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Letters

Effect of Baseline Anemia on Outcomes After Left Main Coronary Revascularization

Anemia is an independent predictor of mortality, major adverse cardiovascular events (MACE), and bleeding after percutaneous coronary intervention (PCI) and coronary artery bypass graft (CABG) surgery (1-3). The relationship between pre-existing anemia and revascularization outcomes in patients with left main coronary artery disease (LMCAD) has not been assessed. We thus examined the impact of baseline anemia in a pre-specified substudy from the EXCEL (Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease) trial, in which 1,905 patients with LMCAD and SYNTAX scores ≤32 were randomized to PCI with everolimus-eluting stents versus CABG (4).

Anemia was defined by World Health Organization criteria (hemoglobin <12 g/dl in women and <13 g/dl in men). The primary endpoint of EXCEL was 3-year rate of MACE, a composite of all-cause death, stroke, or MI, now extended to 5 years. Multivariable analyses were performed using a logistic regression model. Continuous relationships between hemoglobin and outcomes were assessed using restricted cubic splines with 4 knots at the 5th, 25th, 75th, and 95th percentiles.

Anemia was present in 468 of 1,888 (24.8%) patients with known baseline hemoglobin values. Among those with anemia, 254 (54.3%) and 214 (45.7%) were randomized to PCI and CABG, respectively. Mean hemoglobin values in patients with versus without baseline anemia were 11.5 ± 1.1 g/dl and 14.3 ± 1.1 g/dl, respectively. Patients with anemia were older; more commonly women; and more likely to have prior stroke, congestive heart failure, and other comorbidities. The use of oral anticoagulants and antiplatelet agents at 30 days and 5 years was comparable in patients with and without anemia.

Patients with baseline anemia had higher 5-year all-cause death compared with those without anemia (20.4% vs. 8.5%; adjusted odds ratio [OR]: 2.00; 95% confidence interval [CI]: 1.39 to 2.88; $p = 0.0002$), driven primarily by increased cardiac death (12.6% vs. 4.1%; adjusted OR: 2.26; 95% CI: 1.41 to 3.64; $p = 0.0007$). The presence of baseline anemia was also associated with greater 5-year rates of Thrombolysis In Myocardial Infarction (TIMI) major or minor bleeding (13.7% vs. 6.3%; adjusted OR: 2.02; 95% CI: 1.37 to 2.99; $p = 0.0004$) and blood transfusions (16.5 vs. 7.5%; adjusted OR: 2.15; 95% CI: 1.49 to 3.12; $p < 0.0001$), but not with MACE, noncardiac death, MI, or stroke.

No significant interactions occurred between anemia status and PCI vs. CABG for 5-year rates of MACE (31.0% vs. 24.6%, respectively; adjusted OR: 1.50; 95% CI: 0.93 to 2.42 in patients with anemia and 18.7% vs. 17.5%, respectively; adjusted OR: 1.12; 95% CI: 0.82 to 1.51 in patients without anemia, $p_{interaction} = 0.304$), nor were significant interactions present between anemia (overall and mild) and revascularization type for 5-year rates of death, MI, stroke, or TIMI bleeding. When baseline hemoglobin was assessed as a continuous measure, there were borderline interactions between hemoglobin level and 5-year MACE (**Figure 1**) and TIMI bleeding ($p_{interaction} = 0.040$), but not all-cause death (**Figure 1**). However, despite significant interaction, 5-year rates of blood transfusions were less after PCI than CABG in both patients with (12.9% vs. 20.8%; adjusted OR: 0.51; 95% CI: 0.29 to 0.90) and without (3.0% vs. 11.8%; adjusted OR: 0.20; 95% CI: 0.12 to 0.35) baseline anemia ($p_{interaction} = 0.02$).

This study demonstrates that baseline anemia is strongly and independently associated with 5-year all-cause and cardiac death, as well as clinically important bleeding and blood transfusions after PCI and CABG in patients with LMCAD. Although relative outcomes of PCI and CABG were largely consistent in patients with and without baseline anemia, major bleeding complications and the need for blood transfusions were less after PCI than CABG regardless of anemia status.

