News and Views From the Literature

Ischemic Heart Disease

Myocardial Perfusion and ACE Inhibition

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Two important topics are investigated: the value of an index of myocardial perfusion and targeting angiotensin-converting enzyme (ACE) inhibitors in patients with cardiovascular disease.

For years, the standard method of angiographic assessment of outcomes after reperfusion therapy has been the Thrombolysis in Myocardial Infarction (TIMI) flow grade. Some of the limitations of this method of evaluation appear to have been overcome recently by using a new index of coronary blood flow called the Corrected TIMI Frame Count (CTFC), in which the number of frames required for dye to reach standardized landmarks on the coronary tree are counted. Faster (lower) 90-minute CTFCs are related to improved in-hospital and 1-month clinical outcomes after thrombolytic administration in both univariable and multivariable models. Even among patients classified as having normal TIMI grade 3 flow, a CTFC of 40 identifies a lower-risk subgroup.[1]

There has, however, been a shift in focus toward an assessment of myocardial perfusion, in addition to flow in the infarct-related artery, at an epicardial level. Several studies have used myocardial contrast echocardiography or MRI to evaluate the extent of myocardial perfusion.[2,3]

Relationship of TIMI Myocardial Perfusion Grade to Mortality After the Administration of Thrombolytic Drugs

Gibson CM, Cannon CP, Murphy SA, et al.
Circulation. 2000;101:125-130.

The article by Gibson and colleagues in the TIMI Study Group discusses a new and simple angiographic method to assess the filling and clearance of contrast in the myocardium as an index of myocardial perfusion (the extent of myocardial blush). Although this method requires further validation, this study emphasizes the importance of myocardial perfusion, as opposed to the immediate and more transparent objective of achieving normal flow in the epicardial vessel. In 762 patients in the TIMI 10B trial, TIMI myocardial perfusion (TMP grade) was scored from 0 to 3, with grade 3 reflecting more extensive myocardial perfusion (Figure). There was a striking mortality gradient across TMP grades, ranging from 2% with TMP grade 3 to 4.4% and 6% in patients with TMP grade 2 and grades 0 to 1, respectively. The differences in mortality are particularly striking among patients with normal TIMI grade 3 flow in the epicardial arteries. In this subset with ostensibly normal epicardial flow in the infarct-related artery, 30-day mortality was 0.73% for TMP grade 3, compared with 2.9% and 5% for patients with TMP grades 2 and 0 to 1, respectively. This relationship persisted after multivariate adjustments.

Studies such as this point us toward 1 of the new frontiers of reperfusion therapy: the elimination of reperfusion injury and microvascular dysfunction. These 2 entities are interrelated, but their impact on the objective of reperfusion therapy—namely myocardial salvage—is similar. The mechanisms are complex and include diverse pathophysiologic processes, such as inflammation (mediated via activation of neutrophils and the complement system), microvascular spasm and embolization, an altered metabolic milieu and, perhaps, ischemic preconditioning. The potential therapeutic targets are extensive, and several trials are ongoing. Generally, initial results have not been encouraging, although in the Acute Myocardial Infarction Study of Adenosine (AMISTAD) trial,[4] the use of adenosine appeared to be promising in reducing infarct size, particularly in patients with anterior infarct undergoing thrombolysis. Although preliminary investigations of other agents that are aimed at attenuating reperfusion injury have been unsuccessful, these are "early days," and there is a great deal to be learned from a mechanistic standpoint. Nonetheless, as the problems of restoring and maintaining epicardial flow are gradually overcome, our attention will shift downstream to the integrity of the microvasculature and epicardium.

