

respectively), although the curves did not diverge until well after 24 months, the maximum duration of follow-up reported by THAOS investigators.

We believe our single-center data, although smaller in numbers, have the advantage of a closer follow-up for a longer period of time, with the potential to have received a more uniform standard of care. Our observation of a significantly shorter survival of patients with mt-ATTR due to the Val122Ile mutation strongly suggests that Val122Ile ATTR cardiac amyloidosis is a more aggressive disease than wild-type ATTR and argues for caution not only in interpreting multisite database data but also when considering the design of future studies of ATTR cardiac amyloidosis in which both mutant and wild-type patients are enrolled.

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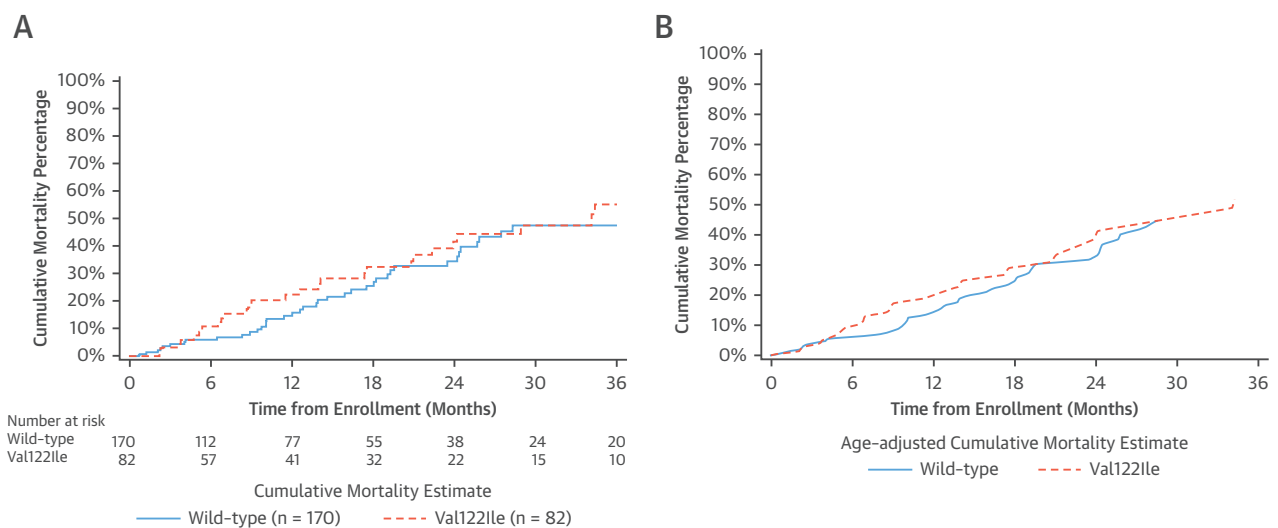
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REPLY: Val122Ile mt-ATTR Has a Worse Survival Than wt-ATTR Cardiac Amyloidosis



Dr. Singh and colleagues present single-center data that demonstrate a worse survival among subjects with transthyretin cardiac amyloid (ATTR) cardiac amyloid due to the Val122Ile mutation than that of those with wild-type ATTR (wt-ATTR), with differences emerging after 2 years of follow-up. Such data are consistent with those of other single-center reports (1), as well as the small multicenter TRACS (Transthyretin Amyloidosis Cardiac Study) study (2) in 29 subjects, but differ from data reported in international multicenter THAOS (Transthyretin Amyloid Outcome Survey) in a larger cohort (3). In THAOS, survival from time of enrollment rather than survival from diagnosis was reported as defining onset of the disease retrospectively, which is difficult given the association of ATTR cardiac amyloid with common age-related conditions. Concerns were raised about the completeness of follow-up, and we acknowledged that this could confound our reported results. Prompted by the analyses of Singh and colleagues, we evaluated survival from enrollment in THAOS over

FIGURE 1 Survival Post Enrollment in THAOS in ATTRwt Compared to Val122Ile



Survival from enrollment in THAOS over 3 years (A: overall survival in which 36-month estimate ± SE is 47.5% ± 6.1% for Wild-type and 55.1% ± 8.0% for Val122Ile) and age adjusted (B: age-adjusted hazard ratio for Val122Ile versus Wild-type = 1.947; Wald chi-square p value = 0.0132).

3 years and found that, although overall survival still did not differ between wt-ATTR and Val122Ile (Figure 1A), age-adjusted survival was worse for Val122Ile patients than for wt-ATTR patients (Figure 1B). Such data would support stratifying enrollment of future clinical trials by mutation status.

Perhaps most importantly, if there are differences between outcomes for American black patients with ATTR cardiac amyloidosis due to the Val122Ile mutation and those of Caucasians with the wild-type ATTR amyloidosis, which are phenotypically similar, we need to understand if these differences are due to nature (e.g., the presence of a mutation) or nurture (e.g., disparities related to access to care). Indeed, we are particularly troubled by the observation that American black patients present with more advanced disease than Caucasians with ATTR cardiac amyloid (4), despite having a noninvasive method for early identification (genetic testing). Further research to determine if this is the result of inadequate access to care or has a biological basis is warranted.

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