Knowledge acquired in the past few decades indicates that the process of chronic heart failure (CHF) consists not only of inadequate responses to mechanical load but also of pathological signaling, including activation of cellular proliferation/hypertrophy, inflammation, oxidative stress, and endogenous nitric oxide synthase deprivation. Beneficial effects of β-blockers and renin-angiotensin system inhibitors in CHF have been largely attributed to their suppressive effects on these signal pathways.

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Statins primarily affect 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate pathway for cholesterol synthesis. Importantly, the inhibition of HMG-CoA reductase subsequently reduces farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which are crucial for downstream subcellular signal molecules by prenylation of the guanosine triphosphate-binding proteins Rho, Ras, and Rac1,2 (Figure 1). As is well established, the Rho signal pathway is involved in the activation of inflammatory cytokines and chemokines, Ras proteins are responsible for cell proliferation and hypertrophy, and Rac proteins are involved in the production of reactive oxygen species. Therefore, it is presumed that inhibition of HMG-CoA reductase by statins may reduce the ominous signal pathways mediated by knowledge acquired in the past few decades indicates that the process of chronic heart failure (CHF) consists not only of inadequate responses to mechanical load but also of pathological signaling, including activation of cellular proliferation/hypertrophy, inflammation, oxidative stress, and endogenous nitric oxide synthase deprivation. Beneficial effects of β-blockers and renin-angiotensin system inhibitors in CHF have been largely attributed to their suppressive effects on these signal pathways.

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number of subjects whose etiology of CHF was ischemic (100% in CORONA and 40% in GISSI-HF). In addition, in GISSI-HF, side-by-side conducted n-3 polyunsaturated fatty acids (n3-PUFA) arms showed a small but significant amelioration of cardiovascular deaths in patients with n3-PUFA.

Issues remaining in the post-CORONA and GISSI-HF era are: (1) the fixed dose of rosuvastatin (10 mg/day) was inadequate for patients with advanced CHF, (2) the hydrophilic nature of rosuvastatin may confer specific differences from other lipophilic statins, and (3) statin-sensitive races such as Asians may express different responses.

Based on favorable experimental results by pitavastatin in pressure-overloaded mice with CHF, the PEARL (Pitavastatin heart failure) study was conducted by Takano et al. It was a prospective, multicenter, randomized, placebo-controlled trial in 574 Japanese patients with CHF to test a hypothesis that a lipophilic statin, pitavastatin (2 mg/day), would ameliorate a composite of cardiovascular death and hospitalization for worsening CHF. During the 2-year follow-up period, the primary outcome occurred equally in the pitavastatin arm (18.0%) and the control group (19.9%). The adjusted hazard ratio was 0.92 with a P-value of 0.672. Although the study was a bit underpowered, the data were essentially consistent with those from CORONA as well as GISSI-HF. Taken together, the PEARL study informs us that statins do not provide additional improvement in CHF patients whether (1) the statin is lipophilic or hydrophilic, (2) the dose is modest or the maximal (3) the etiology of CHF is ischemic or non-ischemic, and (4) the patient is of a particular race or nationality. Statin therapy, the putative “frog prince” for CHF treatment, is, unfortunately, only a frog.

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Rho, Ras, and Rac in CHF. Statin treatment has also been shown to favorably affect endothelial function and slow the progression of coronary atherosclerosis.

In contrast to these expectations, there are several theoretical considerations against statin treatment in CHF, the most relevant being the endotoxin lipoprotein hypothesis, the coenzyme Q10 (ubiquinone) hypothesis, and the selenoprotein hypothesis (Figure 1). The endotoxin lipoprotein hypothesis is related to lower cholesterol levels. Several studies have addressed the relation and relevance of serum cholesterol levels to outcome in CHF patients, and the results consistently suggest that lower cholesterol is associated with increased mortality. Namely, for each mmol/L decrease in total cholesterol, mortality increases by 25%. This phenomenon of “paradoxical epidemiology” in CHF is not unique for cholesterol levels, and also exists for body mass index and blood pressure. The ubiquinone hypothesis reasons that inhibition of mevalonate synthesis by statins decreases the production of ubiquinone, which is involved in the production of ATP and the metabolic demands of cells. The selenoprotein hypothesis postulates that statins interfere with the enzymatic isopentenylation of selenocysteine tRNA and prevent its maturation to a functional tRNA molecule, resulting in a decrease in available selenoproteins.

Under the emerging attention, 2 large, randomized, double-blind, placebo-controlled clinical trials [CORONA: Controlled rosuvastatin multinational study in heart failure (n=5,011) and GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza cardiac-heart failure, n=4,631)] were conducted. In both of them, rosuvastatin, one of the most powerful statins, did not reduce the number of deaths from cardiovascular causes or from any cause in CHF patients with systolic dysfunction (Figure 2). Of note is that both studies failed to improve the outcomes, despite the inclusion of a substantial number of subjects whose etiology of CHF was ischemic (100% in CORONA and 40% in GISSI-HF). In addition, in GISSI-HF, side-by-side conducted n-3 polyunsaturated fatty acids (n3-PUFA) arms showed a small but significant amelioration of cardiovascular deaths in patients with n3-PUFA. Issues remaining in the post-CORONA and GISSI-HF era are: (1) the fixed dose of rosuvastatin (10 mg/day) was inadequate for patients with advanced CHF, (2) the hydrophilic nature of rosuvastatin may confer specific differences from other lipophilic statins, and (3) statin-sensitive races such as Asians may express different responses.

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Figure 2. Kaplan-Meier estimates for composite cardiovascular events in (A) the CORONA trial and (B) the GISSI-HF study (adapted from Kjekshus et al and GISSI-HF with permission, respectively).
tricular ejection fraction (LVEF). Namely, patients with LVEF between 30% and 45% showed a significant improvement whereas patients with LVEF <30% rather tended to worse. The underlying mechanism is totally unclear; however, the result suggests that statin therapy is a double-edged sword for CHF patients who are facing a balancing act between pathological signaling and the metabolic and cellular demands requiring cholesterol.

References