Another challenge will be the noninvasive assessment of epicardial flow. Myocardial contrast echocardiography is highly promising, but will the newer intravenous contrast agents be adequate to the task? Continuous 12-lead ST-segment resolution analysis is an inexpensive and at-

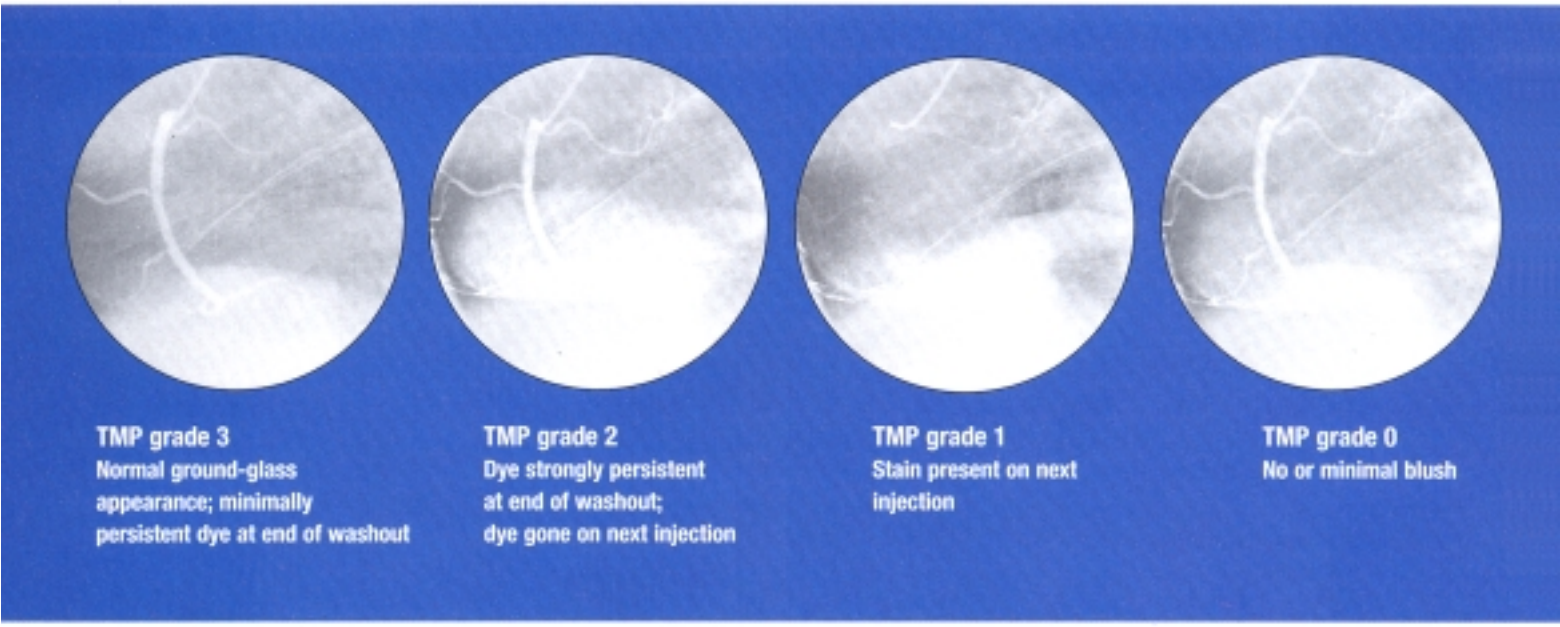

Figure. TIMI myocardial perfusion (TMP) grades. Diffuse myocardial blush characterizes TMP grade 3, giving a ground-glass appearance; at the end of the washout period, there is minimal or no dye. In TMP grade 2, dye enters the myocardium but accumulates and exits more slowly; dye in the myocardium strongly persists at the end of the washout phase. In TMP grade 1, dye stays in the myocardium; there is either a focal stain on the next injection or a diffuse glow of the myocardium. In TMP grade 0, dye does not enter the myocardium, and minimal or no blush is seen during the injection and washout phases. (TIMI, Thrombolysis in Myocardial Infarction.)

tractive option that predicts 30-day outcomes independent of TIMI flow grades in patients receiving thrombolytic therapy.[5] Moreover, among patients undergoing primary percutaneous transluminal coronary angioplasty (PTCA), an ECG performed before the intervention was compared with an ECG performed immediately on return to the intensive coronary care unit after PTCA. The presence or absence of a 50% or greater reduction in ST-segment elevation on an ECG post-PTCA identified patients who were less likely to benefit from early restoration of flow in the infarct-related artery, probably because of microvascular damage and, hence, less myocardial salvage.[6]

Although the methodology may change, the emphasis on the integrity of myocardial perfusion as the primary objective of acute reperfusion therapy will likely continue to be a major focus of investigation in the near future.

