therapy has been optimized and the severity of MR subsequently reassessed.” This is precisely the point we attempted to make, and we thank Dr. Sharma for allowing us to clarify it. The recent American Heart Association/American College of Cardiology Guidelines on Valvular Heart Disease emphasize disease staging, in which stage C is asymptomatic severe MR and stage D is symptomatic severe MR (2). We believe that stage C or D functional MR should not be defined by a single echocardiogram at a given point in time, but rather by persistent evidence of severe MR despite optimization of medical therapy, cardiac resynchronization, and revascularization (3). Even then, there is no convincing evidence that surgical or percutaneous mitral valve intervention improves survival (2,3). The evaluation of severe functional MR and the decision to intervene is quite complex, with an emerging consensus that it should be made by a multidisciplinary heart team (1-4).

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Please note: Dr. Grayburn has received grant support from Abbott Vascular and Medtronic; has served as a consultant for Abbott Vascular, Tendyne, and Bracco Diagnostics; and has had Echo Core Lab contracts for Valtech Cardio, Guided Delivery Systems, and Tendyne. Dr. Gillam has had Core Lab Research contracts for Edwards Lifesciences and Medtronic. Dr. Liang serves on the medical advisory board for and has received research support from Philips Healthcare. Dr. McCarthy has served as a consultant for Edwards Lifesciences, and is an inventor of IMR ETlogix. Dr. Miller has served on the PARTNER Executive Committee for Edwards Lifesciences; has served as a consultant for Medtronic Cardiovascular Division and Abbott Vascular Structural Heart (MitraClip); and has served on the scientific advisory board for GenTAC. Dr. Siegel has served as a speaker for Philips and Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Underutilization of High-Intensity Statin Therapy After Hospitalization for Coronary Heart Disease

A Cause for Concern, But a Few Words of Caution

We read with interest the paper by Rosenson et al. (1), who performed a retrospective analysis showing that only a “disappointing” 27% in a 5% random sample of Medicare patients 65 to 74 years of age hospitalized for acute myocardial infarction or revascularization from 2007 to 2009 had been prescribed high-intensity statins. Stricter adherence to the 2013 American Heart Association/American College of Cardiology (AHA/ACC) Guidelines was called for in the accompanying editorial comment. We would like to offer some words of caution.

Mounting evidence for harms (e.g., rhabdomyolysis, diabetes, acute renal failure) (2) associated with high-intensity statins published in the data and treatment at our institution of 3 recent consecutive cases of severe rhabdomyolysis (2 lethal and 1 severely debilitating, resulting in flaccid quadriplegia) in patients treated with high-intensity statins according to the new AHA/ACC guidelines prompted us to review the main evidence behind those recommendations, with respect to benefits on “hard” endpoints such as all-cause mortality or cardiovascular mortality.

In chronic stable coronary heart disease (CHD), 3 major secondary prevention trials were identified: TNT (Treat to New Targets), IDEAL (Incremental Decrease in End Points Through Aggressive Lipid Lowering), and SEARCH (Study of the Effectiveness of Additional Reduction in Cholesterol and Homocysteine). From these trials’ data, and using the latest Cochrane methodology and focusing on outcomes that are most relevant to patients, it was shown that high-intensity statins had no effect on total mortality as compared to standard dose statins (relative risk: 0.99; 95% confidence interval: 0.93 to 1.06). High-dose statins increased withdrawals due to adverse effects (relative risk: 1.45; 95% confidence interval: 1.34 to 1.58;
absolute risk increase: 2.5%) as compared to standard
dose statins (3).

In acute coronary syndromes, 2 major trials were
identified:

1. The A-to-Z trial compared 80 mg with 20 mg of
simvastatin in 4,497 patients with acute coronary
syndromes. There was no significant benefit in
total or cardiovascular mortality over the 2-year
duration of the study. The National Institute for
Clinical Excellence (NICE) 2014 reviewers labeled
the trial as having a high risk of bias.

