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Accelerated aging and frailty in cardiovascular diseases

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Aging is the greatest risk factor for cardiovascular disease (CVD), which is the most common cause of death in European countries.[1] It is estimated that during the period from 2020 to 2022, there were 9.0% more excess deaths from CVD than expected.[2] By 2030, approximately 20% of the population will be aged 65 years and older, and CVD will account for 40% of deaths in this age group,[3] imposing a significant burden on the healthcare system and society as a whole. Aging is related to frailty, which represents the dynamic progression of physical and physiological decline in older adults. Frailty limits an individual's ability to recover from acute stressors and serves as a predictor of clinical adverse outcomes. Despite the uncertainties in screening, assessing, and managing frailty in clinical practice, emphasizing the connections between frailty, aging, and CVD will provide new insights for the prediction, prevention, and management of CVD in the aging population.

Frailty is a marker of high risk for CVD, with at least half of heart failure (HF) patients affected by frailty. It is associated with increased risks of all-cause mortality, all-cause readmission, and HF readmission.[4] Recent multicenter prospective cohort studies have suggested a strong and progressive association between pre-frailty and frailty status with the risk of death or hospitalization due to HF.[5] Furthermore, a clinical controlled trial found that baseline frailty may identify HF patients with reduced ejection fraction, reflecting which populations are most likely to benefit from aerobic training and cardiac rehabilitation, thereby reducing the risk of all-cause hospitalization.[6] Additionally, another large-scale SPRINT randomized controlled trial found that frail patients have a higher risk of major cardiovascular events, and intensive blood pressure treatment in severely frail patients does not increase the risk of serious adverse events. These findings suggest that for high-risk cardiovascular populations, frailty should not be a barrier to intensive blood pressure management and HF treatment.[7]

Moreover, among cardiac surgery patients, frailty is recognized as a major health challenge. In new perioperative care plans, routine frailty screening has become a standard procedure. This adjustment has not only enhanced surgical success rates but also reduced postoperative complications.[8] This implies that with early screening, targeted interventions, and personalized treatment, we can expect to significantly improve the prognosis of CVD patients, particularly those at high risk due to frailty.

In the absence of effective interventions targeting the mechanisms of the aging process itself, aging is largely considered unalterable. In contrast, frailty can be reversed through medical means. Frailty is a multidimensional and dynamic clinical condition,[4] and there may be a bidirectional relationship between CVD and frailty. A large-scale prospective cohort study found that different changes in frailty status are associated with varying risks of developing CVD. Progression of frailty increases the risk of CVD, while recovery from frailty reduces this risk.[9] Therefore, changes in frailty status can influence the outcomes of CVD, and reversing frailty might be a therapeutic strategy for CVD, differing from established pharmacological treatments.

Notably, a longitudinal prospective cohort study utilizing large-scale proteomics technology identified that out of 83 HF-related proteins, 48 proteins were cross-sectionally associated with frailty. These proteins were enriched in canonical pathways related to fibrosis and inflammation, suggesting potential shared biological pathways between frailty and HF.[10] Mechanistically, frailty is associated with subclinical alterations in cardiac structure and function. As the cardiovascular system ages, structural and fu-

nctional changes occur, including increased cardiomyocyte death due to heightened oxidative stress and reactive oxygen species production. Both frailty and HF are characterized by widespread inflammatory markers in circulation, with inflammation playing a crucial role in CVD. A comprehensive review of the literature indicates that chronic activation of inflammation in the elderly can complicate the clinical features of CVD, leading to an imbalance in catabolic energy and disruption of homeostatic signaling, ultimately resulting in frailty.[3]

Integrating findings from recent large-scale prospective clinical studies and randomized controlled trials on the management of frailty and CVD, we provide specific recommendations for incorporating frailty into CVD prevention (screening) and treatment (reversing frailty) strategies (Figure 1).

