likely achieved isolation distal to the PV left atrial junction. As demonstrated in our group I results, this approach would have limited the long-term cure rate. In addition, we have observed that many recurrences within the first two months’ postprocedure do not necessarily reflect a “true” failure. The time of assessment of the procedural success in our series could also have been partially responsible for the difference in the overall cure rate after the first procedure.

We disagree strongly to the conclusion that our patient selection criteria explain the better outcomes. Indeed, as evidence from our population (1) shows, it is obvious that we did not exclude any patient because of a history of AF or the presence of structural heart disease. In our cohort, nearly 50% of these patients had persistent or permanent AF, and about 21% had structural heart disease. Our only selection criteria were the refractoriness to at least two antiarrhythmic drugs and the presence of symptomatic AF.

Turco et al. also questioned our monitoring protocol postablation. However, as mentioned in our Methods section, we have used transtelephonic monitoring in addition to the routine Holter monitoring. Indeed, 100% of the patients reported in our series had one month of transtelephonic monitoring, and 96% underwent an additional month of transtelephonic monitoring during the six months following the procedure. Analysis of daily transmissions in our patients showed markedly different results than previously reported in other AF studies. As a matter of fact, asymptomatic episodes of AF were seen only in 2 of the 430 patients who underwent PV isolation at our institution. Conversely, 48% of the patients recorded episodes of symptomatic premature atrial contractions in addition to their daily transmissions. Indeed, 100% of the patients reported in our series had one month of transtelephonic monitoring, and 96% underwent an additional month of transtelephonic monitoring during the six months following the procedure. Analysis of daily transmissions in our patients showed markedly different results than previously reported in other AF studies. As a matter of fact, asymptomatic episodes of AF were seen only in 2 of the 430 patients who underwent PV isolation at our institution. Conversely, 48% of the patients recorded episodes of symptomatic premature atrial contractions in addition to their daily transmissions. These findings confirm that a highly symptomatic population was considered for ablation in our series.

Finally, Turco and colleagues strongly advised placements of both right and left atrial linear lesions in addition to PV isolation or as an alternative to PV isolation. However, in our series both right and left atrial flutters did not appear to be a relevant clinical problem when all PVs were successfully isolated. In fact, left atrial flutter was seen only in 3 of 430 patients post-PV isolation. Similarly, of the 108 patients with preablation documentation of atrial flutter/AF, only 3 required a right atrial isthmus line after successful PV isolation (5). In contrast, in our CARTO series (3) we reported a 20% occurrence of left atrial flutter, which reflected an inefficient approach in isolating most of the targeted PVs.

Therefore, we do not advocate preemptive placement of linear lesions, which seems to be important mostly when the PVs are not effectively isolated. We do realize that ablative strategies for the treatment of AF are rapidly evolving, and we appreciate the importance of alternative approaches as long as they are supported by rigorous testing.

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Statistical Versus Clinical Significance of the CURE Study in Acute Coronary Syndromes

In a recent issue of JACC, Drs. Khot and Nissen focused on the statistical versus clinical significance of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study in acute coronary syndromes (1). Several of their comments and concerns are appropriate, but we would like to point out a number of inaccuracies in their report.

They suggest that the CURE study (2) used a definition of myocardial infarction (MI) that included patients with only elevated serum troponin levels. In fact, the CURE definition of MI required at least two of the following: ischemic symptoms; elevation of markers (creatinine kinase-MB fraction or troponin) to at least twice the upper limit of normal; electrocardiographic changes. This definition is more strict than the recent European Society of Cardiology/American College of Cardiology (ESC/ACC) consensus document (3). Further evidence of a reduction in significant MIs was a 1.2% absolute decline in the rate of subsequent Q-wave infarctions. All MI events were adjudicated.

With respect to bleeding, it was suggested that the definition of minor bleeding was revised between the time of ACC presentation and its publication. In fact, no such change occurred in the definition. The 15.3% rate of minor bleeding reported by the ACC was an error that was corrected in the final report.

