

Primary Percutaneous Coronary Intervention

TO THE EDITOR: In their review of primary percutaneous coronary intervention (PCI) for myocardial infarction with ST-segment elevation, Keeley and Hillis (Jan. 4 issue)¹ cite the guidelines of the American College of Cardiology and American Heart Association (ACC–AHA): “Primary PCI is preferred if a . . . catheterization laboratory with surgical backup [is] available and if the procedure can be performed within 90 minutes after initial medical contact. . . .”² Nationally, for 55% of patients who have myocardial infarction with ST-segment elevation, the door-to-balloon time is less than 90 minutes.³ Between January 2006 and July 2006, the hospital with the highest percentage of patients with myocardial infarction with ST-segment elevation meeting this criterion was a rural hospital that did not have surgical backup: 100% of the patients had door-to-balloon times of less than 90 minutes, and the average time was 55 minutes. Among these patients, there was no increase in complications.

Some rural areas have sufficient population to support a program in interventional cardiology but not a program in cardiac surgery. In rural communities, traffic congestion is rarely a problem, so that an interventional team could get to the hospital quickly. Primary PCI can be performed safely with superior results in rural settings without surgical backup.⁴ The ACC–AHA guidelines might compromise the care provided to patients with myocardial infarction with ST-segment elevation who live in rural communities.

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TO THE EDITOR: In their article on primary PCI for patients who have myocardial infarction with ST-segment elevation, Keeley and Hillis describe the management of this potentially fatal coronary event, including medical treatment and mechanical therapy with primary PCI. However, some additional points should be addressed. The authors state that clopidogrel should be administered after it has been determined that emergency bypass surgery is not required. Recent study data indicate that the administration of clopidogrel before PCI significantly reduces the incidence of death from cardiovascular causes or from ischemic complications without a significant increase in bleeding.^{1,2} Furthermore, the addition of the selective aldosterone blocker eplerenone to optimal medical therapy has been shown to reduce morbidity and mortality among patients with acute myocardial infarction complicated by left ventricular dysfunction and heart failure and thus should have been mentioned in this article.³ Finally, because of possible adverse effects on the clinical outcome, the risk of thrombocytopenia induced by treatment with heparin or glycoprotein IIb/IIIa inhibitors should also be noted.

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TO THE EDITOR: Keeley and Hillis ignore atheroembolic renovascular disease as a cause of nephropathy in patients who have undergone PCI. Atheroembolic disease accounts for approximately 5 to 10% of cases of acute renal failure¹ and is an increasingly common cause of renal insufficiency in the elderly. A review of 372 autopsies identified cholesterol emboli in 2.4% of renal-tissue samples. Inciting events, including vascular surgery, arteriography, angioplasty, anticoagulation

with heparin, and thrombolytic therapy, can be identified in 50% of cases of cholesterol embolization. Arteriographic procedures are the most common cause of cholesterol embolization.² Showers of cholesterol emboli occur in about 50% of PCIs when a guiding catheter is passed through the aorta.^{3,4} Most of these showers are clinically silent. In approximately 1% of high-risk patients, an acute cholesterol emboli syndrome develops, which is manifested as acute renal failure, mesenteric ischemia, decreased microcirculation to the extremities, and, in some cases, embolic stroke.³ Since most cases of atheroembolic kidney disease are triggered by angiography, radiocontrast-induced nephropathy is easily invoked as an alternative diagnosis.¹

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THE AUTHORS REPLY: We congratulate Brown et al.¹ on their excellent outcomes with the use of primary PCI at a rural hospital without surgical backup, but we disagree that this procedure can be performed consistently in this setting and under these circumstances "safely with superior results." The favorable results of primary PCI reported in selected community hospitals that do not have surgical backup, such as the data reported by Brown et al.,¹ may not be achieved reliably at other facilities. Although urgent coronary-artery bypass grafting (CABG) is not commonly required for patients undergoing primary PCI, it is, in fact, necessary for an occasional patient, and the need often cannot be predicted. When CABG is required, the resultant delay incurred by the transfer of the patient to another facility can result in

high morbidity and mortality.² Primary PCI has been clearly shown to be safe and effective at high-volume centers with surgical backup, with supporting data from 23 randomized, controlled trials.³ In contrast, only one randomized trial comparing primary PCI and fibrinolytic therapy at community hospitals without surgical backup has been reported.⁴ As a result, according to the ACC-AHA guidelines,⁵ primary PCI without surgical backup is a class IIb indication.

