

EDITORIAL COMMENT

Angiotensin-Converting Enzyme Inhibitors: Ischemia Is Not the Correct Measure of Benefit*

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Many or even most patients with coronary disease and chronic stable angina will obtain complete relief of symptoms with percutaneous coronary intervention (PCI) (1). When coupled with appropriate management of cardiovascular risk factors, PCI offers coronary patients the possibility of long intervals of active, event-free lives. Nevertheless,

See page 2049

some chronic angina patients are not able to benefit from PCI. Personal choice may preclude a procedure, as may technical features of the coronaries, for example, the presence of diffuse disease in small vessels, chronic occlusions, or inability to treat all lesions (i.e., incomplete revascularization). In these cases medical management of ischemia and angina may be required.

MEDICATIONS FOR CHRONIC STABLE ANGINA

The recently published American College of Cardiology/American Heart Association 2002 Guideline Update for Management of Patients with Chronic Stable Angina contains a comprehensive review of medications used for this purpose (2). Three classes of agents reviewed (beta-blockers, calcium antagonists, and nitrates) are effective for angina on the basis of altering the supply-demand imbalance created by flow-limiting coronary stenoses. These agents can reduce heart rate, blood pressure, and coronary vascular resistance, and redistribute coronary blood flow from subepicardial to subendocardial regions. The net effect is reduction in myocardial ischemia that leads to angina. The guideline update very importantly also reviews three other classes of agents used in chronic stable angina that affect fundamental activities of the vascular endothelium, either by altering endothelial cell function in certain favorable ways, or by reducing "inflammation" (a series of cytokine and leukocyte responses), or by preventing thrombosis. These other three therapeutic classes are antiplatelet agents, lipid-lowering agents (especially statins), and angiotensin-converting enzyme (ACE) inhibitors. The importance of these other

classes in addition to the traditional triad of beta-blockers, calcium antagonists, and nitrates cannot be overstated.

VASCULAR ENDOTHELIUM

Aberrations in physiologic functioning of vascular endothelium are involved in all stages of coronary atherothrombotic disease: initiation of fatty streaks and their development into plaques, plaque growth and progression, and, finally, deterioration and degeneration with plaque rupture and acute thrombosis. The endothelial dysfunction central to all this can result from many causes, operating either alone or together in concert. Traditional coronary risk factors such as smoking, hypertension, diabetes, and elevated cholesterol all produce endothelial dysfunction, and this likely is how they each operate to increase coronary risk (3). Additionally, chronic "inflammation" as a cause, or an effect, or perhaps only a marker of endothelial dysfunction has been the focus of increasing attention in recent years (4,5). But whatever the multiplicity and interconnectedness of the causes, once atherosclerosis has progressed to the point of forming one or more flow-limiting stenoses, chronic stable angina may ensue. This gives rise to the paradigm that chronic stable angina could be viewed (at some level) as essentially a vascular endothelial disorder.

ANGIOTENSIN

One of the key substances involved in regulating arterial vascular function is angiotensin. Within vascular endothelial cells, angiotensin interacts with various oxidases to reduce the production of nitric oxide and increase the production of reactive oxygen species like superoxide. This imbalance reduces coronary vasodilator capacity, and promotes leukocyte adhesion, vascular smooth muscle cell proliferation, and platelet aggregation (6,7). Furthermore, angiotensin either directly or indirectly interacts with lipoprotein oxidation pathways to increase oxidized low-density lipoprotein, a promoter of atherogenesis (8,9). The counterpoint to all of this is that inhibition of angiotensin can ameliorate these undesirable actions.

Clinically, angiotensin inhibition achieved by reducing its formation (ACE inhibitors), or blocking its specific cell surface receptors (angiotensin receptor blockers [ARBs]), has been found beneficial in many abnormal cardiovascular states or even in patients with only cardiovascular risk factors. For instance, ACE inhibitors and ARBs are used to treat hypertension, one of their traditional and most notable applications. Furthermore, apart and separate from this, ACE inhibitors and ARBs have been shown to reduce adverse cardiovascular events and improve survival in patients with left ventricular dysfunction and heart failure, as well as in patients after myocardial infarction and bypass surgery. Some of these effects fall into the category of secondary prevention, an area where statins are known to be useful, and there is evidence of an additive effect of ACE

