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Valvuloarterial Impedance and 5-Year Mortality in Severe Aortic Stenosis

SCIENTIFIC LETTER

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INTRODUCTION

Severe aortic stenosis (AS) is generally treated by surgical or transcatheter valve intervention once symptoms develop. However, the optimal timing of aortic valve (AV) intervention in asymptomatic severe AS remains debated.[1] There is therefore a need to identify individuals who may be at higher risk or who may benefit from earlier intervention. Valvuloarterial impedance (Zva) is a measure of global left ventricular afterload which is calculated as the sum of systolic blood pressure (SBP) and AV mean gradient (MG) divided by stroke volume index.[2] Current international guidelines do not routinely recommend the measurement of Zva for risk-stratification in individuals with AS, since more study evidence is needed.[3] In this study, we aimed to assess whether Zva is a predictor of 5-year all-cause mortality in individuals with untreated severe AS using data from the National Echocardiographic Database of Australia (NEDA).

METHODS

The NEDA is a large observational registry that has been described previously in detail.[4] Briefly, NEDA consists of routinely acquired echocardiographic data from individuals managed at participating centers throughout Australia, commencing from the year 2000.[4] All data transferred to the registry are cleaned and transformed into a standard NEDA format to ensure consistency and to remove duplication and impossible measurements. The registry also has the capacity to link echocardiographic findings with long-term mortality using Australia's National Death Index.[1] NEDA is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12617001387314) and ethical approvals across Australia from a variety of institution, university, and government Human Research Ethics Committees have been obtained.

For study analyses, only data from the last recorded echocardiogram were used (n = 631 824). Severe AS was defined as AV MG > 40 mm Hg, AV peak velocity > 4 m/s or AV area <1 cm^2.[3] High Zva was defined as ≥5 mm Hg/mL/m^2.[2,5] Individuals without SBP data (n = 558 853), with previous AV intervention (n = 22 610), without data for AS severity determination (n = 4178), and without 5-year follow-up (n = 20 338) were sequentially excluded. Differences between groups were compared using chi-square test or Mann–Whitney *U* test where appropriate. The association between Zva and 5-year mortality in individuals with severe AS was analyzed using Cox regression analysis and presented as hazard ratios (HR) with 95% CI. Time-to-event data were compared using the log-rank test. Kaplan–Meier survival curves were constructed for the comparison of low versus high Zva. Predicted survival by different Zva values was estimated using Cox regression analysis. All analyses were performed using the survival package in R statistical language. A *P*-value <.05 was used to define statistical significance.

RESULTS

Of 25 845 individuals, 526 (2.0%) had severe AS and Zva could be quantified in 219 (41.1%). In the 219 individuals, the median age was 81 years with an interquartile range (IQR) of 16 years, 113 (51.5%) were male, median Zva was 4.2 mm Hg/mL/m^2 with an

IQR of 0.9 mm Hg/mL/m^{2,} and 5-year mortality was 118 (53.9%). Increasing Zva, as a continuous variable, was a significant predictor of mortality (HR: 1.140, 95% CI: 1.038-1.252, $P=.006$), even after adjusting for age (Zva, HR: 1.121, 95% CI: 1.009-1.246, $P=.035$ and age, HR: 1.038, 95% CI: 1.020-1.057, $P<.001$).

Zva ≥ 5 mm Hg/mL/m^2 was present in 74 (33.8%) of the 219 individuals, with no significant difference in age (82 years IQR 16 years versus 79 years IQR 17 years, $P=.068$) or sex (52.7% versus 51.0% male sex, $P=.815$) compared to those with Zva <5 mm Hg/mL/m^2. Zva ≥ 5 mm Hg/mL/m^2 was significantly associated with greater mortality compared with Zva <5 mm Hg/mL/m^2 (P=0.006), as presented in Figure 1. Predicted survival based on Zva values are presented in Figure 2, where predicted mortality increases with increasing Zva. In individuals with severe AS (n = 526), there was no significant difference in 5-year survival between those with and without quantifiable Zva (P = .560).

DISCUSSION

Aortic stenosis is a disease that is not limited to the valve. Hypertension and age-related vascular changes are common in individuals with AS, leading to reduced arterial compliance and increased vascular resistance and atherosclerosis. Additionally, higher left ventricular afterload leads to ventricular remodeling and impaired diastolic and systolic function. Valvuloarterial impedance not only considers the valvular component of left ventricular afterload (e.g., AV obstruction) but also the arterial component. In individuals with severe AS, higher Zva has previously been shown to be associated with adverse outcomes, such as the development of symptoms (such as syncope) and need for AV replacement and mortality.[6-8] The findings of previous studies, together with that of the current study, which has the longest follow-up to date (5 years), suggest that Zva provides complimentary prognostic information and could potentially be used to identify individuals with severe AS who are at greater risk of death if left untreated.[6,7] Studies have also shown that Zva may predict adverse outcomes after transcatheter AV replacement, including quality of life, exercise performance, and all-cause mortality.[5,9,10] Importantly, Zva is easily quantifiable non-invasively during routine echocardiography.

