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# Frailty and cardiovascular disease: A two-way street?

**D**ESPITE A MARKED INCREASE in awareness in recent years surrounding the prevalence and prognosis of frailty in our aging population and its association with cardiovascular disease, itself highly prevalent in elderly cohorts, the exact pathobiological links between the 2 conditions have not been fully elucidated. As a consequence, this has led to difficulty not only in accurately defining cardiovascular risk in vulnerable elderly patients, but also in adequately mitigating against it.

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It is well accepted that cardiovascular disease, whether clinical or subclinical, is associated with an increased risk of developing the frail phenotype.<sup>1,2</sup> Frailty, in turn, has been consistently identified as a universal marker of adverse outcomes in patients at risk of, and in patients with already manifest, cardiovascular disease.<sup>2,3</sup> However, whether or not frailty is its own unique risk factor for cardiovascular disease, independent of co-associated risk markers, or is merely a downstream byproduct indicating a more advanced disease state, has yet to be determined. Furthermore, the question of whether modification of frail status may impact the development and progression of cardiovascular disease has not yet been established.

The article by Orkaby et al<sup>4</sup> in this issue delves deeper into this question by looking specifically at the interaction between frailty and standard risk factors as they relate to the prevention of cardiovascular disease.

## ■ **NEEDED: A UNIVERSAL DEFINITION OF FRAILITY**

It is important to acknowledge up front that before we can truly examine frailty as a novel risk entity in the assessment and management of cardiovascular risk in older-age patients, we need to agree on an accepted, validated definition of the phenotype as it relates to this population. As acknowledged by Orkaby et al,<sup>4</sup> lack of such a standardized definition has resulted in highly variable estimates of the prevalence of frailty, ranging from 6.9% in a community-dwelling population in the original Cardiovascular Health Study to as high as 50% in older adults with manifest cardiovascular disease.<sup>1,2</sup>

The ideal frailty assessment tool should be a simple, quantitative, objective, and universally accepted method, capable of providing a consistent, valid, reproducible definition that can then be used in real time by the clinician to determine the absolute presence or absence of the phenotype, much like hypertension or diabetes. Whether this optimal tool will turn out to be the traditional or modified version of the Fried Scale,<sup>1</sup> an alternative multicomponent measure such as the Deficit Index,<sup>5</sup> or even the increasingly popular single-item measures such as gait speed or grip strength, remains to be determined.

Exact choice of tool is perhaps less important than the singular adoption of a universal method that can then be rigorously tried and tested in multicenter studies. Given the bulk of data to date for the original Fried phenotype and its development in an older-age community setting with a typical prevalence of cardiovascular risk factors, the Fried Scale appears a particularly suitable tool to use for

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disease**

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this domain of disease prevention. Single-item spin-off measures from this phenotype, including gait speed, may also be useful for their increased feasibility and practicality in certain situations.

### ■ A TWO-WAY STREET

Given what we know about the pathophysiological, immunological, and inflammatory processes underlying advancing age that have also been implicated in both frailty and cardiovascular disease syndromes, how can we determine if frailty truly is an independent risk factor for cardiovascular disease or merely an epiphenomenon of the aging process?

We do know that older age is not a prerequisite for frailty, as is evident in studies of the phenotype in middle-aged (and younger) patients with advanced heart failure.<sup>6</sup> We also know not only that frail populations have a higher age-adjusted prevalence of cardiovascular risk factors including diabetes and hypertension,<sup>1</sup> but also that community-dwellers with prefrailty (as defined in studies using the Fried criteria as 1 or 2 vs 3 present criteria) at baseline have a significantly increased risk of developing incident cardiovascular disease compared with those defined as nonfrail, even after adjustment for traditional risk factors and other biomarkers.<sup>3</sup> Exploring the differences between these subgroups at baseline revealed that prefrailty was significantly associated with several subclinical insults that may serve as adverse vascular mediators, including insulin resistance, elevated inflammatory markers, and central adiposity.<sup>3</sup>

A substudy of the Cardiovascular Health Study also found that in over 1,200 participants without a prior history of a cardiovascular event, the presence of frailty was associated with multiple noninvasive measures of subclinical cardiovascular disease, including electrocardiographic and echocardiographic markers of left ventricular hypertrophy, carotid stenosis, and silent cerebrovascular infarcts on magnetic resonance imaging.<sup>7</sup>

These findings support a mechanistic link between evolving stages of frailty and a gradient of progressive cardiovascular risk, with a multifaceted dysregulation of metabolic processes known to underpin the pathogenesis of

the frailty phenotype likely also triggering risk pathways (altered insulin metabolism, inflammation) involved in incident cardiovascular disease. Although the exact pathobiological pathways underlying these complex interlinked relationships between aging, frailty, and cardiovascular disease have yet to be fully elucidated, awareness of the bidirectional relationship between both morbid conditions highlights the absolute importance of modifying risk factors and subclinical conditions that are common to both.

