Prevalence of aortic stenosis in a large population of patients with heart failure: any insights into comorbid cardiac amyloidosis?

Authors' reply We would like to thank Dimosiari and colleagues for their interest in and comments on our recently published article on the clinical characteristics of different heart failure (HF) subtypes.[1] The authors highlighted a very interesting issue of the association between the severe type of aortic stenosis (AS) and transthyretin cardiac amyloidosis (ATTR). Our population is very different from the ones analyzed in publications cited in the commentary.[2,3] We aimed to identify patients with confirmed HF; therefore, we could have missed many individuals diagnosed with cardiomyopathy but without HF. It may have led to a potential selection bias concerning patients diagnosed with amyloidosis who did not have symptoms of HF. It should also be noted that in HF population studies information on the prevalence of amyloidosis is unlikely to be reported.

Moreover, the cited articles on patients with amyloidosis and AS concerned patients at a mean age of over 80 years,[2,3] whereas our population was much younger, even in the group of patients with HF with preserved ejection fraction (HFpEF).[1] Furthermore, with respect to AS, the severity of valvular disease was precisely described in the articles focusing on this condition.[2,3] In our study, AS was considered to occur when it appeared in the medical records, and the degree of its severity was not defined. It must therefore be acknowledged that our population and the populations described by others[2,3] are incomparable, which significantly affects any analysis and conclusions.

In response to the comments, we present some unpublished data. In our sample, we identified 11 individuals with diagnosed amyloidosis (0.4% of the total sample). As suggested by Dimosiari and colleagues, the distributions differed significantly between the HF phenotypes and were as follows: 3 (0.2%), 2 (0.6%), and 6 (0.9%) in HF with reduced EF (HFrEF), HF with mildly reduced EF (HFmrEF), and HFpEF, respectively (a significant difference between HFrEF and HFpEF; $P = 0.029$). Amyloidosis phenotyping revealed that 2 patients had ATTR, 1 was a complication of rheumatoid arthritis, 6 had light chain amyloidosis (AL), and 2 did not have a definitive phenotype but most likely AL. It shows a highly heterogeneous group, unlike the ones presented in studies by Nitsche et al[2] and Castaño et al.[3]

A comparison of the prognosis according to the amyloidosis status showed that only 1 patient (9.09%) (from the HFmrEF group) with amyloidosis as compared with 956 patients (36.91%) without the disease died during the follow-up ($P = 0.047$). However, it must be noted that among individuals with amyloidosis, 1 patient underwent a heart and autologous stem cell transplantation, another one, a heart and liver transplantation, and 1 patient with ATTR received tafamidis treatment. We may suspect that without the urgent bi-organ transplantation, the mortality would have increased to 27.3% (3 deaths) in the amyloidosis group. The median follow-up was comparable in the subgroups with and without amyloidosis (2.21 years; interquartile range [IQR], 0.71–2.55 vs 2.43 years; IQR, 1.56–3.49, respectively; $P = 0.22$). Due to the small number of cases, the data are not sufficient to justify any hypothesis.

We identified only 1 patient with concurrent amyloidosis and AS. Therefore, it is not possible to draw firm conclusions regarding the prognosis of concomitant AS and amyloidosis. Since the prevalence of AS increases with age, our population was also not representative of this comorbidity. However, in each HF phenotype, the survival was worse after 4 years of follow-up in individuals with AS than in those without (31% vs 57%, $P < 0.001$; 33% vs 70%, $P < 0.001$; 25% vs 66%, $P \leq 0.001$ in HFrEF, HFmrEF, and HFpEF, respectively). Nevertheless, the prognosis of patients with AS was comparable in all HF subtypes ($P = 0.1$). Based on these results, it may be hypothesized that AS significantly and negatively influences the prognosis in every HF subtype; however, this effect is not differentiated by HF subtypes. By way of commenting on the letter by Dimosiari and colleagues, it should be noted that in the paper by Nitsche et al,[2] the patients undergoing transcatheter aortic valve replacement had similar survival regardless of the amyloidosis

status, showing that adequate treatment strategy is crucial in this respect. It is important to emphasize that both papers[2,3] not only included a population of older people with AS but the group of patients was carefully selected in each of them, so it is difficult to draw generalized conclusions from these studies.

In summary, we believe that drawing attention to the co-occurrence of amyloidosis with HFpEF, particularly in individuals with AS, is of great importance in terms of the diagnosis and treatment in this group of patients. It must be realized that cardiac amyloidosis can be recorded in 10% to nearly 20% of patients with HFpEF.[4] In addition, the patients with AS and cardiac amyloidosis may present up to 15%, or even 30%, in the case of low-flow and low-gradient stenosis, respectively.[5]

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CONFLICT OF INTEREST None declared.

HOW TO CITE Rywik TM, Drohomirecka A, Doryńska A. Prevalence of aortic stenosis in a large population with heart failure: any insights into comorbid cardiac amyloidosis? Authors' reply. Pol Arch Intern Med. 2022; 132: 16263. doi:10.20452/pamw.16263

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