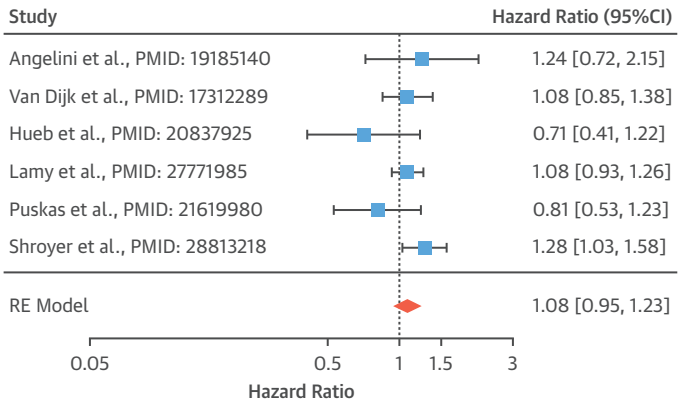
FIGURE 1 Forest Plot of Hazard Ratios for On-Pump Versus Off-Pump Coronary Artery Bypass Grafting



The **orange diamond** denotes the pooled hazard ratio (HR) and 95% confidence interval (CI). **Blue squares** indicate the HR in each study. **Black horizontal lines** represent the 95% CIs. Analyses in meta-analysis were conducted using the "metafor" package of the R software (R-3.1.2).

on-pump versus off-pump CABG needs to be recalculated.

In the present study, the HRs (from log-rank test or Cox regression model) of on-pump versus off-pump CABG were extracted from the 6 articles that were recruited by Smart et al. (1). Two studies did not provide the HR (3,4). According to the observed events in the on-pump and off-pump CABG groups and the p value for log-rank test, we calculated the HR and corresponding 95% confidence interval (CI). Altogether, the pooled HR for this comparison (on-pump vs. off-pump CABG) was 1.08 (95% CI: 0.95 to 1.23; p = 0.24, $p_{Heterogeneity}$ = 0.25) (**Figure 1**). The result indicates that long-term prognosis using on-pump CABG had no significant difference compared with those using off-pump CABG.

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Long-Term Outcomes Following Off-Pump Coronary Artery Bypass Grafting

Fixed-Effects Versus Random-Effects Models

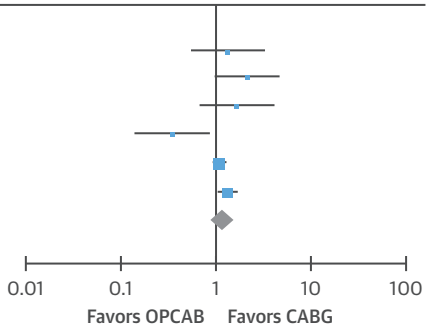
We read with interest the paper by Smart et al. (1) reporting superior mortality of coronary artery bypass grafting (CABG) compared with off-pump CABG (OPCAB) at 5-year follow-up. There are, however, some statistical issues that may affect the study's conclusions. The choice of fixed-effects model may be inappropriate. The fixed-effects model may be considered if all included studies are functionally identical (i.e., patient characteristics, surgeons, surgical techniques, etc., are identical across studies) and if the results are not intended to

FIGURE 1 Forest Plot for Off-Pump Versus On-Pump Coronary Artery Bypass Grafting

A

Study or Subgroup	OPCAB Events	OPCAB Total	CABG Events	CABG Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Mortality							
Van Dijk	12	142	9	139	8.1%	1.33 [0.54, 3.27]	2007
Angelini	20	200	10	201	9.9%	2.12 [0.97, 4.66]	2009
Hueb	13	155	8	153	7.9%	1.66 [0.67, 4.12]	2010
Puskas	7	98	18	99	7.7%	0.35 [0.14, 0.87]	2011
Lamy	346	2375	322	2377	35.4%	1.09 [0.92, 1.28]	2016
Shroyer	168	1104	131	1099	30.9%	1.33 [1.04, 1.70]	2017
Subtotal (95% CI)		**4074**		**4068**	**100.0%**	**1.19 [0.89, 1.58]**	
Total events	566		498				

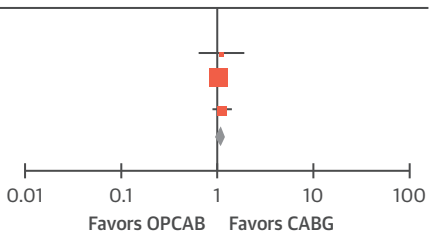
Heterogeneity: Tau^2 = 0.05; Chi^2 = 11.28, df = 5 (P = 0.05); I^2 = 56%
Test for overall effect: Z = 1.19 (P = 0.23)