Limitations of this study include its retrospective and observational nature. Information regarding symptoms was not available and SBP was not performed or documented at transthoracic echocardiography in the majority, which may reflect real-world practice but limits the number of individuals where Zva could be calculated for the study. Despite this, the current study remains one of the larger Zva studies in severe AS, with the longest follow-up to date. Due to the potential for selection bias, we performed an analysis which suggests that the study sample had similar survival to that of individuals with severe AS but where Zva could not be quantified based on available echocardiographic data.

HIGHLIGHTS

- Valvuloarterial impedance (Zva) is a measure of global left ventricular afterload and its measurement is not routinely performed.
- This study demonstrates an association between Zva and 5-year mortality in individuals with severe aortic stenosis (AS).
- Measurement of Zva could identify individuals with untreated severe AS who may benefit from closer follow-up or earlier intervention.

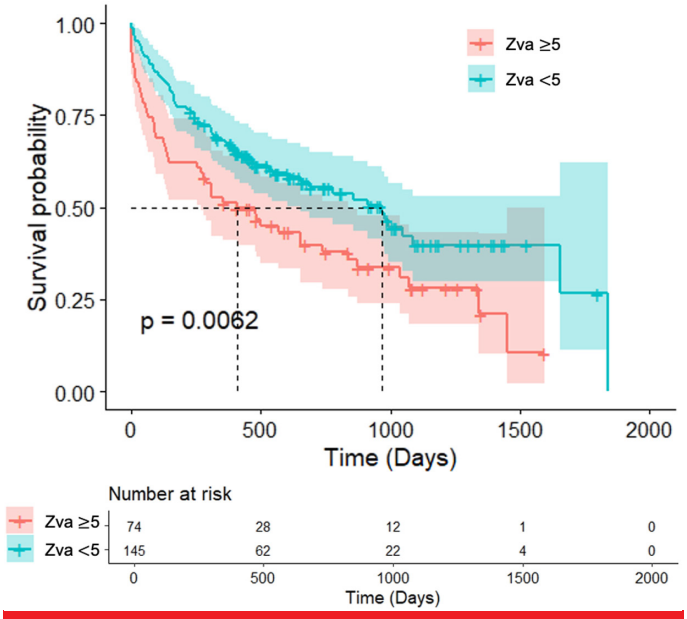

Figure 1. Kaplan–Meier curves showing significant difference in 5-year mortality between valvuloarterial impedance (Zva) of ≥5 and <5 mm Hg/mL/m^2 in individuals with severe aortic stenosis. Zva is in mm Hg/mL/m^2.

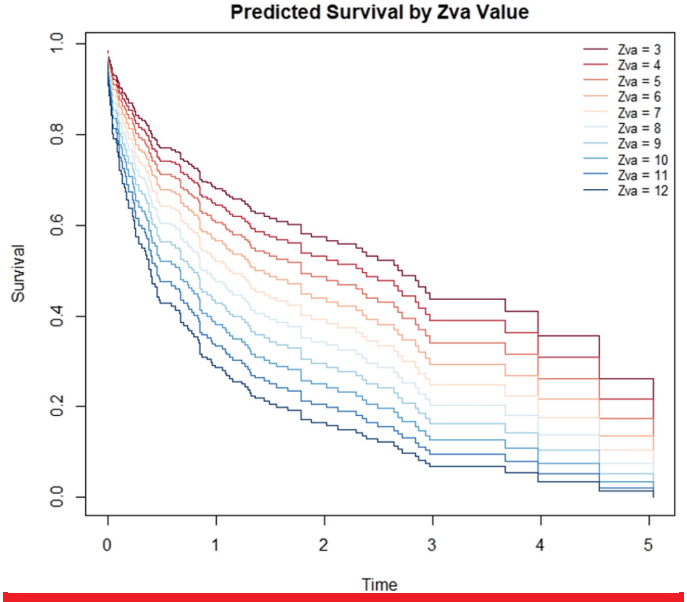

Figure 2. Kaplan–Meier curves showing predicted survival by valvuloarterial impedance (Zva) value. Time is represented in years and Zva in mm Hg/mL/m^2.

In conclusion, this analysis suggests that Zva is a significant predictor of 5-year mortality in individuals with untreated severe AS. Prospective longitudinal studies should assess whether individuals with severe AS and high Zva benefit from closer follow-up or earlier intervention.

Ethics Committee Approval: NEDA is approved by the Sydney Local Health District Human Research Ethics Committee (X15-0387). NEDA has also obtained ethical approval across Australia from a variety of institutional, university and government Human Research Ethics Committees (HREC). NEDA was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN1261 7001387314).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

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