These results should be considered cautiously as subgroup testing is inherently underpowered, and the trial was not powered for assessment of several secondary endpoints that were not adjusted for

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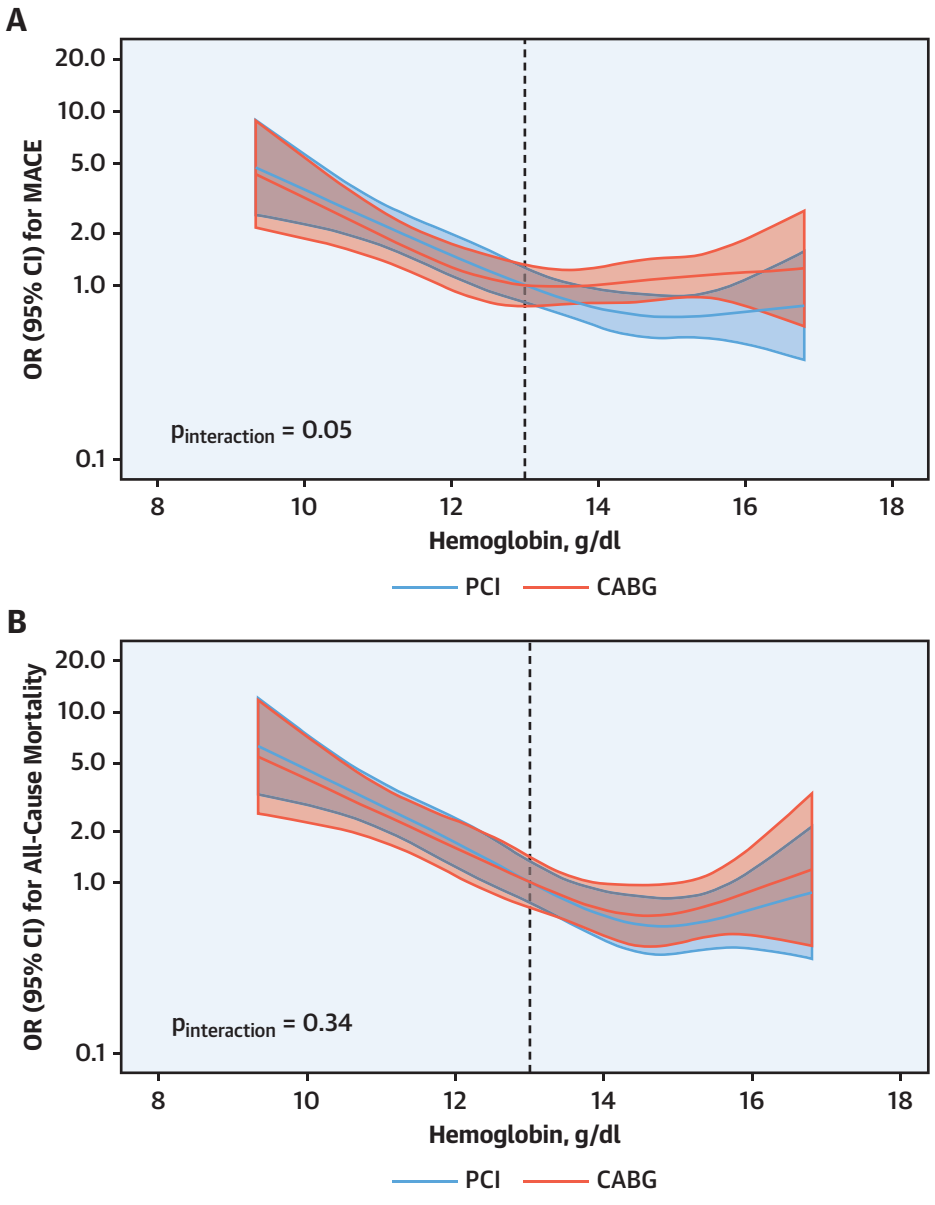
FIGURE 1 Spline Functions of 5-Year Outcomes According to Baseline Hemoglobin Level and Revascularization Modality



