

etin, stimulates the growth of thrombopoietin-dependent cell lines in vitro, and raises the platelet count in normal volunteers. In this phase 1 trial of eltrombopag in patients with chronic ITP who did not have a response to at least one previous type of treatment, the drug raised the platelet count to 50,000 or more per cubic millimeter in 21 of 26 patients who received 75 mg per day, in 19 of 27 who received 50 mg per day, and in 8 of 29 who received 30 mg per day. As with AMG 531, the durability of the response and the long-term safety of the compound are unknown. In a companion paper in this issue of the *Journal*, McHutchison et al. report their results regarding eltrombopag in the treatment of thrombocytopenia associated with cirrhosis due to hepatitis C infection.<sup>12</sup> In this small trial, treatment with eltrombopag raised the platelet count to 100,000 or more per cubic millimeter in most patients who received the highest dose of the compound, thereby enabling the initiation of antiviral therapy. Notably, during the 12-week period of antiviral treatment, platelet counts fell despite the continuation of eltrombopag therapy, but the levels remained above the baseline. Whether this observation has implications for the durability of the response to eltrombopag in patients with ITP is not known.

The results reported for thrombopoietin-receptor agonists are too preliminary for any definitive statement about applications in clinical practice, but they surely encourage further work in this direction. Hematologists everywhere are thwarted by patients with ITP in whom every available treatment has failed to improve the platelet count.

A new, safe way of treating the disease would be a considerable advance.

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## Statins for Ischemic Systolic Heart Failure

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Hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) represent one of the most important pharmacologic advances in the prevention of cardiovascular disease in decades. Since the publication of the Scandinavian Simvastatin Survival Study in 1994,<sup>1</sup> several trials have demonstrated important benefits of statins in patients with established coronary disease. These findings have resulted in strong recommendations for the use of statins in clinical-practice guidelines.<sup>2</sup> Statins

are one of the few classes of drugs that are embedded in clinical-performance measures for coronary artery disease, which indicates that clinicians should be considered remiss if they do not prescribe these agents for all their eligible patients.<sup>3</sup>

In the context of the strong evidence base and recommendations supporting the use of statins for secondary prevention of cardiovascular disease, in this issue of the *Journal* Kjekshus et al.<sup>4</sup>

report on a study assessing the efficacy of 10 mg of rosuvastatin daily in patients with heart failure and left ventricular systolic dysfunction attributed to coronary artery disease. The study, called the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), was a randomized, placebo-controlled trial involving patients who were at least 60 years of age (mean, 73 years) who were receiving high rates of evidence-based therapy for left ventricular systolic dysfunction, including angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and beta-blockers. As compared with placebo, treatment with rosuvastatin resulted in no significant difference in the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, even though the drug was associated with substantial reductions in levels of low-density lipoprotein (LDL) cholesterol and high-sensitivity C-reactive protein. Patients in the rosuvastatin group had significantly fewer hospitalizations for cardiovascular causes, including heart failure; rates of adverse drug events did not differ between the two study groups. Rosuvastatin therapy had no effect on the health status of patients, as assessed on the basis of New York Heart Association class and the McMaster Overall Treatment Evaluation questionnaire, which were designated as tertiary outcomes.

Results aside, one might ask whether a study of a statin for secondary prevention in this population was warranted. Although the numbers of patients with systolic heart failure who have been enrolled in previous secondary-prevention trials have been inadequate to generate robust evidence, observational studies have suggested benefits of statin therapy on morbidity and mortality in this population.<sup>5</sup> Statins also have a favorable effect on surrogate end points (e.g., endothelial function), which in theory would be beneficial for patients with heart failure.

Given these facts, it might be tempting to assume that patients with ischemic left ventricular systolic dysfunction would accrue benefits from statins similar to those identified in previous trials. However, there are several reasons to resist this temptation. First, the limitations of assumptions based on observational data<sup>6</sup> and surrogates<sup>7</sup> are well documented. Furthermore, the need to understand specifically the balance of risks and benefits of drug therapy in patients with heart failure is magnified by particular characteristics of this

population. Although patients with ischemic left ventricular systolic dysfunction have high rates of adverse outcomes, their risk of ischemic cardiovascular events — outcomes that statins seem most likely to prevent — may occur less frequently than in other patients with coronary disease. Moreover, heart failure disproportionately affects older persons, who often have a substantial risk of coexisting illnesses, a factor that raises questions about the applicability of evidence from clinical trials involving younger patients with a single, dominant clinical problem.<sup>8</sup> Finally, typical regimens for this population involve multiple drugs, both because of the burden of coexisting illnesses and the number of drugs used to treat heart failure.<sup>9</sup> The addition of a new drug to an already complex regimen increases not only the cost but also the risk of adverse drug interactions. When coupled with a theoretical concern about possible adverse drug effects from statins specific to patients with heart failure,<sup>10</sup> such factors amplify the need to understand the safety and efficacy of this therapy.