Regarding the applicability of the CURE trial to practice in the U.S., the proportion of patients in CURE undergoing cardiac procedures (catheterization [Cath] 44%; percutaneous coronary intervention [PCI] 21%; coronary artery bypass graft surgery [CABG] 16%) is very similar to other recent ACS trials (e.g., PURSUIT [4] [Cath 59%; PCI 24%; CABG 14%]). We agree that clopidogrel should be stopped five days before CABG if at all possible. With respect to the timing of surgery in U.S. practice, more recent data from the TACTICS/TIMI-18 study (5) demonstrate that the average time to cardiac surgery in the invasive arm in the U.S. was 5.5 days. In routine clinical practice outside of a clinical trial, it is likely that the waiting period is longer. Most patients in the U.S. who require surgery can therefore potentially benefit from this medication. In the small percentage of patients who require early surgery for clinical indications, the increased risk from bleeding on clopidogrel is only one of the issues that has to be considered in this high-risk patient group.

letters to the editor
With respect to cost-effectiveness of clopidogrel in acute coronary syndromes, data from the CURE study (6) show that the cost per event avoided with clopidogrel in the study is comparable to other cost-effective therapies in cardiovascular disease.

Strategies to prevent major cardiovascular events such as MI, cardiovascular death, and stroke are clinically important. Preventing two events per 100 people for nine months of therapy is comparable to most other treatments in the prevention of cardiovascular events, including aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins in patients following MI (7). Moreover, the cumulative impact of these various strategies add up to a large benefit. Therefore, we believe that CURE is not only statistically significant, but also that the results are clinically relevant and important.

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REPLY
We appreciate the interest by Drs. Joyner and Flather in our Viewpoint.

We did not intend to imply that troponin elevations alone were sufficient to meet the end point of myocardial infarction (MI), but rather that the addition of troponin to creatine kinase-MB fraction (CK-MB) measurements would increase the number of events counted as MI within the appropriate clinical context (chest pain/ electrocardiographic changes). Nevertheless, as noted in our Viewpoint, we acknowledge that clopidogrel reduces nonfatal MI.

The definition of minor bleeding—“other hemorrhages that led to interruption of the study medication” (1)—is considerably more selective than that used in other similar clinical trials (2). Requiring interruption of the study medication to achieve this end point will dramatically reduce reported minor bleeding (3). Thus, it is important to know the incidence of minor bleeding with clopidogrel using conventional definitions.

The rate of procedures in Clopidogrel in Unstable angina to prevent Recurrent Events (CURE), although similar to PURSUIT as a whole, is markedly less than that for U.S. patients in PURSUIT (catheterization 83%; percutaneous coronary intervention 35%; coronary artery bypass graft surgery [CABG] 20%) (4). Furthermore, the rate of revascularization during initial hospitalization is 55% in the U.S. compared with only 22% in CURE. Thus, CURE reflects a conservative management strategy not widely used in the U.S.

Citing an average time to surgery of 5.5 days in the U.S. from TACTICS/TIMI-18, the CURE investigators contend that stopping clopidogrel for five days prior to surgery would not delay the performance of CABG. This, however, is misleading. For one, they have chosen to cite the mean time to surgery from randomization rather than the median time. The mean time will, by its nature, be skewed higher by outliers yielding a larger value for the time to surgery. In contrast, the median time to surgery for all patients in TACTICS/TIMI-18 was only 3.7 days from randomization; it is almost certainly less in the U.S. (5). Furthermore, the most relevant time frame is the time from catheterization rather than randomization, as the decision to withhold clopidogrel will not occur until surgical anatomy is determined by cardiac catheterization. With catheterization being performed a median of one day after randomization, the CURE investigators are asking cardiologists and surgeons to routinely delay CABG for an average of six days after initial presentation. We find it very difficult to rationalize a routine six-day waiting period in this high-risk subgroup, who typically have severe left main and/or critical multivessel coronary artery disease.

Although clopidogrel may be “cost-effective,” this does not mean that it is without cost. Our simple calculations vividly illustrate the billions of dollars that would be spent to achieve the purported benefits of clopidogrel.

Finally, suggesting that clopidogrel is similar to aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, and statins greatly overstates its benefit. These four therapies all clearly reduce mortality; clopidogrel does not. Clopidogrel’s benefit is limited to nonfatal MI, making it crucially important to account for clinically significant end points such as major bleeding and strategic concerns regarding early CABG. Accounting for these real risks leads to the conclusion that routine administration of clopidogrel remains unwarranted, particularly in centers practicing an early revascularization strategy.

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