publication. The apparently contradictory findings between our study and that of others are potentially reconcilable when one appreciates that patients with ST segment depression in the LATE study had at least 2 mm of ST depression. This group was not specifically addressed within the Thrombolysis in Myocardial Infarction III study (2) (temporal window 0 to 12 h vs. 6 to 24 h in the LATE study). Moreover, the natural history studies of Lee et al. (3) have demonstrated that more prominent ST segment depression (i.e., ≥2 mm) is highly specific for the subsequent diagnosis of acute myocardial infarction and is also an indicator of increased risk. It is important to clarify that this group of patients did not have unusually prolonged pain but a prolonged time from the onset of pain to clinical presentation (i.e., >6 h).

We were careful to address obvious limitations of our study in the original manuscript and, in particular, did not advocate a change in the current thrombolytic therapy algorithm for acute myocardial infarction. We remain convinced, however, that some patients with significant ST segment depression may benefit from thrombolytic therapy and are pleased that Anderson shares our interest in the need for prospective validation.

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Basal Nitric Oxide Production by Diseased Coronary Arteries

Egashira et al. (1) in their interesting study examined the effects of intracoronary N^G-monomethyl-L-arginine (LNMMA, an inhibitor of nitric oxide synthesis) on basal coronary artery tone in patients with variant angina and normal coronary arteries and in control subjects. They reported that the constrictor response to LNMMA was significantly greater at spastic sites than at nonspastic sites. The magnitude of constriction in the control subjects did not differ significantly from that at the nonspastic sites. Their results indicate that the basal release of nitric oxide is increased rather than decreased at the spastic site in patients with variant angina. The authors did not examine the effect of atheroma on basal nitric oxide production, but they acknowledge this limitation. This limitation is particularly relevant because many patients with spasm have underlying atheroma.

We recently examined (2,3) the effects of an intracoronary infusion of LNMMA in patients with chronic stable angina and coronary artery disease and in patients with normal coronary arteriograms. The diameter of angiographically normal proximal and distal segments and coronary stenoses was measured by quantitative angiography. In response to an LNMMA infusion of 16 μmol/min for 4 min, there was a significant reduction ($p < 0.01$) in lumen diameter of the distal segments of diseased arteries and at the site of stenosis but no change ($p = NS$) in lumen diameter of the proximal segments (3). In patients with normal coronary arteriograms, there was a significant reduction ($p < 0.01$) in lumen diameter of both proximal and distal segments (2).

These results indicate that basal nitric oxide production is preserved at the site of stenotic atheromatous plaques. Because it appears to be absent in the proximal segments of diseased arteries in which the stenoses were mostly located, it is possible that regeneration of basal nitric oxide production has occurred. There is some laboratory evidence to support this hypothesis because the inducible isoform of nitric oxide synthase has been found in human atherosclerotic lesions ex vivo, where it is localized with macrophages, foam cells and vascular smooth muscle cells (4). Furthermore, the amount of nitric oxide synthase present is related to the severity of the lesion. We therefore propose that atherosclerotic coronary arteries can regenerate basal nitric oxide production from an abnormal source.

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Reply

Our study was designed to test the hypothesis that basal production/release of nitric oxide (NO) is altered at site of spasm in patients with

variant angina and normal coronary angiograms. Our results suggest that basal production/release of NO may not be decreased at spastic sites in these patients. We did not investigate the NO-generating capacity or vasomotor responses to vasoconstrictor stimuli at the site of spasm. Therefore, we cannot conclude that the NO-generating capacity is augmented at spastic sites.

Tousoulis et al. proposed an intriguing hypothesis that atherosclerotic human coronary arteries can regenerate basal NO production from an abnormal source, such as the inducible isoform of NO synthase. This hypothesis is based on the fact that patients with variant angina have varying degrees of coronary atherosclerosis and that the inducible NO synthase is found in some human coronary arteries segments with atherosclerotic lesions. It has been demonstrated that total NO-generating capacity is altered during the process of atherosclerosis (1); however, its precise mechanism has not been well understood. There is substantial evidence demonstrating that endothelium-derived NO-related vasodilation is impaired early in atherosclerosis (1). However, the results of recent investigations (2,3) suggest that endothelial constitutive NO synthase messenger RNA and NO protein production are augmented in atherosclerotic vessels. These findings suggest that altered NO-related vasomotion during atherosclerotic process might result from an increased breakdown of NO but is not necessarily related to expression of inducible NO synthase. It is unknown whether NO that is generated from inducible NO synthase contributes to regulation of vasomotor tone. Therefore, I believe that the currently available data are not sufficient to support the hypothesis by Tousoulis et al. Much more investigation remains to be done before their hypothesis is substantiated.

