It was logical but was it the whole truth?

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This editorial refers to ‘Aortic stenosis, atherosclerosis, and skeletal bone: is there a common link with calcification and inflammation?’ by M.R. Dweck et al., on page 1567.

I had . . . . come to an entirely erroneous conclusion which shows, my dear Watson, how dangerous it is to reason from insufficient data.

Sherlock Holmes to Dr Watson in ‘The Adventure of the Speckled Band’, 1892.1

Calcific aortic stenosis (AS) was initially characterized as a degenerative process (disorder) because of a tendency to describe any disorder that was not well understood and often occurred in the ‘elderly’ as degenerative. In the last ‘15–20’ years, the observation of the presence of risk factors for arterial atherosclerosis in patients with calcific AS, the production of aortic valve calcification in animals fed grossly high levels of lipids, the presence of an osteoblast phenotype in calcific AS, and many studies showing features of and similarities to arterial atherosclerosis led to a reasonable conclusion that calcific AS was the result of processes identical/similar to human arterial atherosclerosis and to ‘bone’ formation.2–4 More recently, leading experts in several fields of biological processes, convened under the auspices of the National Heart, Lung, and Blood Institute, developed a review/consensus statement of calcific aortic valve disease.5

All studies of statins have shown beneficial effects in human arterial atherosclerosis. Thus, it was natural to study the effects of statins on the progression/development of calcific AS. Three large randomized trials6–8 failed to show a benefit of statins on calcific AS. The SEAS trial7 documented a reduction of ischaemic cardiovascular events but not of calcific AS. Both calcific and risk factors for human arterial atherosclerosis and calcific AS are common in the older population. The findings of the SEAS trial raised the possibility that the processes from ‘risk factors’ to arterial atherosclerosis and to calcific AS may be different. In other words, risk factors for arterial atherosclerosis are extremely common in the older patients in whom calcific AS is also relatively common. Thus it would not be surprising if both were present in the same patient.

Arthur Conan Doyle was a physician who gave up his clinical practice to write novels full time. He probably was aware of different disorders/events that are frequently present together in the same patient. He applied this observation successfully in writing novels about Sherlock Holmes.

An early event from ‘risk factors’ to calcific AS is the presence of abnormalities in oxidative stress. From the University of Iowa, Miller et al.9 documented that mechanisms generating oxidative stress in atherosclerotic plaques are different from those in patients with calcific AS. In atherosclerotic plaques, increased oxidative stress is due primarily to increases in NAD(P) oxidase activity which documents the increased presence of inflammatory markers and the importance of inflammation. On the other hand, in calcific AS, abnormal endothelial nitric oxide synthase (eNOS) function decreases the normal physiological function of nitric oxide along the valve endothelium. As a result, levels of superoxide and hydrogen peroxide are markedly increased; the uncoupling of nitric oxide synthase plays a role in the generation of superoxide in calcific AS (Figure 1).

A group from the University of Edinburgh now present a sophisticated study of calcific aortic valve disease. Dweck et al.10 using the well-validated techniques of positron emission and computed tomography in 101 patients, compared calcification and associated inflammatory activity in aortic valves with varying degrees of disease severity, and also in coronary arteries, aorta, and skeletal bone. Although >90% of patients also had associated aortic atherosclerosis, active calcification was more pronounced in calcific aortic valves, and markers of inflammation were less prominent compared with aortic atherosclerosis, suggesting that the pathophysiological processes in calcific AS are locally determined and regulated. In their study, [18F]sodium fluoride ([18F]NaF) was assumed to be a surrogate marker of active valvular calcification; the authors acknowledge that the fate and binding/uptake sites of this tracer in the valve and vasculature have to be further validated. Nevertheless, their study documents that disease activity in calcific AS is determined by processes within the valve itself.5,9,10 which are different from arterial atherosclerosis and skeletal bone metabolism. The data of Dweck et al. present important insights that will help to focus research efforts.

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into mechanisms that determine active calcification in calcific AS and then to target appropriate therapeutic manoeuvres.

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References
can College of Physicians/American Society of Internal Medicine; 2000. p79.
3. Shavelle DM, Takasu J, Budoff MJ, Mao S, Zhao XQ, O’Brien KD. HMG Co A re-
8. Chan KL, Teo K, Dumesnil JG, Ni A, Tan J. Effect of lipid lowering with Rosuva-
9. Miller JD, Chu Y, Brooks RM, Rohenbacher WE, Pero-Silva R, Heistad DD, Dys-
regulation of antioxidant mechanisms contributes to an increased oxidative stress in calcific aortic valvular stenosis in humans. J Am Coll Cardiol 2008;52:843–850.
10. Dweck MR, Khaw Hj, Sng Gkz, Luo Elc, Baird A, Williams MC, Makiello PE, Mirsadraee, Joshi NV, van Beek EJ, Boon NA, Rudd JHF, Newby DE. Aortic sten-
ossis, atherosclerosis, and skeletal bone: is there a common link with calcification and inflammation? Eur Heart J 2013;34:1567–1574.