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Cardiovascular Disease

Does the Lysyl Oxidase Gene *Lox* Play a Critical Role in Cardiovascular Disease?

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Inactivation of Lysyl Oxidase Gene *Lox* Leads to Aortic Aneurysms, Cardiovascular Dysfunction, and Perinatal Death in Mice

Mäki JM, Räsänen J, Tikkanen H, et al.

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The pathophysiology of the formation of an aortic aneurysm involves the degradation of elastin. The cross-linking of elastin and collagen is an important determinant of tensile strength, and this cross-linking is mediated by a family of five isoenzymes, called lysyl oxidases.

The study investigators from Finland created a mouse model in which one of the lysyl oxidase genes, called *Lox*, was knocked out. These mice died at birth, and a detailed examination showed fragmentation of elastin lamellae in the aorta, as well as aortic aneurysms and diaphragmatic hernias, in some of the mice. The aortic pulsatility index, as measured by Doppler ultrasonography, was significantly higher in *Lox*-null mice.

These observations suggest that the reduced cross-linking of elastin and collagens causes a reduction in the resilience and tensile strength of the arterial walls, which gives rise to abnormalities of aortic structure and cardiovascular function. It is of interest to note that the mottled blotchy mice that died of aortic rupture before 6 months of age also had a partial deficiency of lysyl oxidase activity resulting from an abnormal copper metabolism. Similarly, in lathyrism, there is an irreversible inhibition of lysyl oxidase, caused by β-aminopropionitrile in peas, in which there is evidence for aortic dissection and the formation of aortic aneurysms, besides other musculoskeletal abnormalities. Taken together, these observations suggest the possibility that *Lox* activity may play a critical role in human cardiovascular disease. ■

Myocardial Infarction

Anticoagulation Post-MI: Are Warfarin and ASA Superior to Aspirin Alone?

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It is well established that thrombosis plays a central role in the pathophysiology of acute myocardial infarction (AMI) and that treatment with thrombolytic agents, anticoagulants, and antiplatelet drugs significantly reduces mortality and morbidity.[1] It is also well known that a significant proportion of recovering MI patients will have reinfarction during the following 2–5 years.[2] Over the past 35 years, the optimal antithrombotic regimen to prevent reinfarction has remained unclear. Currently, there are two common treatments: 81–325 mg of aspirin daily or coumadin with an international normalized ratio (INR) of 2 to 3. Although both regimens have been shown to reduce mortality and morbidity in patients with AMI, it is most common in the United States to treat patients with acetylsalicylic acid (ASA), largely because of its ease of use and relative safety. In a meta-

Table 1
Randomized Clinical Trials Comparing ASA, Warfarin, and the Combination of ASA and Warfarin

Study	N	Anticoagulant Intensity	1° End Point	ASA	Warfarin	ASA+W
ASPECT 2[5]	993	Moderate	D, MI, stroke	9.0	5.0	5.0*
APRICOT[6]	308	Moderate	MI	30	—	18*
CARS[7]	8803	Low	D, MI, stroke	8.6	—	8.4
CHAMP[8]	5059	Low	D, MI, stroke	33.9	—	34
WARIS II[9]	3360	Moderate	D, MI, stroke	20	16.7	15*

ASA, acetylsalicylic acid; W, warfarin; D, death; MI, myocardial infarction.
*$P < .001$ compared with ASA.

analysis of oral anticoagulant therapy in patients with coronary artery disease (CAD), Anand and Yusef[3] demonstrated an 18%–22% reduction in mortality with moderate to high intensity anticoagulation that was equal to ASA therapy. In seven trials comparing ASA with moderate or high dose warfarin, there were no differences in mortality, myocardial infarction (MI), or stroke, although incidence of major bleeding increased by 1.9 times. Accordingly, the American College of Cardiology/American Heart Association practice guidelines for the management of AMI recommend that all patients without a contraindication should receive ASA and that warfarin use is specifically recommended for those who have atrial fibrillation, those with a left ventricular (LV) thrombus, and those who cannot take an antiplatelet drug.[1] It is recommended with less certainty for those with extensive wall motion abnormalities or severe LV dysfunction. Although ASA is the standard of care for post-MI patients, the role of combined ASA and warfarin therapy is less clear.[4] Four clinical trials have addressed the efficacy of ASA in combination with warfarin compared with ASA alone and have had mixed results.[5–7] Because of the uncertainty about combination warfarin and ASA therapy, the Warfarin, Aspirin, Reinfarction Study (WARIS) II trial, a large multi-center randomized trial, was recently reported.[8]

Warfarin, Aspirin, or Both After Myocardial Infarction.