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Cost Efficacy Modeling of Catheter Reuse for Percutaneous Transluminal Coronary Angioplasty

I wish to comment on the report by Mak et al. (1) and indirectly on the accompanying editorial by Natarajan and Williams (2). Although the report by Mak et al. is well written and discusses an important topic, it seems to me that the authors have made several major assumptions in their cost analysis that have gone unstated and unexamined. In particular, the authors assume that the price, or cost, of balloon catheters is a fixed quantity and would not change if the results of their study were applied widely, even for a subset of patients with stable angina. Would the medical device industry really be able to continue to charge the same price for balloon catheters if the total number sold was reduced by 80% ("best" case)? How can this possibly make economic sense, since presumably the marginal cost for the production and sales of any product is dependent, to some extent, on the volume of sales. The authors might argue that their analysis is one of microeconomics and that the "system" would not be affected if the results of their analysis were applied only on a small scale, to their medical center, say. Yet their motivation is clearly macroeconomic in scope because they claim that "If coronary angioplasty equipment could be reused [based on the results of this and other studies], the total cost could be potentially reduced by more than $1 billion per year in the United States." The systemic implications of this type of inquiry are also implied by the accompanying editorial, which refers to the yearly total charges for angioplasty in the United States of $6 billion.

The reason that this glaring oversight is important is that this report, and others like it, will be used by policymakers interested only in short-term cost reduction and not on the larger question of who should bear the cost of innovation, including innovation that might ultimately (but not necessarily immediately) reduce overall costs and improve care. When policymakers advocate reuse, even in "low risk" settings (or any such "cost reduction"), they are reducing the incentive for entrepreneurs and inventors to develop new technologies that might ultimately improve outcomes. This is not to excuse manufacturers from pricing devices or drugs so as to result in unreasonably high profits, but it needs to be remembered that the costs of developing any new medical technology are large and growing, and industry bears the majority of such costs. Those costs are in turn built into the price of each device sold, and if fewer are sold, either the price must rise concomitantly or innovation will simply not occur.

Another cost not mentioned is that associated with the medicolegal ramifications of reuse. Although reuse of balloon catheters labeled "single-use only" is not a prima facie violation of standard of care, it certainly transfers some of the medicolegal burden to those who willingly violate Food and Drug Administration labeling. Thus, one can reasonably assume that in some percentage of cases where reused catheters cause a complication or additional procedure that might not have occurred with a new catheter, a patient will become a plaintiff with a willing attorney and medical expert willing to say that reuse violates standard of care. Furthermore, in some of those cases the jury will agree with the plaintiff and award damage costs on the order of 10 to 20 times actual costs. If this series of assumptions is entered into the cost-efficacy model developed by the authors, it might well shift the cost-efficacy toward single use.

A final issue that was not discussed in the report by Mak et al. relates to the way in which some part of hospital cost savings are implicitly shifted as expenses for physicians, without any clear mechanism for the physicians to recoup those extra expenses. In particular, procedures performed with reused catheters are likely to take longer (81 vs. 68 min was used in the study by Mak et al.), with much of that extra time requiring exposure of the operator to potentially harmful fluoroscopic radiation. Thus, the hospital saves money on catheters while physician reimbursement per unit time falls (because he or she is not likely to collect more for the same procedure, which takes longer simply because of reuse), and his or her long-term risk of radiation exposure rises. Perhaps when physicians and hospitals are in a true revenue-sharing relationship (such as in a provider-owned health maintenance organization or foundation such as the Cleveland Clinic), this cost shifting is irrelevant, but in most delivery systems and hospitals, both for-profit and not-for-profit, including our own University Medical Center, cost savings by the hospital are not transferred to the physicians, even if they incur additional expenses. This is, of course, an issue that goes well beyond that of balloon catheters and gets into the matter of how willing we should be, as physicians and researchers,