Trends in Thoracic Aortic Aneurysms and Dissection:
Out of the Shadows and Into the Light

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In this issue of Circulation, Sidloff and colleagues have presented their findings that, among 18 World Health Organization member states over a period of 16 years (from 1994 to 2010), there has been a reduction in the age-standardized mortality from both thoracic aortic aneurysm and dissection.1 If one considers the United States, the United Kingdom, and Sweden—three countries that have published extensively on the prevalence and mortality of thoracic aortic disease—the trends are quite favorable: Mortality from thoracic aortic aneurysm has declined by approximately 5-10% among males and 3-6% among females; and mortality from aortic dissection has declined by about 2-3% among males and 1-2% among females. However, and not surprisingly, the investigators discovered heterogeneity among mortality trends by country. For example, for males with thoracic aortic aneurysms, while there was a statistically significant reduction in mortality over time in 13 of the 18 countries, in 3 countries there was instead an increase in mortality. Similarly, for males suffering aortic dissection, while there was again a statistically significant reduction in mortality over time in 13 of the 18 countries, in one country there was a significant rise in mortality. Japan and Romania were the two countries with the most consistent increases in mortality.

The investigators then considered the impact of changing prevalence of risk factors on the changing mortality from thoracic aortic disease. In all of the countries studied there was a decline in systolic blood pressure of up to 6% over time, and there was a linear relationship between systolic blood pressure and mortality from both thoracic aortic aneurysm and dissection. This makes good mechanistic sense given the known association between hypertension and both aneurysms and dissection.

In all but Japan there was a decline in cholesterol levels over time, and the investigators also found a linear relationship between cholesterol and mortality from thoracic aortic aneurysm.
At first it may seem logical that a reduction is cholesterol would result in a reduction in death from thoracic aortic disease, since hyperlipidemia is a well known "cardiovascular" risk factor. Moreover, atherosclerosis has been found to be strongly associated with abdominal aortic aneurysms, although whether this association is causative remains unclear. However, the evidence actually indicates that atherosclerosis is negatively rather than positively associated with thoracic aortic aneurysms. So how might the apparent association between the downward trends in both cholesterol and thoracic aortic aneurysm mortality be explained? One possibility, albeit unlikely, is that despite the negative association between atherosclerosis and thoracic aneurysms, there is an independent and positive association with cholesterol itself and thoracic aortic aneurysm. An alternative, and far more plausible, explanation would be that much of the downward trend in cholesterol was at least in part the result of an increase in the use of statin drugs; for example to the use of statin drugs among American males aged 65-74 climbed from 26% in 1999-2008 to 50% in 2005-2008, and in women aged 75 and above it increased from 18% to 39% in over that same interval.

But if atherosclerosis is not itself mediating thoracic aortic aneurysms, why would statin therapy then be beneficial in this disease? It is known that in thoracic aortic aneurysms there is increased activity of matrix metalloproteinases, which can degrade extracellular matrix proteins. It is also known that statin therapy can reduce tissue levels of matrix metalloproteinases and may therefore confer a protective effect. Indeed, in a mouse model of Marfan syndrome, McLaughlin et al demonstrated that therapy with pravastatin significantly reduced the rate of aortic root growth compared with the untreated Marfan mouse. Moreover, in humans, Goel et al found that among patients with bicuspid aortic stenosis undergoing elective aortic valve replacement surgery, those who had been previously treated with statin therapy had significantly
smaller ascending thoracic aortic diameters than those not treated with a statin.8 It is therefore possible that the increased use of statin therapy rather than the actual fall in cholesterol levels accounts for the association of decreasing thoracic aortic aneurysm mortality with decreasing cholesterol.

A more surprising finding in this report is that of a significant linear but inverse relationship between body mass index and thoracic aortic aneurysm mortality in males and females, as well as aortic dissection mortality in females. However, mechanistically this association is difficult to explain. In fact, in contradistinction, in a cross-sectional population of subjects without known thoracic aortic disease body mass index was positively associated with aortic root diameter.9 Nevertheless, in a recent report the same investigators found a very similar inverse association between body mass index and abdominal aortic aneurysms,10 suggesting that this finding is reproducible. But a causal explanation is elusive so, for now, we may consider this to be yet another example of the apparent "obesity paradox."11

In their discussion the authors of the current report note that "Changes in the treatment of thoracic aortic aneurysm have occurred over time," yet curiously they tend to dismiss the impact of such changes on mortality from thoracic aortic disease. While it is fair to argue that risk factor modification has clearly played a role in improved outcomes, there are three ways in which changes in clinical practice are likely to also have contributed to the observed reduction in mortality. First, most thoracic aneurysms are detected incidentally on a diagnostic imaging study ordered for another purpose, and since the rates of echocardiography, CT scanning, and magnetic resonance imaging have increased steadily over recent decades, the rates at which aortic enlargement is detected has increased as well. To this point, Olsson et al found that in the Swedish population the rates of detection of thoracic aortic aneurysms increased by 52% in
males and 28% in females from 1987 to 2002. Second, the past two decades have seen a collective increased awareness of the risks of thoracic aortic disease and the need for timely intervention. For example, Olsson et al found that the rates of thoracic aortic repair increased 7-fold in males and 15-fold in females over that same time period, dramatically outpacing the increased rates of aneurysm detection. Third, with improvements in open surgical techniques and the advent of thoracic endovascular stent-grafting (TEVAR), mortality from thoracic aortic repair has been steadily declining: In the Olsson report, 30-day mortality fell from 25% to 13% over the 15 years. Similarly, in England and Wales, hospital admissions for thoracic aortic aneurysms and dissection increased between 1999 and 2010 whereas mortality for both conditions steadily declined over that same period. In the United States, the rates of descending thoracic aortic repair have increased over the past decade and a half, primarily due to a rise in TEVAR, while the mortality rates of both open and endovascular repair have steadily declined for both intact and ruptured aneurysms.

We have entered an era in which thoracic aortic disease has come out of the shadows and into the light, finally commanding the attention needed to improve outcomes. We are detecting thoracic aortic aneurysms more often, we are managing risk factors better, and we are intervening more often and with better results. Collectively this has led to a reduction in overall mortality from thoracic aortic aneurysms and dissection. But despite the favorable progress there is still much work to be done: We have yet to find ways to detect thoracic aortic aneurysms proactively, rather than incidentally. We must still determine optimal medical therapies to reduce aneurysm growth, rupture, and dissection. We should strive to better characterize the patient and aneurysm factors that should prompt timely intervention. And we must continue to educate our patients and our colleagues about the importance of consistent blood pressure control and
lifelong surveillance.

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