### ■ CAN RISK BE MODIFIED IN FRAIL ADULTS?

Orkaby et al<sup>4</sup> nicely lay out the guidelines for standard cardiovascular risk factor modification viewed in light of what is currently known—or not known—about how these recommendations should be interpreted for the older, frail, at-risk population. It is important to note at the outset that clinical trial data both inclusive of this population and incorporating the up-front assessment of frailty to predefine frail-or-not subgroups are sparse, and thereby evidence for how to optimize cardiovascular disease prevention in this important cohort is largely based on smaller observational studies and expert consensus.

#### Hypertension

However, important subanalyses derived from 2 large randomized controlled trials (Hypertension in the Very Elderly Trial [HYVET] and Systolic Blood Pressure Intervention Trial [SPRINT]) looking specifically at the impact of frail status on blood pressure treatment targets and related outcomes in elderly adults have recently been published.<sup>8,9</sup> Notably, both studies showed the beneficial outcomes of more intensive treatment (to 150/80 mm Hg or 120 mm Hg systolic, respectively) persisted in those characterized as frail (via Rockwood frailty index or slow gait speed).<sup>8,9</sup> Importantly, in the SPRINT analysis, higher event rates were seen with increasing frailty in both treatment groups; across each frailty stratum, absolute event rates were lower for the intensive treatment arm.<sup>9</sup> These results were evident without a significant difference in the overall rate of serious adverse events<sup>9</sup> or withdrawal rates<sup>8</sup> between treatment groups.

**For better risk assessment, frail patients must be better represented in randomized trials in populations at risk of or with cardiovascular disease**

Hypertension is the primary domain in which up-to-date clinical trial data have shown benefit for continued aggressive treatment for cardiovascular disease prevention regardless of the presence of frailty. Despite these data, in the real world, the “eyeball” frailty test often leads us to err on the side of caution regarding blood pressure management in the frail older adult. Certainly, the use of antihypertensive therapy in this population requires balanced consideration of the risk for adverse effects; the SPRINT analysis also found higher absolute rates of hypotension, falls, and acute kidney injury in the more intensively treated group.<sup>9</sup> These adverse effects may be ameliorated not necessarily by modifying the target goal that is required, but by employing alternative strategies in achieving this goal, such as starting with lower doses, uptitrating more slowly, and monitoring with more frequent laboratory testing.

Currently, consensus guidelines in Canada have recommended liberalizing blood pressure treatment goals in those with “advanced frailty” associated with a shorter life expectancy.<sup>10</sup>

### Dyslipidemia

Regarding the other major vascular risk factors, trials looking at the role of frailty in the targeted treatment of hyperlipidemia with statins in older patients for primary prevention of cardiovascular disease are lacking, although the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial showed a significant positive benefit for statin therapy in adults over age 70 (number needed to treat of 19 to prevent 1 major cardiovascular event, and 29 to prevent 1 cardiovascular death).<sup>11</sup> This again may be counterbalanced by the purported increased risk of cognitive and potential adverse functional effects of statins in this age group; however, trial data specific to frail status or not is required to truly assess the benefit-risk ratio in this population.

### Hyperglycemia

Meanwhile, recent clinical trials looking at the impact of age, functional impairment, and burden of comorbidities (rather than specific frailty measures) on glucose-lowering targets and cardiovascular outcomes have failed to

show a benefit from intensive glycemic control strategies, leading guideline societies to endorse less-stringent hemoglobin A<sub>1c</sub> goals in this population.<sup>12</sup> Given the well-documented association between hyperglycemia and cardiovascular disease, as well as the purported dysregulated glucose metabolism underlying the frail phenotype, it is important that future trials looking at optimal hemoglobin A<sub>1c</sub> targets incorporate the presence or absence of frailty to better inform specific recommendations for this population.