Hurlen M, Abdelnoor M, Smith P, et al.
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This trial was a randomized, open label, multicenter study that involved 20 hospitals in Norway. Patients (N = 3630) were randomized to aspirin, warfarin, or combined therapy and followed for approximately 4 years. The primary end point was the composite of death, nonfatal infarction, or thrombotic stroke, whichever came first. There were 625 events (17.2%) of which 283 (7.8%) were deaths. The study showed a significant benefit from both warfarin alone (19% risk reduction; $P = .03$) and the combination of warfarin and ASA (29% RR; $P < .001$) compared with ASA alone. The main benefit was a reduction in both re-infarction and thromboembolic stroke since the incidence of death was not different among the three groups. Although bleeding was four times more common in those receiving warfarin, major bleeding was infrequent (0.56%–0.68%) and no more common in those receiving warfarin and aspirin compared with warfarin alone.

This study revives a clinical question that has been studied since the 1960s, when warfarin was found to be effective in reducing the incidence of stroke and pulmonary embolism. Three studies were conducted in the 1960s and 1970s, and two showed benefit of warfarin for AMI. More recently, four trials have evaluated the benefit of the combination of warfarin and ASA. The Anticoagulants in the Secondary Prevention of Events in Coronary Thrombosis (ASPECT) trial compared two dose regimens of warfarin. One group received high-dose warfarin (goal INR of 3–4), and another received moderate-dose warfarin (goal INR of 2–2.5) in combination with 80 mg of ASA. A third group received 80 mg of ASA alone.[5] The combined end point of death, MI, or stroke occurred in 9% of the ASA group and 5% of the warfarin groups. Similar benefits of combination therapy were demonstrated in the Antithrombotics in the Prevention of

Reocclusion In Coronary Thrombolysis (APRICOT) study. In this study of 308 patients post-thrombolysis, the combination of ASA and warfarin resulted in a re-occlusion rate of 18%, compared with 30% for ASA alone.[6] Two additional studies compared low-dose warfarin (INR < 2.5) and ASA to ASA alone. The Coumadin Aspirin Reinfarction Study (CARS) enrolled 8803 patients with AMI.[7] After 14 months, the combined end point of death, MI, or stroke was 8.6% in the ASA alone group and 8.4% in the combined low fixed-dose warfarin and ASA group. The open-label Combination Hemotherapy and Mortality Prevention (CHAMP) study also found no difference in the incidence of mortality, nonfatal MI, and stroke when low-dose warfarin was combined with ASA.[8] Anand and Yusef[3] reviewed the results of 31 randomized trials of oral anticoagulants from 1969 to 1999 in patients with CAD.[3] They confirmed in a meta-analysis of this broader group of patients that high- and moderate-intensity warfarin and ASA reduced future events by 6–7 times, whereas low-dose warfarin and ASA was no better than ASA alone. They also showed, in 3 trials of warfarin and ASA versus ASA alone, a 56% reduction in death, MI, or stroke. In contrast to high-intensity warfarin, the combination of low-intensity warfarin (INR < 2.0) plus ASA versus ASA alone, in three randomized trials, showed no significant difference in benefit. The major reluctance of clinicians to use the combination has been the high bleeding rate that was seen in earlier trials of moderate to high intensity warfarin. The WARIS II trial should relieve this concern. Although bleeding was more common, the incidence of major bleeding was less than 0.6% and no more common when ASA was added to warfarin. These findings should lead to a change in our management of patients following AMI and suggest that patients without contraindications should receive combination therapy. A strong case can be made that those who are at high risk of re-infarction or have had a complicated MI would particularly benefit. With the introduction of new oral anticoagulants, this question will undoubtedly be readdressed. ■

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