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The Heart Outcomes Prevention Evaluation (HOPE) studies have major implications for clinical practice and add an important new chapter to the constantly unfolding story of ACE inhibition in the treatment of patients with cardiovascular disease.

Effects of an Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients. The Heart Outcomes Prevention Evaluation Study Investigators

Yusuf S, Sleight P, Pogue J, et al.
N Engl J Med. 2000;342:145-153.

Effects of Ramipril on Cardiovascular and Microvascular Outcomes in People With Diabetes Mellitus: Results of the HOPE Study and MICRO-HOPE Substudy

Heart Outcomes Prevention Evaluation (HOPE) Study Investigators.

Lancet. 2000;355:253-259.

The HOPE study enrolled 9297 high-risk patients aged 55 years or older who had evidence of either cardiovascular disease or diabetes plus 1 other risk factor but were not known to have an ejection fraction of less than 40 or a history of heart failure. Patients were randomized to ramipril, 10 mg/d, or placebo, and there was a composite of cardiovascular causes, myocardial infarction (MI), and stroke.

The trial was a 2 × 2 factorial study evaluating both ramipril and vitamin E, but this review will be confined to the former.

The results are strikingly positive, with a reduction not only in the primary composite end point but also in multiple other end points. Treatment with ramipril reduced death from cardiovascular causes (6.1% vs 8.1%, $P < .001$), MI (9.9% vs 12.3%, $P < .001$), stroke (3.4% vs 4.9%, $P < .001$), and all-cause mortality (10.4% vs 12.2%, $P = .005$). In addition, the other secondary end points, such as revascularization procedures, cardiac arrest, congestive heart failure, and complications related to diabetes, were significantly reduced in the ramipril group. The results in a subset of 3577 patients with diabetes (all of whom were aged 55 years or older, had a prior cardiovascular event, or had at least 1 cardiovascular risk factor and were without evidence of proteinuria) were similar. Ramipril was beneficial for both cardiovascular events and the development of overt nephropathy.

Initial trials of ACE inhibitors in survivors of an MI or in patients with left ventricular dysfunction were based on the strong experimental evidence suggesting that ACE inhibition prevented left ventricular remodeling, dilatation, and congestive heart failure, primarily as a result of an afterload reduction.[1-3] These trials were overwhelmingly positive, but less easily explicable (at least on the basis of the generally proposed mechanisms involving remodeling) was the marked reduction in recurrent ischemic events in patients treated with enalapril and captopril.

Nonetheless, for many years, experimental work had drawn attention to the very powerful but complex cellular and molecular effects of the renin-angiotensin-aldosterone system, in concert with angiotensin II, on vascular smooth muscle function, inflammation, and thrombogenesis.[4] In the experimental models, ACE inhibition was demonstrated to reduce angiotensin to an increased nitric oxide activity, thus reducing vascular smooth muscle growth, proliferation and migration, inflammation, oxidative stress, and thrombogenicity mediated by aplatelet and plasminogen activator inhibitor type I activity. In addition, at a cellular level, angiotensin II appears to be a powerful promoter of the development of left ventricular hypertrophy, tissue remodeling, and collagen deposition.

In this respect, the HOPE trial, in which a relatively small drop in blood pressure seems insufficient to account for the magnitude of benefit, appears to provide quite convincing "proof of concept" of the effects of ACE inhibition at a cellular level. Nonetheless, it should be mentioned that an alternative explanation is that even very small blood pressure–lowering effects may have a significant impact on mortality in high-risk patients, such as those included in the HOPE trial.