2. The PROVE IT–TIMI 22 (Pravastatin or Atorvastatin
Evaluation and Infection Therapy-Thrombolysis In
Myocardial Infarction 22) trial investigators (4),
compared 80 mg of atorvastatin to 40 mg of prav-
astatin in 4,162 patients in acute coronary syn-
dromes. The PROVE IT–TIMI 22 trial was reported
as strongly positive and considered to be the
cornerstone trial leading to the “sea changing” era
of intensive target-driven (“the lower, the better”) statin therapy. It is the only one of 5 blinded trials
testing high intensity statin treatment to claim a
benefit with respect to hard endpoints such as total
mortality and CHD mortality, as there were statisti-
cally significant reductions in total and CHD
mortality under the higher dose.

But a closer look at the PROVE IT–TIMI 22 trial
shows negligible absolute benefits.

For the “hardest” endpoints (Table 1), such as
death from all causes, at the 24-month mark, the
absolute risk reduction was a mere 1% (3.2% on prav-
astatin 40 mg vs. 2.2% on atorvastatin 80 mg); for
deaths from CHD, the absolute risk reduction was
smaller, at 0.3% (about 6 patients), the differ-
ence between 1.4% (or about 28 patients) on pravas-
tatin 40 mg versus 1.1% (or about 22 patients) on
atorvastatin 80 mg. In the published paper, when
expressed as relative risk reductions, the benefits
look much more impressive: reductions of 28% for
death and 30% for CHD death. Moreover, we do not
know what to think about the erratum (4) published
2 years later, wherein the authors admitted to multiple
inaccuracies (typo errors quite unlikely) in the
reporting of the numbers of patients at risk at every
time mark (6, 12, 18, 24, and 30 months) and in both
groups.

The authors have neither redone the calculations
of the Kaplan-Meier curves nor retracted the paper.
Had they redone the calculations, would the small
differences of 1% in absolute risk reduction in overall
mortality—and the 0.3% absolute risk reduction in
CHD mortality—in the high-intensity group have
remained unaffected?

In conclusion, worthwhile benefits have not been
clearly demonstrated with high-intensity statins, as
compared to lower doses, with respect to “hard” end-
points such as total mortality or CV mortality.

It is doubtful that the small, if any, benefits of high-
potency statins on soft and less patient-relevant
outcomes, outcomes that are highly susceptible to
biases (5), would outweigh the combined risks of
acute kidney injury, rhabdomyolysis, diabetes, and
severe muscular failure, not to mention dozens of
other adverse reactions (2). Because the benefits do
not bear scrutiny of the evidence, the harms caused
may be substantial and the societal costs incurred by
abiding to the new AHA/ACC guidelines would be
enormous. We therefore suggest that until proven
otherwise, a cause for concern is not with “under-
utilization of high-intensity statins” but rather may
be with their “overutilization.”

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http://dx.doi.org/10.1016/j.jacc.2015.02.083

Please note: Both authors have reported that they have no relationships rele-
ant to the contents of this paper to disclose.

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| Table 1: RRR and ARR for the Major Endpoints in the PROVE IT Trial |
|------------------------|------------------------|------------------------|------------------------|------------------------|
| Endpoints at the 2-Year Mark | Pravastatin 40 mg (n = 1,973) | Atorvastatin 80 mg (n = 2,003) | RRR† | ARR† |
| All-cause mortality | 3.2 | 2.2 | 28 | 1.0 |
| Death from CHD | 1.4 | 1.1 | 30 | 0.3 |
| Death/nonfatal MI | 10.0 | 8.3 | 18 | 1.7 |

Values are % unless otherwise indicated. RRR% Relative risk reduction (RRR) not published initially.
†Absolute risk reduction (ARR) not published in the original text but as calculated by us.
CHD = coronary heart disease; MI = myocardial infarction.