(A) Major adverse cardiovascular events (MACE); **(B)** all-cause death. Median (quartile 1, quartile 3) follow-up = 1,825 days (1,807, 1,825 days). CABG = coronary artery bypass graft; CI = confidence interval; OR = odds ratio; PCI = percutaneous coronary intervention.

multiplicity. In addition, randomization was not stratified by anemia status, and thus unmeasured confounders cannot be excluded. Specific thresholds for transfusion were not study mandated, and may have varied among the sites (and between PCI and CABG). Overall, based on these findings, risk factors other than baseline anemia should be considered when deciding between PCI and CABG for LMCAD.

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High-Density Lipoproteins Are the Main Carriers of PCSK9 in the Circulation

Proprotein convertase subtilisin/kexin type 9 (PCSK9), a secreted protein that regulates circulating low-density lipoprotein (LDL) through the hepatic LDL receptor degradation pathway, is the latest therapeutic target to further lower cholesterol in patients on maximal statin therapy (1). Circulating PCSK9 has been shown to bind to LDL and lipoprotein(a) (Lp[a]). The latter is an LDL particle carrying apolipoprotein(a) as an additional protein component (2,3). Furthermore, the multimeric state of PCSK9 is thought to be influenced by lipoproteins, including high-density lipoprotein (HDL), regulating the LDL receptor–degrading capabilities of PCSK9 (4). However, the presence of PCSK9 on other lipoprotein particles is less well established, in particular in humans.

The potential associations of PCSK9 with different human lipoproteins was first determined by immunocapture, as previously described (5). Alirocumab, a human monoclonal antibody to PCSK9, was coated as a capture antibody to measure plasma PCSK9 in 20 healthy volunteers. Antibodies specific for apolipoprotein(a), apolipoprotein B (ApoB), and apolipoprotein A1 were then used to interrogate PCSK9-lipoprotein associations with Lp(a), ApoB-containing lipoproteins, and HDL, respectively. Measurement of lipoprotein-associated PCSK9 suggested a predominant association of PCSK9 with HDL (**Figure 1A**). For validation, plasma was subject to an anti-ApoB immunoprecipitation (Sun Diagnostics, New Gloucester, Maine). Successful removal of ApoB-carrying lipoproteins, including Lp(a), as confirmed by targeted mass spectrometry, led to only a <20% removal of PCSK9 as measured by enzyme-linked immunosorbent assay (DY3888, R&D Systems, Minneapolis, Minnesota; data not shown). In contrast, HDL removal using an HDL immunodepletion column (Genway Biotech, San Diego, California) resulted in a >90% removal of PCSK9 from fasting plasma (data not shown).

Next, nondepleted plasma, HDL-depleted plasma, and the HDL fraction were compared for apolipoprotein A1 (ab52945, Abcam, Cambridge, United Kingdom) by immunoblotting (**Figure 1B**). Notably, efficient HDL depletion resulted in a profound enrichment of both full-length and furin-cleaved PCSK9 (ab181142, Abcam) in the HDL fraction. Targeted mass spectrometry, however, also revealed a nonspecific removal of up to 50% of ApoB upon HDL depletion. OptiPrep density gradient centrifugation (Sigma Aldrich, St. Louis, Missouri) has been used previously in the determination of PCSK9 association with LDL (2). When pooled fasting plasma was separated using OptiPrep gradients, apolipoprotein A1 was observed in the “heavy” and “medium” fractions. Thus, the LDL-containing “medium” fraction is not devoid of HDL. Finally, to address the ApoB contamination upon HDL depletion, the HDL immune isolation was repeated from the ApoB-depleted, “heavy” OptiPrep fraction. This experiment