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EDITORIAL COMMENT

Clonal Hematopoiesis and Transcatheter Aortic Valve Replacement

A Fatal Connection*

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As we age, we accrue mutations in all cells throughout the body.[1] Though many of these mutations will be either neutral or cause cellular demise, sometimes they may be advantageous, leading to expansion of the mutant clone. The hematopoietic system is no exception to this phenomenon, where it has been discovered that many elderly individuals carry expanded blood cell clones with advantageous mutations. This condition has been coined clonal hematopoiesis of indeterminant potential, or "CHIP," and has been gaining clinical interest over the past 5 years.[1] Individuals with CHIP harbor mutations within specific "driver" genes that are recurrently mutated in hematologic malignancies, such as *DNMT3A*, *TET2*, and *ASXL1*. Although these mutations facilitate clone expansion, they also may alter the immunologic profile of progeny leukocytes. Recently, CHIP has emerged as a novel risk factor for cardiovascular disease, where it may increase disease risk independently from traditional risk factors. Studies using mouse models have provided causal evidence, revealing that mutant blood cell progeny can drive cardiovascular disease by perpetuating inflammation.[2]

Aortic valve stenosis (AVS) is the most common age-related valve disease.[3] It is characterized by degenerative fibrocalcific remodeling of the aortic heart valve and, when left untreated, can result in inadequate cardiac output, heart failure, and mortality due to cardiovascular causes. Although the etiology of AVS is complex, it is understood that chronic inflammatory processes play a part. Transcatheter aortic valve replacement (TAVR) has emerged as a treatment option for individuals with severe AVS that are at high risk for surgery. Although the advent of TAVR has led to substantial improvements in patient survival and quality of life, the procedure is still associated with a significant level of mortality. It has been found that patients with high levels of systemic inflammation after TAVR present a greater risk of mortality. Given the connection between post-TAVR mortality, cardiovascular disease, inflammation, and CHIP, it can be speculated that the presence of CHIP may predict poor survival in AVS patients that have undergone TAVR.

In this issue of *JACC: Basic to Translational Science*, Lassalle et al[4] examined the relationship between CHIP and survival after TAVR. Using conventional next generation DNA sequencing, the authors analyzed the blood of 258 patients with AVS who were undergoing the TAVR procedure for 67 different CHIP gene mutations. Long-term survival after TAVR was examined over a follow-up period of around 5 years. First, the authors noted that CHIP appeared to be enriched in patients with AVS undergoing TAVR. Specifically, it was found that 68% of patients with AVS harbored CHIP mutations, which is considerably higher than previously studied patient cohorts that had undergone a similar DNA sequencing strategy, including those with heart failure. Given the high prevalence of CHIP in patients with AVS undergoing TAVR, it could be speculated that CHIP contributes to AVS severity per se, particularly as TAVR is usually reserved for patients with severe AVS. In support of this, inflammation is known to contribute to aortic valve calcification and

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remodeling, so it is possible that CHIP mutations are involved in exacerbating these inflammatory processes.[3] Nevertheless, studies assessing the relationship between CHIP and AVS are needed to test this directly. Curiously, for the survival analyses, the authors restricted their analysis to patients with relatively low variant allele frequencies (VAFs) (2%-10%) of CHIP mutations, which resulted in the exclusion of 53 patients. Nevertheless, it was observed that AVS patients with CHIP had an inferior survival after TAVR, which appeared to occur in a gene-specific manner. In particular, it was found that AVS patients carrying *TET2* mutations had poorer long-term survival compared with those without CHIP and with those with CHIP without *TET2* mutations. Interestingly, patients with AVS carrying mutations in *DNMT3A*, the most frequently mutated CHIP gene, had a survival rate similar to those without CHIP. This possibly suggests that *DNMT3A* mutations, at least at low VAFs, are benign with respect to mortality after TAVR. Also, it was noted that in patients that carried both *DNMT3A* and *TET2* mutations, post-TAVR survival was slightly improved compared with individuals without CHIP. This finding is surprising and raises the possibility that *DNMT3A* mutations may "cancel out" the detrimental effect of *TET2* mutations on mortality after TAVR or somehow work synergistically to yield a more favorable outcome. However, the analysis of larger patient cohorts and mechanistic experiments in model systems would be required to test this provocative hypothesis.

An earlier study by Mas-Peiro et al also reported an association between CHIP and a lower survival after TAVR.[5] However, in contrast to Lassalle et al,[4] Mas-Piero et al limited their analysis to CHIP associated with *DNMT3A* and *TET2* mutations only.[5] Mas-Piero et al also focused on both gene mutations together and thus it was unknown as to whether there were any individual gene-specific associations with survival after TAVR. Findings from the present study indicate that there are clearly differences between *DNMT3A* and *TET2* mutations with respect to survival post-TAVR. From a mechanistic perspective, experimental studies have suggested that *TET2* and *DNMT3A* mutations confer divergent effects on leukocytes and thus likely contribute to disease processes differently. On this point, it has been found that *TET2* mutant macrophages produce higher levels of interleukin-1β, whereas *DNMT3A* mutant macrophages generate higher amounts of the chemokines CXCL1 and CXCL2.[2] Thus, it could be interpreted that the mechanisms by which *TET2*-mediated CHIP promotes disease have a greater effect on post-TAVR mortality than *DNMT3A*-mediated CHIP, although this notion warrants further investigation. Despite this possibility, it also should be noted that the predecessor study did not use an upper VAF cutoff of 10%,[5] and therefore it may be plausible that larger *DNMT3A* clones are less benign after TAVR. However, future studies are needed to explore this possibility.

Another key difference between the studies is the follow-up time after TAVR. Lassalle et al[4] examined patients for 5 years after TAVR, whereas Mas-Peiro et al[5] followed patients for around 8 months. It is conceivable that death within the first 8 months more closely reflects complications after the procedure, whereas death more than 1 year on is more related to age-related frailty or complications with comorbid conditions, particularly as the average procedural age is usually around 80 years. Indeed, *TET2*-mediated clonal hematopoiesis has been associated with heart failure, diabetes, ischemic stroke, and advanced biological aging,[1] all of which may lead to premature mortality.

Despite the caveats mentioned above, the findings from Lassalle et al[4] indicate an association between *TET2*-mediated CHIP and a higher mortality after TAVR. Although larger patient cohorts are required to confirm this association, the presence of *TET2* mutations in the blood may represent a novel prognostic indicator for poor survival after TAVR and guide the clinical care of patients with these mutations.

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