Still searching for the elusive Scarlet Pimpernel of today

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Online publish-ahead-of-print 2 May 2012

This editorial refers to ‘The impact of prosthesis–patient mismatch on long-term survival after aortic valve replacement: a systematic review and meta-analysis of 34 observational studies comprising 27 186 patients with 133 141 patient-years’, by S.T. Head et al., on page 1518

Since the first description of valve prosthesis–patient mismatch (VP-PM) in 1978, the problem has been addressed in a large number of studies that have evaluated its effect on patient outcomes. Data regarding the reduction of long-term survival in those with VP-PM have been conflicting. To resolve this conflict, using pooled estimates, Head et al. have provided a systematic review of 34 selected studies assessing the impact of VP-PM after aortic valve replacement (AVR). In these 34 studies, 44.2% of the patients had severe or moderate VP-PM which was associated with an increased incidence of all-cause mortality that was statistically significant; however, the incidence of VP-PM associated with cardiac-related mortality was not statistically significant. In seven of these 34 studies, when both moderate and severe VP-PM were analysed separately, both moderate and severe VP-PM were associated with statistically significant increases in all-cause as well as cardiac-related mortality. These apparently different findings may be explained by methodological differences. Because of methodological differences, Bailar stated ‘it is not uncommon to find that 2 or more meta-analyses done at the same time by investigators with the same access to the literature reach incompatible or even contradictory conclusions.’

In the past, the search for a deleterious effect of VP-PM on survival has been carried out in many studies and has been intensive (the search was ‘here, there, and everywhere’ as it was for the Scarlet Pimpernel), but the findings have been conflicting. The review and meta-analysis by Head et al. does not provide data which convincingly demonstrate that VP-PM independently resulted in increased mortality. Their problematic findings are only partly related to their own analyses but are also related to the majority of the studies that were available to them for review. These issues can be summarized as follows.

1. The VA randomized trial showed that after AVR, 60% of the adjudicated deaths were related to associated cardiac and non-cardiac co-morbid conditions. A prosthetic heart valve was the cause of death in only 40%, in whom the major causes were bleeding and sudden deaths. Thus, one should be very careful about assuming that VP-PM contributed in a significant way either to all-cause or to cardiac-related mortality. Head et al. also did not evaluate the effect of the role of co-morbid conditions in all-cause and cardiac-related mortality.

2. The authors state that their criteria of severe VP-PM [effective orifice area index (EOAi) of ≤0.65 cm²/m²] and of moderate VP-PM (EOAi 0.65–0.85 cm²/m²) is ‘universally accredited’ which is questionable. Mohty-Echahidi et al. in a large study from the Mayo Clinic used the criterion of ≤0.6 cm²/m² for severe VP-PM. An additional eight studies from the USA and Europe that were included in their review had also used the criterion of ≤0.6 cm²/m² as severe VP-PM. We too used this criterion to assess whether left ventricular outflow obstruction was severe both for aortic valve stenosis and for VP-PM. The universe is larger than a few highly selected centres in North America, Europe, and Asia.

3. Of the 34 cited studies, EOAi was actually measured in only eight; in 26 of 34 studies the EOAi was ‘projected’. Pibarot et al. showed the sensitivity and specificity of predicted EOAi in relation to measured EOAi were 73% and 80%, respectively. Bleiziffer et al. carefully demonstrated that the correlation of projected EOAi with measured EOAi was very modest (r = 0.62), and in their study projected EOAi had a sensitivity of 54% and specificity of 83% for predicting severe VP-PM. Florath et al. demonstrated that the correlation of projected with measured EOAi was poor (r = 0.49).

4. Several of the studies cited by Head et al. did not include hospital/early mortality in the long-term mortality data.

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1 doi:10.1093/eurheartj/ehs003

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In all the cited studies, the cause(s) of death were not adjudicated. The Scarlet Pimpernel used many disguises and therefore was not apprehended. Similarly, VP-PM has been disguised under the cloak of all-cause and/or cardiac-related cause of death, and therefore it has been elusive. If one wants to determine successfully whether VP-PM increases mortality, then the search should be focused.

**Conflict of interest:** S.A.D. declares no conflict of interest. S.H.R. has received Honoraria for educational lectures from the American College of Cardiology Foundation; American College of Physicians; Society of Thoracic Surgeons; University of California Los Angeles; University of California Irvine; Cornell University; Creighton University; Thomas Jefferson University; Cedars-Sinai Medical Center; Harvard Medical School; University of Wisconsin; University of Hawaii; Cardiologists Association of Hong Kong, China; University of California, Fresno; University of AZ, Tucson Medical Center; ATS; St. Jude Medical; Carbomedics; Edwards Life Sciences; Merck; and Pfizer.

**References**