All good trials provide answers and generate new questions; in this respect, HOPE is no different. Does this mean that all patients with cardiovascular disease or hypertension should receive ACE inhibitors? Should all MI survivors, and not just those with left ventricular dysfunction, be treated with ACE inhibitors? Should our patients, many of whom are elderly, be taking an ACE inhibitor in addition to ß-blockers, or should the former replace a ß-blocker? This is obviously relevant in postinfarct survivors in whom the benefits of ß-blockade are well established. What about side effects in patients already on other vasodilators and preload-reducing agents, such as nitrates and diuretics?

With regard to diabetics and hypertension, ACE inhibitors have been considered first-line therapy for years, and few would argue about their role in patients with diabetes who have nephropathy or in patients with severe peripheral vascular disease. What is more controversial is patients with stable coronary artery disease: MI survivors with a well-preserved ejection fraction and a negative stress test in whom risk-factor reduction (including lipid-lowering therapy) is already being initiated. There are 2 other large trials still in progress and, hopefully, they may clarify some of the issues. The Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) trial is being carried out in North America and Italy using trandolapril, and the European Trial on Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) is using perindopril. Preliminary data from the latter (M. Simoons, personal communication, January 2000) suggests that the HOPE population is at particularly high risk among patients with peripheral vascular disease, diabetes, prior stroke, or transient ischemic attack and hypertension.

Hopefully, the results of these 3 trials will amplify our knowledge of who will or will not benefit from ACE inhi-

bition. Other issues that need to be addressed in the near future include the question of a class effect (ramipril vs other ACE inhibitors) and interactions with aspirin. The latter is currently one of the objectives of the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial.[5] (B. Massie, personal communication, March 2000). Nonetheless, it must be clear that the indications for ACE inhibition will be radically expanded during the next 5 years. Vasodilation may be good, but the impact of these agents has exceeded all initial expectations and probably goes way beyond that expected from afterload reduction alone.

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Women's Cardiovascular Health

Estrogen Replacement Therapy

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Prospective cohort studies have suggested that estrogen replacement therapy decreases the risk of coronary events in postmenopausal women.[1-3] Although much of the apparent benefit of hormone treatment has been attributed to a favorable alteration in lipid profile,[4] modulation of coronary vasoactivity and protection by estrogen of low-density lipoprotein (LDL) cholesterol from oxidation have also been implicated.[5-7]

Use of vitamin E supplements has also been reported to decrease cardiovascular events in women.[8] In addition, vitamin E, the most abundant lipid-soluble antioxidant in biologic membranes, has been shown to improve endothelium-dependent relaxation and protect LDL from oxidation in animal models.[9,10]

Two recent studies have evaluated the vascular effects of these therapies in postmenopausal women.

Vascular Effects of Estrogen and Vitamin E Therapies in Postmenopausal Women

Koh KK, Blum A, Hathaway L, et al.
Circulation. 1999;100:1851-1857.

In this study, 28 healthy postmenopausal women were randomly assigned to conjugated equine estrogens (CE), 0.625 mg/d; vitamin E, 800 IU/d; and their combination in a double-blind, 3-period crossover study (treatment for each of 3 6-week periods, with 6 weeks off all therapies between treatment periods). Measurements were made before and after each treatment period. The ratio of LDL to high-density lipoprotein cholesterol and lipoprotein(a) significantly decreased in patients receiving therapies including CE but significantly increased in those receiving vitamin E therapy alone. Brachial artery flow-mediated dilation, a bioassay for nitric oxide bioavailability, improved significantly in patients receiving any of the therapies, compared with pretreatment values. CE, but not vitamin E, lowered serum markers of inflammation; and CE, alone or in combination with vita-min E (but not vitamin E alone), lowered or showed a trend for lowering plasma levels of plasminogen activator inhibitor type 1. The authors concluded that estrogen and vitamin E therapies similarly improve arterial endothelium-dependent vasodilator responsiveness consistent with increased nitric oxide in healthy postmenopausal women, despite divergent effects on atherogenic lipoproteins. Only estrogen, however, reduced markers of vascular disease.

