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Reply

Is it Not Timely to Consider How to Balance Cardiorenometabolic Benefits and Risks of Statins?

We thank Dr. Koh for his thoughtful comments regarding our paper (1). There is little doubt that statins are one of the most effective drug classes of our generation. The mechanisms underlying their effectiveness continue to be studied carefully, and there is growing recognition that their nonlipid (pleiotropic) effects (their anti-inflammatory actions in particular) may impart an important portion of the benefits of statins to the atherosclerotic milieu. In support of this concept, we recently observed that the beneficial impact of atorvastatin on atherosclerotic inflammation, as measured by fluorodeoxyglucose–positron emission tomography/computed tomography imaging, was not significantly related to the magnitude of low-density lipoprotein reduction (1). Furthermore, a growing number of studies have highlighted anti-inflammatory benefits of statins that extend beyond atherosclerotic diseases, including the example raised by Dr. Koh, wherein high-dose atorvastatin was found to reduce periodontal inflammation (2). Such observations may ultimately pave the way for even broader use of statins, pending confirmation in clinical endpoint trials. Moreover, the recently published Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults makes recommendations for statin dosing based more on risk assessment than on lipid targets (3) and is predicted to increase the number of Americans who will be treated with statins (4).

Accordingly, the point raised by Dr. Koh is both important and timely: as we continue to expand the use of statins and contemplate new indications for them, we should in parallel continue to carefully study the mechanisms underlying their negative effects, especially in higher doses. It is hoped that a better understanding of the mechanisms underlying both the benefits and the untoward effects of statins will ultimately contribute to the development of novel, more effective therapies.

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http://dx.doi.org/10.1016/j.jacc.2014.03.038

Please note: Merck & Co., Inc. provided funding for the original study. Drs. Tawakol and Fayad received consulting fees and their institutions received grants from Roche and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Dr. Farkouh's institution received grants from Merck Sharp & Dohme Corp. Dr. Rudd is supported by the NIHR Cambridge Biomedical Research Centre. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Pulmonary Hypertension of Sickle Cell Disease Beyond Classification Constraints

We read with interest the "Updated Clinical Classification of Pulmonary Hypertension" by Simonneau et al. (1) in a recent issue of the *Journal*. We are concerned that although systemic sclerosis, portal hypertension, schistosomiasis, and chronic hemolysis result in pulmonary hypertension (PH) that spans several diagnostic groups, the rules for subgroup inclusion into Group I have not been consistently applied. On behalf of the American Thoracic Society–sponsored Clinical Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension in Sickle Cell Disease Committee (2), we would like to clarify several points. PH associated with chronic hemolysis has been moved to Group V in the 2013 classification based on: 1) different histopathology and lower pulmonary vascular resistance (PVR) compared with other pulmonary arterial hypertension (PAH) subgroups; and 2) no proven response to PAH-specific medications.

Although we agree that sickle cell disease–PH is multifactorial, the hemodynamics of pre-capillary PH in SCD need to be clarified. We have defined pre-capillary SCD-PH similar to other PAH subgroups: mean pulmonary arterial pressure ≥25 mm Hg with mean pulmonary capillary wedge pressure or left ventricular end-diastolic pressure ≤15 mm Hg, plus increased PVR. However, what constitutes increased PVR in SCD differs from other PAH subgroups. Anemia-induced elevation of cardiac output and reduction in blood viscosity results in a lower pre-morbid PVR (3). In idiopathic PAH, increased PVR is defined as ≥240 dynes·s·cm^{-5}, 2 SDs above the pre-morbid PVR of ≤80 to 120 dynes·s·cm^{-5}. Three hemodynamic studies (4–6) have demonstrated that SCD adults without PH had a mean cardiac output of 8 to 9 l/min with a PVR of 72 to 74 ± 25 to 38 dynes·s·cm^{-5}. In the absence of a consensus definition of elevated PVR in SCD, experts consider values that are 2 to 3 SDs above normal (i.e., ≥160 dynes·s·cm^{-5}) to be significant.

We agree that the literature evaluating PAH therapy in SCD-PH is limited. However, we also believe that the 3 clinical trials conducted in these patients are insufficient to determine whether SCD patients with pre-capillary PH should receive PAH therapy. These trials collectively enrolled only 14 patients with pre-capillary PH (fewer than one-half of whom received vasodilators), resulting in imprecisely estimated effects (7,8). There are 4 case series in which SCD patients with pre-capillary PH were treated with bosentan, sildenafil, and/or epoprostenol. Vasodilator therapy led to an increase in 6-min walk distance 41 to 144 m above baseline (9–11), with improvements in mean pulmonary arterial pressure, PVR, and cardiac index (11). On the basis of these studies combined with our clinical experience, we weakly recommended a trial of either an endothelin receptor antagonist or a prostacyclin analog for select SCD patients with symptomatic pre-capillary PH. We are concerned that the 2013 classification will limit access for these patients to clinically beneficial PAH-specific medications.

The reclassification of SCD-PH as Group IV, Group I, and now as Group V reflects the imprecise nature of the classification. It stresses the need to define PH subgroups so that all patients may benefit from the available treatment options.

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http://dx.doi.org/10.1016/j.jacc.2014.01.081

Please note: Dr. Gladwin has served as a consultant for Bayer. All other authors have reported that they have no relationships relevant to the contents of this article to disclose.

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Reply

Pulmonary Hypertension of Sickle Cell Disease Beyond Classification Constraints

The Second World Symposium on Pulmonary Hypertension, held in Evian, France, in 1998, settled the basis of the current classification system, representing a significant step forward as compared to the previous approach that separated pulmonary hypertension (PH) into primary or secondary forms (1).

Since then, PH has been classified into 5 different categories trying to group together patients sharing similar hemodynamic profile, pathological findings, and therapeutic approach/response.

Hemolytic anemia as an associated condition to the development of pre-capillary PH has been changed into group 5 not just because of the hemodynamic profile. Indeed, recent cohorts on PH associated to hemolytic anemias demonstrated a singular hemodynamic profile, as a consequence of high cardiac output, with elevated pulmonary pressures and low pulmonary vascular resistance (2–4). This fact was markedly relevant to support the decision of not including pulmonary vascular resistance as a mandatory part of the definition of PH, since different cardiac output states would demand different cutoffs of abnormality. Even more importantly, the available data on the pathological findings and treatment trials for patients with PH associated to hemolytic anemia have also been reviewed. As mentioned by Klings et al. (2), literature evaluating pulmonary arterial hypertension (PAH) therapy in sickle cell disease associated PH is limited. In fact, there is no consistent controlled data supporting the use of specific PAH therapy in this setting. Regarding pathology findings, differently from all other subforms of PAH included in group 1, many inconsistencies also exist regarding the pulmonary vascular findings in patients with sickle cell disease and PH. In the study from Haque et al. (5), 1 of the largest available series, most of the