As noted above, an occasional patient undergoing primary PCI requires urgent CABG. In such a patient, previous administration of clopidogrel substantially increases the risk of perioperative bleeding. For this reason, clopidogrel should not be given in the setting of primary PCI until it is clear that bypass surgery is not required. In some patients undergoing PCI, thrombocytopenia may develop after the administration of a combination of a platelet glycoprotein IIb/IIIa inhibitor and heparin; the risk is similar among those undergoing primary PCI for myocardial infarction with ST-segment elevation and those undergoing elective PCI. Currently, administration of the selective aldosterone blocker eplerenone is not considered a standard of care for patients who have myocardial infarction with ST-segment elevation.

Although an occasional patient undergoing an arteriographic procedure may have cholesterol embolization, most cholesterol emboli, as noted by Kashyap et al., are clinically silent. Only rarely do cholesterol emboli cause acute renal failure.

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the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *Circulation* 2004;110:588-636. [Erratum, *Circulation* 2005;111:2013.]

Effects of Dietary Nitrate on Blood Pressure

TO THE EDITOR: Larsen and colleagues (Dec. 28 issue)¹ report that oral nitrate (NO_3^-) can lower mean arterial blood pressure and is associated with an elevation in blood levels of nitrite (NO_2^-). They point out that nitrate is reduced by oral bacteria to nitrite, which can be converted into nitric oxide or absorbed, and they suggest that the mechanism involved in the blood-pressure-lowering effect needs to be clarified.

In studies conducted over the past 5 years, we have shown that nitrite is an intrinsic vasodilator.^{2,3} Within the vasculature, nitrite is reduced to nitric oxide by reaction with deoxygenating hemoglobin and possibly other heme proteins.^{4,5} These studies show that nitrite levels are higher in the arteries than in the veins in humans, indicating metabolism across the peripheral circulation, and that when nitrite is infused into the brachial artery, it causes vasodilatation. We recently completed a study evaluating the effect of low-dose nitrite infusion in 15 healthy volunteers and found that levels as low as 350 nM resulted in measurable vasodilatation in the forearm; mean (\pm SE) values of blood flow ranged from 3.0 ± 0.3 to 3.4 ± 0.3 ml per minute per 100 ml of forearm tissue ($P=0.04$). We are therefore not surprised that increases in nitrite levels from 138 nM to 219 nM caused by increased dietary intake of nitrate are associated with decreases in blood pressure.

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THE AUTHORS REPLY: We agree that nitrite reduction to nitric oxide is a likely explanation of the hypotensive effects of nitrite, as reported in our letter. We were also not very surprised, since we had previously shown that the administration of oral nitrate leads to increased levels of circulating nitrite¹ and that near-physiologic levels of nitrite induce cyclic guanosine monophosphate-dependent vasodilatation in vitro.² Multiple pathways for systemic nitrite conversion to nitric oxide have now been described,^{3,4} but the letter format did not allow a detailed discussion. Dejam and colleagues report vasodilatation at very low plasma levels of nitrite, which supports our findings, although a local infusion of nitrite into the forearm is not directly comparable to oral nitrate supplementation. Dietary nitrate gives sustained delivery of low-dose nitrite to the circulation, and oral commensal bacteria are essential, since mammalian enzymes cannot effectively metabolize this anion. Circulating nitrate is greatly enriched in saliva, and nitrite is then formed by bacterial nitrate reductases.⁴ An astonishing overall conclusion from this finding is that, in fact, symbiotic bacteria are involved in the regulation of cardiovascular function in humans.

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