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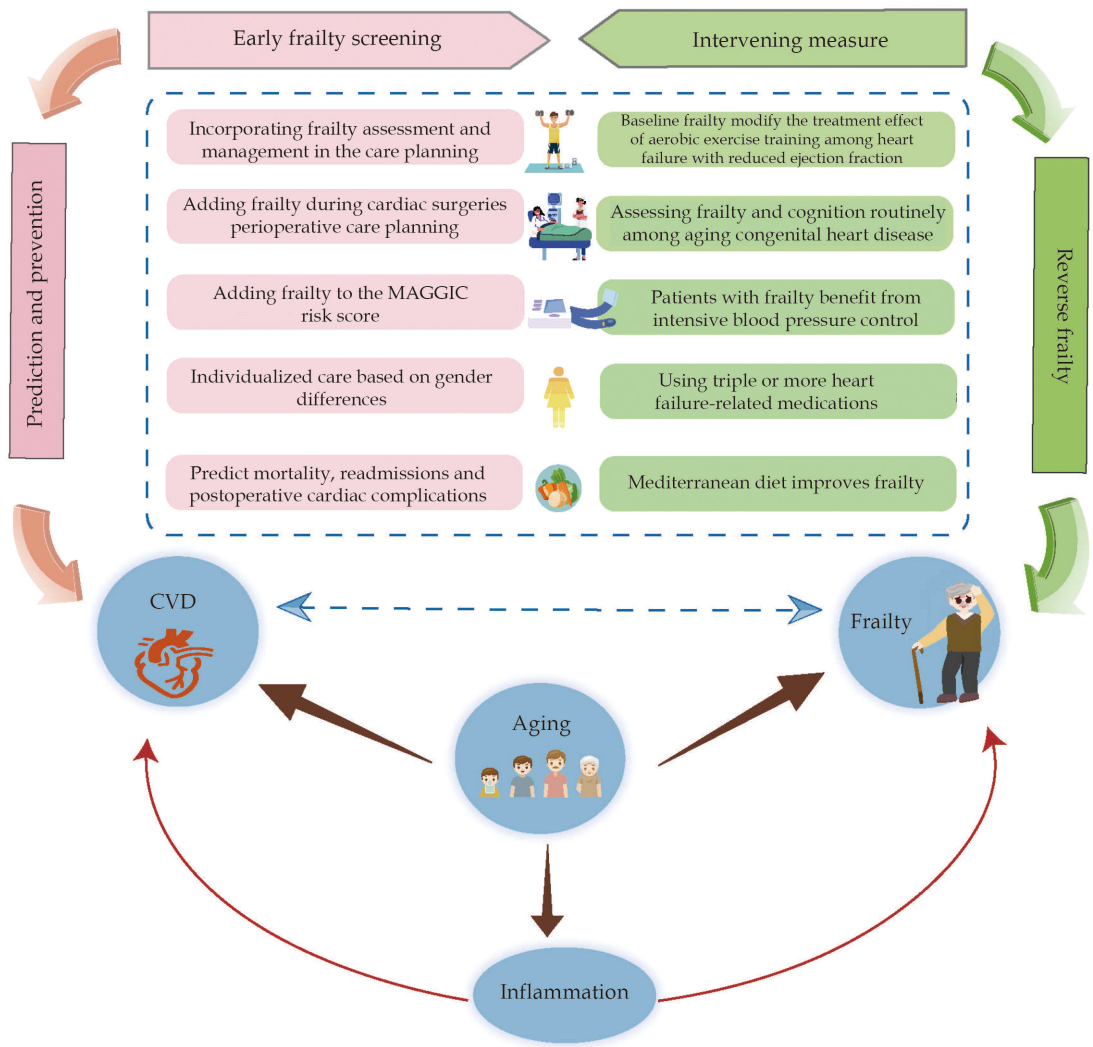

Figure 1 Proposed schematic diagram integrating the prevention and reversal of frailty into CVD interventions, as well as the mechanisms of how inflammation and aging impact CVD and frailty. CVD: cardiovascular disease.

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