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EDITORIAL COMMENT

Slowing the Progression of Cardiovascular Disease*

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Large databases containing clinical records provide the opportunity to address questions that have not been answered adequately in prospective trials. To the extent that these data repositories contain accurate and appropriate entries, they provide at best a window into the results of clinical practice in a "real-world" environment. Any observations of therapeutic efficacy based on these data usually require caveats because clinical experience cannot replicate the controlled conditions mandated by randomization in clinical trials. Thus, the analysis by Evans et al. (1) in this issue of the *Journal* appears to support the overwhelming evidence from clinical trials (2,3) that long-term use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) (renin-angiotensin-aldosterone system [RAAS] inhibitors) reduces mortality in patients who have sustained a myocardial infarction or other vascular events, even if they have renal insufficiency that may have excluded them from participation in previous clinical trials. Unaddressed, of course, is whether the clinical decision to use these drugs rather than not use them may have reflected a perception of better health that could have been partly responsible for the better outcome in the treated group.

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The interest in recent years in analyzing the association between renal disease and cardiovascular disease (4,5) has resulted in a number of observations and hypotheses about how renal insufficiency may aggravate cardiovascular disease. Such analyses have been fostered by access to these data repositories because renal function measurements are usually available and cardiovascular morbid events are always reported. The demonstrated relationship between renal dysfunction and cardiovascular disease is often approached as a mystery in need of resolution. Furthermore, clinical trials in cardiovascular disease usually exclude participation of patients with renal insufficiency, because the renal disease may influence trial drug metabolism and reduce long-term survival.

Missing from most previous analyses, and usually missing from large database studies, is a focus on pathophysiology. Associations, as we all know, do not necessarily translate into cause and effect. The search for how renal disease affects cardiac disease often disregards the fact that most adult-age renal disease is a manifestation of vascular disease, usually small artery disease associated with atherosclerosis and endothelial dysfunction (6). Thus, renal involvement in patients with atherosclerosis may merely reflect the severity of the disease in the artery wall, which is likely to result in a higher frequency of all cardiovascular morbid events. Because renal failure may therefore by identified as a cardiovascular disease, its association with cardiovascular morbid events is hardly surprising, regardless of whether some aspect of renal failure may also be contributing to cardiovascular disease (**Figure 1**).

With regard to the use of RAAS inhibitors, their effect on renal function is well known. Angiotensin mediates glomerular efferent arteriolar constriction that maintains intraglomerular pressure and kidney filtration. Angiotensin-inhibiting drugs, therefore, reduce glomerular pressure and lower filtration rate. This is not an unwanted adverse effect of these drugs, but is rather consistent with their pharmacological action. A modest rise in creatinine levels is therefore expected with the pharmacological effect of these

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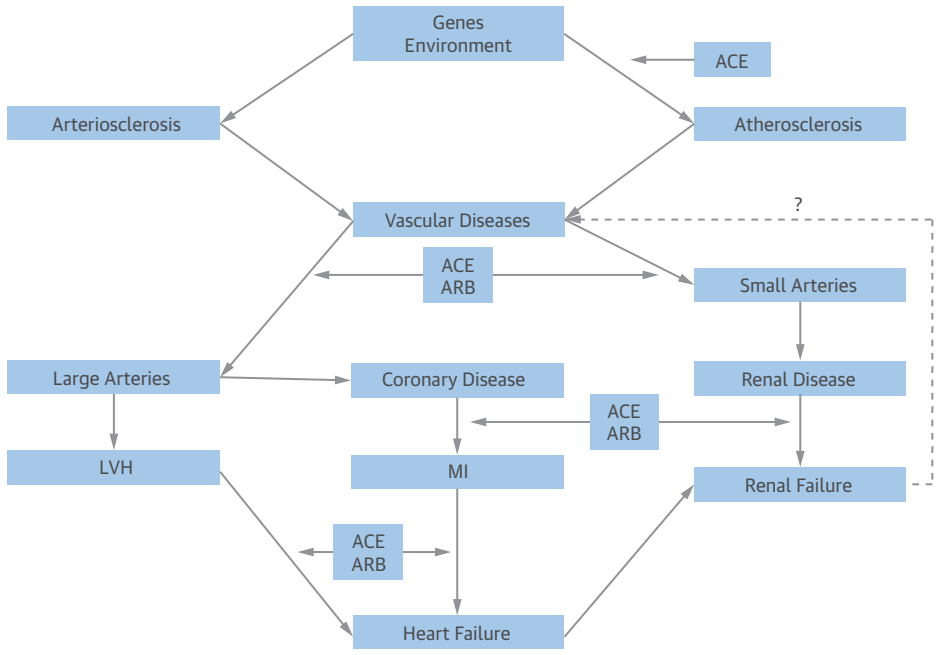
FIGURE 1 Mechanisms of Progression of Cardiovascular Disease



