Are statins failing in heart failure?

John Kjekshus∗

Department of Cardiology, Rikshospitalet University Hospital, University of Oslo, Norway

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This editorial refers to ‘The effect of statin therapy on heart failure events: a collaborative meta-analysis of unpublished data from major randomized trials†, by D. Preiss et al., on page 1536.

Statins are a well-established treatment for primary and secondary prevention of atherosclerotic cardiovascular disease. They have been shown to slow and even reverse the development of coronary and cerebral atherosclerosis and to improve outcomes in non-heart failure (HF) patients with ischaemic heart disease.1,2 Moderate doses and early left ventricular dysfunction, whereas late-onset HF is more complicated anterior infarct are primarily related to infarct size and early left ventricular dysfunction, whereas late-onset HF is more related to the extent of coronary artery disease and recurrent events.4 The Scandinavian Simvastatin Survival Study (4S) showed that patients with coronary heart disease without HF benefited from long-term simvastatin treatment by a 30% reduction in all-cause mortality during 5.4 years follow-up.5 Retrospective analysis also demonstrated a 19% reduction in the report of new-onset HF.6 Almost half the patients with new-onset HF had a non-fatal myocardial infarct prior to the registration of HF. Incident HF quadruples the risk for cardiovascular events, and this therefore has important clinical implications. Because of the higher risk, absolute treatment benefit will be larger. Studies that are more recent have added uncertainty to the alleged preventive effects of statin on incident HF.7–9 Some of the discrepancies are due to different definitions of HF, exclusion of early-onset HF after an acute MI because they are assumed to be one event, different statin dose regimens, and missing sensitive biomarkers of acute myocardial infarcts and left ventricular dysfunction.

It is therefore commendable that Preiss and co-workers have examined the statin effects on the risk of HF hospitalization and HF death by analysing all primary and secondary randomized controlled trials with statins between 1994 and 2014 in a standardized fashion.10 Seventeen trials with 132 568 patients, virtually all without HF at baseline, were eligible. LDL was reduced by 0.97 mmol/L, resulting in 26% fewer non-fatal MIs on treatment. The authors observed reduced numbers of first HF hospitalizations [risk ratio (RR) 0.90, 95% confidence interval (CI) 0.84–0.97] and the composite of first non-fatal HF hospitalization or HF death (RR 0.92, 95% CI 0.85–0.99), but not HF death alone. The numbers needed to treat in the secondary prevention trials over 5 years was 200 to avoid one non-fatal HF hospitalization. Thus, the effect on HF hospitalization was modest. The efficacy of statins may have been underestimated because the authors could not account for repeated hospitalizations and the definition of HF differed between the involved trials. In the CORONA trial of patients with clinical HF, cumulated hospitalizations over a median follow-up of 33 months were reduced by rosuvastatin by ~15–20%.11

Although Preiss et al. observed a clear reduction in LDL and non-fatal MI, these effects were not related to the risk of first non-fatal or fatal HF event. Less than 15% of the first HF endpoints were preceded by a documented myocardial infarct. The small number may have been underestimated due to the low incidence of MI heterogeneity in the HF diagnosis, insensitive diagnostic biomarkers, and that the study excluded patients with incident HF within 30 days after a myocardial infarct. Furthermore, the analysis did not demonstrate any different effect of statins on HF outcomes related to an in-study MI or not. This may not be surprising since it takes between 6 and 12 months to observe treatment effects of statins. However, registry studies have observed that early statin therapy of acute MI was associated with a significantly lower rate of early complications including HF events as compared with no statin therapy. Results derived from registry studies are difficult to interpret because of allocation bias. The interpretation is also limited by the fact that patients were not randomized for occurrence or non-occurrence of MI.

The effect of statins on the composite endpoint of non-fatal HF hospitalizations and HF death was exclusively driven by incident non-fatal HF hospitalization with no effect on HF mortality. HF death is an end-stage that primarily follows extensive left ventricular...
dysfunction. The cause and mode of death differ between patients with stable coronary artery disease without HF and patients with established HF. Non-HF patients are more likely to die suddenly from acute MI and ventricular fibrillation. In contrast, HF patients die primarily from progressive HF and stroke.4,12 It is therefore not surprising that statins have no effect on HF deaths. The same contrast between statin effects on non-fatal HF hospitalization and HF deaths was observed in the CORONA and GISSI trials, where patients with documented HF were treated with rosuvastatin.13,14 There was no effect of rosuvastatin treatment on HF death, but benefits for non-fatal HF hospitalization and atherosclerotic events were observed.11 Acute coronary events and incidence of HF are declining due to effective preventive treatment of arteriosclerosis including statins, yet the prevalence of HF is increasing.15 The improved survival among HF patients is caused by interventions that target downstream pathophysiological mechanisms by unloading the failing left ventricle and by blunting detrimental effects of neurohormonal activation (beta-blockers, renin–angiotensin–aldosterone inhibitors, and resynchronization devices), thereby reducing myocardial energy requirement and electrical instability. Conversely, beta-blockers and inhibitors of the renin–angiotensin–aldosterone system have small and insignificant effects in stable coronary disease without HF.16 The target for statin treatment in patients with stable coronary artery disease is the development of coronary and cerebral arteriosclerosis,1,2 but this has minor impact in patients with established HF13 mostly because the events are determined by the failing myocardium and less by progression of atherosclerosis. However, a retrospective analysis of CORONA, restricted to ‘atherothrombotic’ events, defined as fatal and non-fatal MI and fatal and non-fatal non-ischaemic strokes, showed a borderline significant difference favouring rosuvastatin (P = 0.05). Preiss et al. also suggest other explanations whereby statins may reduce the risk of developing HF by preventing ischaemic events including pleiotropic anti-inflammatory effects unrelated to the LDL-lowering effect. This might be interesting especially because HF is a driver of inflammation, but the lack of statin effects in established HF on major composite endpoints13,14 and the recent positive results of the IMPROVE-IT with ezetimibe, a non-statin, cholesterol-lowering agent, probably brought this discussion to an end.17

The study by Preiss and co-workers is important because incident HF carries a dismal prognosis. It reminds us that prevention of new-onset HF can be achieved by statin treatment. This is different from prevention of HF death, which primarily is determined by mechanisms most probably dependent on left ventricular remodelling and myocardial dysfunction. The study therefore also suggests different aetiologies for non-fatal HF events and fatal HF.

For the same reason, the two endpoints should not be lumped together in clinical studies. Prevention of new-onset HF and HF hospitalization requires a treatment approach that is different from treatment of established HF and prevention of HF death (Figure 1).

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References