### ■ ONE SIZE MAY NOT FIT ALL

Overall, if both prefrailty and frailty are independent risk factors for, and a consequence of, clinical cardiovascular disease, it is worth bearing in mind that the modification of “intensive” or best practice therapies based on qualitatively assessed frailty may actually contribute to the problem. With best intentions, the negative impact of frailty on cardiovascular outcomes may be augmented by automatically assuming it to reflect a need for “therapy-light.” The adverse downstream consequences of inadequately treated cardiovascular risk factors are not in doubt, and it is important as the role of frailty becomes an increasingly recognized cofactor in the management of older adults with these risk factors that the vicious cycle underlying both syndromes is kept in mind, in order to avoid frailty becoming a harbinger of undertreatment in older, geriatric populations.

What is clear is that more prospective clinical trial data in this population are urgently needed in order to better delineate the exact interactions between frail status and these risk factors and the potential downstream consequences, using prespecified and robust frailty assessment methods.

Perhaps frailty should be seen as a series of stages rather than simply as a binary “there or not there” biomarker; through initial and established stages of the syndrome, which have been independently associated with both clinical events and subclinical surrogates of cardiovascular disease, risk factors should continue to be treated aggressively and according to best available evidence. However, as guideline societies are already beginning to endorse as high-

**Recent trials in hypertensive populations indicate that we need to avoid viewing frailty as a reason to undertreat cardiovascular risk factors**

lighted above, once the phenotype becomes tethered with a certain threshold burden of comorbidity, cognitive or functional impairment, or more end-stage disease status, then goals for cardiovascular disease prevention may need to be readdressed and modified. If frailty is truly confirmed as a cardiovascular disease equiva-

lent, not only appropriately treating associated cardiovascular risk factors but also seeking therapies that actively target the frailty syndrome itself should be an important goal of future studies seeking to impact the development of both clinical and subclinical cardiovascular disease in this population. ■

### REFERENCES

1. Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001; 56:M146–M156.
2. Afilalo J, Alexander KP, Mack MJ, et al. Frailty assessment in the cardiovascular care of older adults. *J Am Coll Cardiol* 2014; 63:747–762.
3. Sergi G, Veronese N, Fontana L, et al. Pre-frailty and risk of cardiovascular disease in elderly men and women: the Pro.V.A. study. *J Am Coll Cardiol* 2015; 65:976–983.
4. Orkaby AR, Onuma O, Qazi S, Gaziano JM, Driver JA. Preventing cardiovascular disease in older adults: one size does not fit all. *Cleve Clin J Med* 2018; 85:55–64.
5. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. *BMC Geriatr* 2008;8:24.
6. Joyce E. Frailty in advanced heart failure. *Heart Fail Clin* 2016; 12:363–374.
7. Newman AB, Gottdiener JS, McBurnie MA, et al; Cardiovascular Health Study Research Group. Associations of subclinical cardiovascular disease with frailty. *J Gerontol A Biol Sci Med Sci* 2001; 56:M158–M166.
8. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people: an investigation of the impact of frailty upon treatment effect in the Hypertension in the Very Elderly Trial (HYVET) study, a double-blind, placebo-controlled study of antihypertensives in people with hypertension aged 80 and over. *BMC Med* 2015; 13:78.
9. Williamson JD, Supiano MA, Applegate WB, et al; SPRINT Research Group. Intensive vs standard blood pressure control and cardiovascular disease outcomes in adults aged  $\geq 75$  years: a randomized clinical trial. *JAMA* 2016; 315:2673–2682.
10. Mallery LH, Allen M, Fleming I, et al. Promoting higher blood pressure targets for frail older adults: a consensus guideline from Canada. *Cleve Clin J Med* 2014; 81:427–437.
11. Glynn RJ, Koenig W, Nordestgaard BG, Shepherd J, Ridker PM. Rosuvastatin for primary prevention in older persons with elevated C-reactive protein and low to average low-density lipoprotein cholesterol levels: exploratory analysis of a randomized trial. *Ann Intern Med* 2010; 152:488–496.
12. Ismail-Beigi F, Moghissi E, Tiktin M, Hirsch IB, Inzucchi SE, Genuth S. Individualizing glycemic targets in type 2 diabetes mellitus: implications of recent clinical trials. *Ann Intern Med* 2011; 154:554–559.

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