B

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Mortality					
Angelini	0.09342168	0.28079411	5.2%	1.10 [0.63, 1.90]	2009
Lamy	0.03342376	0.07864831	65.8%	1.03 [0.89, 1.21]	2016
Shroyer	0.11394335	0.11853672	29.0%	1.12 [0.89, 1.41]	2017
Subtotal (95% CI)			**100.0%**	**1.06 [0.94, 1.20]**	

Heterogeneity: Tau^2 = 0.00; Chi^2 = 0.34, df = 2 (P = 0.85); I^2 = 0%
Test for overall effect: Z = 0.94 (P = 0.35)



Outcomes shown for **(A)** odds ratio analysis and **(B)** hazard ratio analysis of 5-year mortality following OPCAB versus CABG. CABG = coronary artery bypass grafting; CI = confidence interval; df = degrees of freedom; IV = inverse variance; M-H = Mantel-Haenszel; Random = random effects model; OPCAB = off-pump CABG; SE = standard error.

be generalized beyond the narrowly defined population (2). Thus, the fixed-effects assumption may be implausible for this study. The random-effects model is more appropriate due to its relatively conservative and generalizable estimates; the fixed-effects model is often reported only for comparison (3). Using corrected data and the random-effects model, there was no difference in 5-year mortality between OPCAB and CABG (13.9% vs. 12.2%, respectively; odds ratio [OR]: 1.19; 95% confidence interval [CI]: 0.89 to 1.58; I^2 = 56%) (**Figure 1A**).

Furthermore, the authors used OR for analysis of long-term outcomes. As opposed to "point-in-time" data, meta-analysis of survival using hazard ratios (HRs) is preferred due to the accounting for censoring, tolerance of unusual Kaplan-Meier curve behavior, and description of the entire patient experience over time (4,5). Three studies (including the 2 largest and most recent randomized trials) reported HR and showed no aggregated difference in 5-year mortality between OPCAB and CABG (HR: 1.06; 95% CI: 0.94 to 1.20; I^2 = 0%) (**Figure 1B**). The results were consistent between the new OR and HR analyses. Therefore, based on the statistical analysis presented by Smart et al. (1), it may be premature to make conclusions on long-term mortality following OPCAB versus CABG.

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REPLY: On the Use of Odds Ratios Versus Hazard Ratios, Meta-Regression, and Heterogeneity in Meta-Analyses

We thank the editor of the *Journal* for the opportunity to respond to the letters by Dr. Shah, Dr. Ma and colleagues, and Dr. Zhao and colleagues, which all make similar statements about 3 aspects of the methodology used in our recent meta-analysis. As the points raised are sufficiently similar, we will address them as if they were derived from the same letter.

First, the use of odds ratios instead of hazard ratios was raised in the letters to the editor. We concede that hazard ratios are preferable when they are reported because they take account of time to events and not only number of patient events. However, if, as in this case, some studies do not report hazard ratios and 95% confidence intervals or standard errors, then one cannot pool mortality data using this outcome. However, if studies report number of events as a proportion of total participants for each treatment arm, then one can calculate odds ratios or relative risk. Some of the authors of the letters took the trouble of calculating hazard ratios, but, depending on which letter one believes, 2 or 3 studies did not report hazard ratios, so this constituent data is inevitably unreliable across 2 or 3 of the 6 included studies.

Second, the absence of meta-regression analyses in our work was questioned. The Cochrane collaboration handbook section 9.6.4 suggests that a minimum of 10 included studies is required to justify meta-regression (1); as we only included 6 studies, we remain convinced that we made the correct decision not to conduct meta-regression analyses.

Third, the letters to the editor suggested heterogeneity in our analyses was moderate and a random effects model should have been used. In fact, 1 letter suggested that even if heterogeneity is low, a random effects model should be used. While we are familiar with the concept that meta-analyses by definition have an inherent element of randomness (2), we are also aware of the alternative view, shared by guidance from the Cochrane collaboration handbook (1), that a fixed-effects model is adequate unless heterogeneity is high, and $I^2\%$ = 49% is not considered high.

Taken together, the 3 points raised above have led to the authors of the 3 letters to conduct alternative analyses that suggest our findings should be tempered. It is premature to suggest there is truly a difference in outcomes in on-pump versus off-pump cardiac surgery. Perhaps we can agree that the methodological differences are unequivocal evidence that further trial work of a homogenous nature in this area is required.

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Elevated Cardiac Troponin T in Skeletal Myopathies

Skeletal TnT Cross-Reactivity and/or Cardiac TnT Expression?

We read with interest the paper by Schmid et al. (1), who described elevated cardiac troponin T (cTnT) concentrations in patients with skeletal myopathies in which they suggested cross-reaction of the high-sensitivity (hs-)cTnT immunoassay with skeletal muscle troponin T (skTnT) isoforms as the most likely cause. Others found cTnT messenger RNA expression in skeletal muscle, although it remained unknown if cTnT messenger RNA was quantitatively