Arteriosclerosis and atherosclerosis are separate vascular disease processes resulting from genetic and environmental factors. Large artery disease causes coronary events and contributes to left ventricular hypertrophy (LVH), both of which may lead to heart failure. Small artery disease affects renal function and may lead to renal failure, which may have an unexplained adverse effect on vascular disease. Inhibitors of the renin-angiotensin system act at a number of sites to slow the progression of cardiovascular disease. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; MI = myocardial infarction.

drugs, particularly in individuals with some depression of renal function because of microvascular disease of the kidney.

In the early years of ACE inhibitor treatment of heart failure, I was plagued by primary care providers and nephrologists who insisted on stopping or reducing the dose of ACE inhibitors when the creatinine level increased modestly. Confrontations between our cardiology consulting team and the nephrology consults often ensued. They were inordinately concerned about renal failure, I felt, despite the rarity of advanced renal failure in this population. We interpreted the rise in creatinine not as a sign of renal damage, but rather as a signature of the drug usage. It did not, we thought, serve as a warning signal for impending renal failure.

The data from Evans et al. (1) are therefore reassuring. All of the data in their study came from patients with established atherosclerotic disease of the coronary arteries who presented with an acute myocardial infarction. A high incidence of renal dysfunction would be expected in this population because of the likely frequency of vascular disease in the renal circulation, most likely small artery disease of the kidney. The observation that kidney failure was so rare, and only marginally related to ACE inhibitor or ARB use, reaffirms our recommendation to continue treatment with these drugs even if creatinine levels rise modestly.

The mechanism of the benefit in atherosclerosis of inhibiting angiotensin's effect on the arteries and heart needs to be understood. The initial recognition of the action of ACE inhibitors and ARBs to slow or reverse left ventricular remodeling in patients with acute myocardial infarction (7) led to the eventual mandate for its use in heart failure. But the effect of these drugs on the atherosclerotic process itself may be of equal importance. ACE inhibitors appear to inhibit the development of atherosclerotic plaques, perhaps by restoring endothelial function, and their effectiveness in preventing cardiovascular morbid events in patients with advanced cardiovascular disease may relate to a number of pharmacological actions, including antioxidative stress, antiproliferative, and antihypertensive effects (8). The trial data, now buttressed by the Swedish data, should

help to establish these drugs as standard therapy in patients with atherosclerotic disease. Because renal dysfunction may serve as a signal for more severe vascular disease, its presence should, if anything, enhance the message.

Whether the analysis by Evans et al. (1) was necessary or not, it has provided the opportunity to re-emphasize the virtue of RAAS inhibitors in secondary prevention. These so-called antihypertensive drugs should not necessarily be aimed at blood pressure control. Their pharmacological effect is to slow progression of cardiovascular disease.

The focus should now be on how to recognize the cardiovascular disease in need of treatment. There are 3 potential strategies: 1) wait until a morbid event occurs, as in the Swedish database; 2) apply algorithms such as the Framingham or the more recent American Heart Association/American College of Cardiology score to identify individuals at high risk; or 3) utilize noninvasive methods to screen and evaluate individuals for the presence of early disease, regardless of blood pressure levels, which is an approach that appears to be more discriminating (9).

Let the debate begin.

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