % for patients on statins compared with 20.3 % without [Cox-adjusted HR, 0.81 (95 % CI, 0.7–0.94); P = 0.029]. A similar post-hoc analysis of the β-blocker in the HF study CIBIS II (Cardiac Insufficiency Bisoprolol Study II) [73] has shown that statin use at baseline was associated with a significant survival benefit compared with no statin use [HR, 0.6 (95 % CI, 0.39–0.94)] and a significant interaction effect with bisoprolol.

There are similar results in post-hoc analyses of the large LDL-lowering studies, such as the 4S (Scandanavian Simvastatin Survival Study) [1]. Here, there was an overall survival benefit over 10 years of follow-up in the simvastatin group, and the mortality rate in patients developing HF was 25.5 % in the simvastatin group compared with 31.9 % in the placebo group. In ELITE II (Evaluation of Losartan In The Elderly trial II) [74], a study examining the effect of an AngIIRA (AngII receptor antagonist) in HF, 19.6 % of patients were receiving statins at the end of the study. Although non-randomized, there was a significantly lower mortality in the statin group (10.6 %) compared with those who were not (17.6 %).

The answer to the question of high- compared with low-dose statin use has been difficult to elucidate, with seemingly contradictory post-hoc clinical outcome and surrogate data. Both the UNIVERSE study [58] and the study by Bleske and co-workers [59] used high-dose statin therapy, with the results suggesting that the higher dose may be detrimental. A recent subgroup analysis of a large statin study in predominantly coronary heart disease patients found fewer hospitalizations with high-dose statin therapy than a low dose [75]. Subjects with advanced HF or an EF <30 % were excluded from entry into this study. As we have seen with many aspects of HF management (e.g. the obesity paradox), it is far from clear that what applies to a high-risk cohort without HF also applies to patients with overt established HF. Nevertheless, 7.8 % of the subjects in that study [75] actually had ‘HF’, and it was in those patients that the greatest benefit of high-dose statin was seen. No mortality data were reported for this group. Furthermore, this was a post-hoc subgroup analysis of a secondary end point.

Lastly, diastolic HF is another group that has traditionally been under-represented in all studies on cardiovascular disease, especially that of the large statin studies. It is interesting that a retrospective study observed an 80 % lower mortality in patients on statins with diastolic HF [76]. Thus in observational studies of patients with heart disease and systolic and diastolic HF, there is a suggestion of a benefit of statin therapy in these groups.

**SUMMARY**

Despite the plethora of research in recent years regarding statins and HF, a prospective study of statin therapy on a clinically relevant end point, survival, has not been completed. Two large-scale prospective trials, GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico-HF) and CORONA (CONTrolled ROSuvastatin multiNAtional Trial in HF), are however currently under way and are due to report their primary results in 2007. Furthermore, because both of these trials are focussing predominantly on HF patients with an ischaemic aetiology, separating out true effects of statins on HF progression compared with inhibition of ischaemic processes may be difficult.

**Future directions**

In the meantime, although there is a large amount of post-hoc and retrospective evidence supporting a mortality benefit with statin use, there remains considerable uncertainty. This is due predominantly to a number of unanswered questions: whether a low LDL from statin use results in the same outcome as an innately low LDL?; whether LDL represents an appropriate surrogate marker in the setting of HF?; whether BNP (brain natriuretic peptide) concentrations can predict benefit from statin use [77]; questions regarding the dose relativity of the statin; whether there is a correlation between markers of remodelling and mortality post-statin?; and whether there is an interaction effect on mortality of the addition
of other medications which are anti-inflammatory and/or inhibitors of the renin–angiotensin pathway?

Until this evidence is available, prescribing statins in HF involves weighing up unknown risks and benefits. Therefore use of statins in this condition should be restricted to patients in whom there is a co-existent need in a clinical condition proven to benefit from use of these agents.

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