Interestingly, although the authors hypothesized that the differing biologic effects of estrogen and vitamin E therapies might result in dissimilar vascular effects, in fact, conventional-dose CE therapy and high-dose vitamin E therapy had similar effects on brachial artery flow-mediated dilation and had no additive effect when the therapies were combined; however, the absence of the latter effect may be because of the large improvement in flow-mediated dilation from each therapy alone. It may not be possible to demonstrate an additive effect of these therapies in healthy postmenopausal women. The effects may be more apparent in patients with impaired endothelial function, such as those with hypercholesterolemia.

The authors were careful to measure markers of fibrinolysis inhibition and inflammation that, on the basis of clinical and experimental studies, are potentially affected

by estrogen and vitamin E therapy. Only CE significantly reduced these serum markers, with the greatest effect noted on E-selectin, the cell adhesion molecule specific to the activated endothelium. E-selectin has been localized in atherosclerotic plaque and has been found in high levels when restenosis develops in patients following peripheral balloon angioplasty.

Randomized clinical trials currently in progress may determine the appropriate role of estrogen and vitamin E therapies as primary prevention of atherosclerotic cardiovascular disease in healthy postmenopausal women. Until then, the risks and benefits of these therapies must be considered carefully. Based on available data, it is premature to make population-wide recommendations about vitamin E supplements, although it is prudent to suggest to patients that their daily intake of vitamin E be sufficient to meet the Recommended Dietary Allowance.

Long-term Estrogen Replacement Therapy Is Associated With Improved Exercise Capacity in Postmenopausal Women Without Known Coronary Artery Disease

Redberg RF, Nishino M, McElhinney DB, et al.
Am Heart J. 2000;139:739-744.

To determine whether use of hormone replacement therapy (HRT) is associated with improved exercise capacity, 248 postmenopausal women without known coronary artery disease (CAD) were evaluated. Maximal oxygen uptake ($\dot{V}O_{2max}$) and anaerobic threshold as objective markers of exercise capacity were measured (during symptom-limited, Bruce protocol–exercise treadmill testing with continuous respiratory gas analysis). Factors potentially affecting exercise capacity were recorded. The relationship between exercise capacity and use of HRT was analyzed with the use of logistic regression, controlling for confounding variables.

HRT was currently being used by 44% of patients (48% of whom were using combination treatment), for a mean of 9.9 ± 9.1 years, and was never used in 36% of women. Both the prevalence of hypertension and low-density lipoprotein cholesterol were lower in HRT users, although there was no difference between groups in the prevalence of other risk factors or of osteoporosis. Exercise fitness was significantly greater in HRT users (current or past) than in nonusers, and HRT was an independent predictor of exercise fitness, which was not confounded by age or physical activity level. Furthermore, combination therapy (estrogen plus progestin) did not diminish the increased fitness in the HRT users. The authors concluded that HRT is associated with increased exercise capacity, as measured by $\dot{V}O_{2max}$ and anaerobic threshold, in postmenopausal women without known CAD.

In addition to its favorable effect on lipid profile, estrogen has been shown to have beneficial effects on the vasculature.[4,5] Short-term estrogen administration has been reported to result in peripheral and coronary artery vasodilation (although long-term administration may attenuate this response) in postmenopausal women with cardiovascular disease.[11-14] Long-term treatment has been shown to improve flow-mediated endothelium-dependent peripheral vasodilation.[15] This estrogen-mediated decrease in peripheral vascular resistance may relate to the increase in exercise fitness reported herein. This study extends our knowledge of the effect of long-term HRT in healthy postmenopausal women. ■

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