How, then, can the clinical findings of the CORONA study be reconciled with the existing randomized trials of statins in patients with established coronary artery disease? First, statins as a class may not be efficacious in patients with ischemic left ventricular systolic dysfunction who are already receiving evidence-based therapy for heart failure. An attenuated effect of statins could reflect the distribution of the causes of outcomes in this population. For example, among patients in the CORONA study, rates of nonfatal myocardial infarction were about one quarter of the rates reported in patients in the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) study,<sup>11</sup> a statin trial that enrolled patients whose mean age was about 75 years and who had a mean follow-up of about 38 months (as compared with 32.8 months in the CORONA study). It is also important to point out that the confidence intervals around the primary end point in the CORONA study are consistent with as much as a 17% relative reduction in risk or an absolute risk reduction of approximately 2%. An absolute benefit of this magnitude would be clinically significant and is similar to that identified in PROSPER. Second, it is possible that even though rosuvastatin lowered levels of LDL cholesterol and high-sensitivity C-reactive protein, the drug does not share the same benefits regarding important health out-

comes with other statins. Although several statins have proven clinical efficacy, supporting the assumption of a class effect, experience with cerivastatin has shown that such assumptions can lead us astray. It is reassuring that in the CORONA study, patients in the rosuvastatin group had fewer hospitalizations for cardiovascular causes and no greater risk of adverse events than did those in the placebo group. Finally, statins may have less incremental benefit in a population of older patients who are at higher risk for competing events, which could reduce the likelihood of ascertaining a benefit for specific cardiovascular outcomes. Although only a minority of deaths in the CORONA study were designated as having noncardiovascular causes, deaths that did not have a clear cause were presumed to be cardiovascular in nature, potentially limiting the quantification of the magnitude of competing risks.

Future trials may shed light on some of these unresolved questions. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) (ClinicalTrials.gov number, NCT00239681) trial<sup>12</sup> should provide additional perspective on the general effect of rosuvastatin on important health outcomes in patients without established cardiovascular disease. The results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Heart Failure Study (GISSI-HF) (ClinicalTrials.gov number, NCT00336336),<sup>13</sup> a randomized trial in which patients with heart failure are receiving either rosuvastatin or placebo, will complement the findings of the CORONA study. The GISSI-HF study is also enrolling patients with nonischemic cardiomyopathies and those with preserved left ventricular systolic function, both important subgroups of the population with heart failure who were not evaluated in the CORONA study.

The results of the CORONA study highlight issues that are central to the conduct of trials involving patients with heart failure. When important questions are raised about the benefits and risks of a therapy that is well established in other populations, it may still be essential to establish treatment effects in the population with heart failure. Admittedly, enrolling subjects in trials that challenge well-established treatment paradigms may be difficult despite equipoise on an intellectual level. Second, trials simply must

focus more attention on including patients who are representative of those seen in clinical practice. In enrolling older patients, the CORONA study made important strides, although the proportion of women who were enrolled (less than 25%) was no higher than that in previous heart failure trials. Finally, because health status (including symptom burden and quality of life) provides a patient-centered understanding of the effect of any treatment, it should be included as an outcome in all studies of heart failure. Ideally, health status outcomes would not be consigned to tertiary status and would be assessed with valid, reliable, and clinically sensitive instruments designed specifically for use in populations with heart failure.<sup>14</sup> Trials enrolling more representative populations and assessing a broader range of outcomes are instrumental to informed decision making.<sup>15</sup>

Meanwhile, enough uncertainty exists about the mechanisms underlying the primary results of the CORONA study that clinicians should continue to prescribe statins for patients with ischemic heart failure and left ventricular systolic dysfunction. Until further evidence accumulates, we cannot tell to what extent the CORONA study reflects the limitations of the use of statins for patients with heart failure, the problems associated with a particular drug, or the intrinsic challenges of treating older patients with complex coexisting illnesses.

Dr. Masoudi reports receiving consulting fees from Amgen, UnitedHealthcare, and Takeda and grant support from Amgen. No other potential conflict of interest relevant to this article was reported.

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This article (10.1056/NEJMe0707221) was published at [www.nejm.org](http://www.nejm.org) on November 5, 2007.

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