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inhibitors (quinapril, in fact) and ARBs on the anti-inflammatory actions of statins (10). They have been shown to slow the progression of both diabetic as well as nondiabetic renal disease (11,12). These benefits appear unrelated to the direct antihypertensive effects of these drugs, and it is likely that changes in endothelial cell function (i.e., re-establishing balance) are at least partly the way ACE inhibitors and ARBs achieve this (6,13). Intriguingly, ACE inhibitors recently have been shown to reduce the incidence of atrial fibrillation in patients with left ventricular dysfunction, possibly by neurohormonal alterations, or reduction in atrial pressure and stretch, or via a direct antiarrhythmic effect (14). It is very likely that in the future the list of potentially beneficial actions from angiotensin inhibition will grow even longer.

CHRONIC ANGINA

Given the established clinical benefits of angiotensin inhibition, and the putative mechanisms by which these benefits arise, it was a natural extension to anticipate that ACE inhibitors might also lead to reduced ischemia and angina in the chronic stable state of coronary disease. The current study reported in this issue of the *Journal* by Pepine et al. (15) investigates this question. The Quinapril Anti-ischemia and Symptoms of Angina Reduction (QUASAR) trial randomly assigned 336 patients with stable coronary disease to the ACE inhibitor quinapril or to placebo. None of the patients had hypertension, left ventricular dysfunction, or other reasons for which ACE inhibitors are usually indicated. Thus, the ACE inhibitor truly was an “additional” agent. Exercise treadmill testing, angina questionnaires, and ambulatory electrocardiogram (ECG) recordings were done at baseline, 8 weeks, and 16 weeks. No significant differences in ischemia were found, either in treadmill measures or ambulatory measures of ischemia. The adverse event rates were low in both groups. These results match closely those from the QUO VADIS trial of 149 patients with coronary disease randomized to quinapril or placebo four weeks before elective bypass surgery and then followed for one year (16). Exercise treadmill tests and Holter monitors were used to measure ischemia at baseline and one year. Just as in QUASAR, QUO VADIS found no differences in ischemic measures between the quinapril and placebo groups. And yet, similar to other clinical trials of ACE inhibitors, with the longer one year follow-up in QUO VADIS, there were fewer adverse cardiovascular events found in the quinapril-treated group compared with the placebo-treated group: 4% versus 15% ($p = 0.02$). Unfortunately, the 16-week duration of the QUASAR trial was likely too brief to find a difference in adverse events.

As the authors of the QUASAR trial point out, the mechanisms leading to chronic exertional angina and recordable ischemia are likely very different from those leading to acute adverse clinical events, that is, fixed, flow-limiting stenoses versus inflammation and sudden plaque rupture.

The coronary vasomotor activities that might affect variables like duration of exercise treadmill time, ECG ST-segment depression during exercise or on Holter monitoring, and the like, probably are already modified by the traditional triad of beta-blockers, calcium antagonists, and nitrates. Adding ACE inhibitors to this successful regimen to reduce ischemia likely confers little benefit. Because the accumulated clinical evidence does indicate, however, that ACE inhibitors reduce adverse clinical events that are due to plaque degeneration, the implications are that the influence of these drugs lies elsewhere, and it is probably on inflammation and acute plaque disruption.

SUMMARY

The investigators in QUASAR have done us a favor and now helped answer a persistently nagging question. Are ACE inhibitors useful adjuncts to current therapy for reducing daily ischemia in chronic stable coronary disease? The answer is no. On the other hand, are ACE inhibitors useful and beneficial agents for reducing adverse cardiovascular events over the long term? The answer appears to be yes, but the mechanism apparently is not by reducing daily ischemia. So we must refocus our attention on other possible mechanisms, and further studies will be needed to unravel these. Inflammatory mediators, cytokines, and oxidation products are promising candidates. Given the relative safety of ACE inhibitors and ARBs, and their apparent clinical benefit with long-term administration, it is likely that the use of these agents will only increase in the years ahead. With the recent redefinition of blood pressure goals that have now created a “prehypertension” category, it is exceedingly likely that many more adults will soon be using these drugs (17). Understanding how and why they are obtaining clinical benefits will be easier now that we have these data indicating that control of chronic stable myocardial ischemia is not the mechanism, and the proper way to measure the benefit lies elsewhere.

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