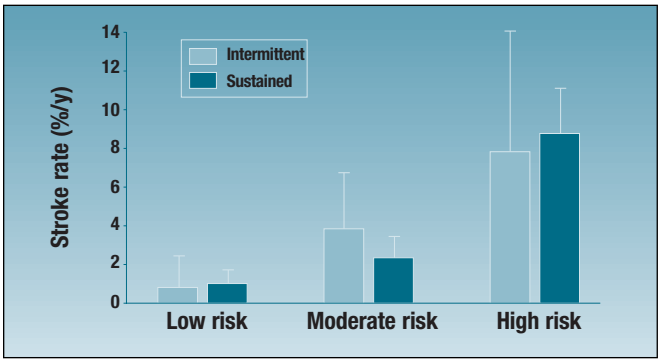

Figure 1. Observed rates of ischemic stroke according to risk category. Adapted with permission from Hart RG et al. *J Am Coll Cardiol*. 2000.

doses, the utility of long-term anticoagulation for reducing stroke risk was not established. Nevertheless, the authors suggest that in the SPAF III trial, those patients given adjusted-dose warfarin had a significantly reduced stroke risk, compared with those treated with aspirin.

Although this study has many limitations, it does provide data from a well-conducted clinical trial involving a large number of patients. Taken together, the data support the presence of significant risk in an elderly population with intermittent AF. Furthermore, the study suggests that the risk factors used in the assessment of patients with chronic AF apply nearly equally in patients with the paroxysmal form of arrhythmia. The event risk in AF patients with underlying ventricular dysfunction may be even higher. Several recent examinations of AF recurrence in patients receiving atrial defibrillators show that up to 75% of recurrent AF episodes are asymptomatic.[15] This presence of underlying disease and the frequent asymptomatic recurrences of AF strongly support the need to reconsider anticoagulation guidelines for these patients. Although data are not available suggesting that treatment alters outcome in these individuals, the strength of a variety of anticoagulation studies suggests that it is highly reasonable to aggressively treat at-risk intermittent AF patients with long-term anticoagulation. Future studies will still be needed to determine the impact of intermittent AF of short duration in younger, healthier individuals and that of asymptomatic AF recurrences that go undetected.

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Thrombosis and Acute Coronary Syndromes

Understanding Plaque Rupture

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Inflammation is increasingly thought to play a significant role in plaque rupture and in its clinical correlate, the acute coronary syndrome. Inflammatory cells, such as macrophages, T-lymphocytes, and neutrophils, are present in the shoulder region of these active plaques.[1] Cytokines, such as interleukin-6 (IL-6), are important messaging systems involved in the stimulation of matrix-degrading enzymes.[2] In parallel, tissue angiotensin-converting enzymes (ACE) with associated higher renin activities are thought to play a role in the acute coronary syndrome as well.[3]

continued

Expression of Angiotensin II and Interleukin 6 in Human Coronary Atherosclerotic Plaques: Potential Implications for Inflammation and Plaque Instability

Schieffer B, Schieffer E, Hilfiker-Kleiner D, et al.
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This study attempts to localize angiotensin II, angiotensin II type 1 (AT1) receptor, ACE, and IL-6 within human coronary atherosclerotic plaques and to investigate the interaction of IL-6 with angiotensin II in vitro. IL-6, which has both anti-inflammatory and proinflammatory activities, is a central regulator of acute phase protein secretion in smooth muscle cells and in the migration and differentiation of activated macrophages.

In smooth muscle cell culture, angiotensin II induces IL-6 transcription and protein release up to 6- to 7-fold for 60 minutes. This response is abolished by the AT1 receptor blocker, losartan. In human atherosclerotic plaque obtained from patients with ischemic cardiomyopathy, macrophages, ACE, angiotensin II, AT1 receptor, and IL-6 colocalize to the shoulder region. In directional atherectomy samples from patients with unstable angina and in postmortem samples from patients who died from myocardial infarction (MI), colocalization of macrophages, renin-angiotensin system (RAS) components, and IL-6 appeared strong. Chymase-containing mast cells were not positive for angiotensin II or IL-6. These findings suggest that the RAS plays an important role in the inflammatory process.

This study, coupled with the recently published Heart Outcomes Prevention Evaluation (HOPE) clinical study, extends our understanding of the importance of the RAS in patients with atherosclerosis.[4] The HOPE study of 9297 patients with coronary artery disease, peripheral vascular disease, stroke/transient ischemic attack, or diabetes showed that the risk of cardiovascular death, MI, or stroke was reduced by 26% with treatment with ramipril, an ACE inhibitor, over a mean follow-up period of 5 years. This protective effect was independent of blood pressure reduction.

The HOPE clinical study, coupled with morphologic observations in the study by Schieffer and colleagues, clearly represents a major step in our understanding and treatment of plaque rupture.

Unfortunately, the event rates remain high in the treatment group in the HOPE study (14% combined outcome, 10.4% total mortality). Certainly, the RAS is an important component in inducing plaque instability, but it is probably not the only pathway. The combination of aggressive lipid-lowering therapy plus ACE inhibition seems to be the state-of-the-art medical therapy for preventing plaque rupture. Whether there is a synergistic effect between the 2 therapies remains to be determined.

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Vascular Biology

Two Views of Nitric Oxide

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Two areas of nitric oxide activity are evaluated: the consequences of reduced bioavailability in hemodialysis patients and the results of overactivity in patients following myocardial infarction.

Cardiovascular disease is the leading cause of death in patients with chronic renal failure undergoing hemodialysis. The increased cardiovascular events in these patients are attributed largely to accelerated atherothrombosis and hypertension. Nitric oxide produced by endothelium is a critical mediator of endothelium-dependent vasodilation and also regulates the interaction of the endothelium with platelets and leukocytes. Thus, nitric oxide is believed to play a key role in the maintenance of healthy vascular structure and function. Recent studies have shown an impairment of nitric oxide–dependent, flow-mediated vasodilation in patients with chronic renal failure who are undergoing dialysis. These observations suggest that reduced bioavailability of nitric oxide may occur in dialysis patients, contributing to enhanced atherothrombosis.