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Frailty and Cardiovascular Disease

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Abstract

Cardiovascular disease (CVD) comprises a vast spectrum of disease states ranging from hypertension (HTN) to valvular heart disease (VHD). CVD is known to be the leading cause of morbidity, mortality, and health-care expenditure throughout the world. According to the World Health Organization, coronary artery disease (CAD) and stroke, both subsets of CVD, are the world's biggest killers, accounting for a combined 15 million deaths in 2015. These diseases have remained the leading causes of death globally in the last 15 years. In 2010, CAD alone was projected to cost the U.S. \$108.9 billion including the cost of health-care services, medications, and lost productivity. The presence of frailty significantly worsens outcomes for patients suffering from CAD. With just this one example of how frailty affects CVD, it is clear that understanding the impact of frailty upon patients afflicted with the spectrum of cardiovascular disease is integral for the care of this very significant patient population.

Keywords: frailty, cardiovascular disease, valvular heart disease, outcomes in cardiovascular disease, hypertension, coronary artery disease, peripheral vascular disease, lipid dysregulation

1. Introduction

Cardiovascular disease (CVD) comprises a vast spectrum of disease states ranging from hypertension (HTN) to valvular heart disease (VHD) and is known to be the leading cause of morbidity, mortality, and health-care expenditure throughout the world. According to the World Health Organization, coronary heart disease (CHD) and stroke, both subsets of CVD, are the world's most impactful causes of mortality, accounting for a combined 15 million deaths in

2015. These diseases have remained the leading causes of death globally in the last 15 years. In 2010, CHD alone was projected to cost the United States (US) \$108.9 billion including the cost of health-care services, medications, and lost productivity. The presence of frailty significantly worsens outcomes for patients suffering from CHD [1]. With just this one example of how frailty affects CVD, it is clear that understanding the impact of frailty upon patients afflicted with the spectrum of CVD is integral for the care of this very significant patient population.

While frailty as an entity is manifested by the interplay of multiple factors, there are some that are pertinent to the relationship between CVD and frailty. Endocrine dysregulation and higher levels of inflammatory markers have been found in frail compared with non-frail persons, and these derangements have been appreciated in patients with CHD. Elevations in some markers of frailty are also risk factors for the development of progressive vascular and CHD [2]. So while it can be inferred that CVD and frailty share common links, the effect of frailty upon the outcomes of CVD is still an area of interest and continued study [3].

We now know that CVD can worsen sarcopenia and lead to frailty, while frailty worsens morbidity and mortality in CVD [4, 5]. Maximal aerobic power (MAP), a measure of frailty, decreases with age due to a decrease in cardiac output. And though CVD is not the primary cause of decline of MAP, CVD clearly exacerbates the said decline [5]. Recently, in a meta-analysis of 54,250 elderly individuals with a mean follow-up of 6.2 years, the presence of atherosclerotic CVD was associated with the coexistence of frailty syndrome (FS) with an odds ratio (OR) of 2.7–4.1 [6]. Also, in patients who did not begin the study with FS, CVD was associated with the onset of FS during follow-up of these patients. There have been several studies that highlight the relationship between CVD and frailty, as described in **Tables 1** and **2**.

Study	Study type/number of patients	Objective	Outcome
Chin et al. [7]	Population-based cohort study/545 men	Assess association between classic cardiovascular risk factors and subsequent functional disability and mental well-being in elderly men.	Combined classic cardiovascular risk factors are predictive of functional disability.
Newman et al. [8]	Observational cohort/4375 patients	Assess the relationship between subclinical cardiovascular disease and frailty.	Cardiovascular disease was associated with an increased likelihood of frail health.
Chaves et al. [9]	Prospective population based cohort/670 patients	Examined the cross-sectional relationship between hemoglobin (Hb) and a recently-validated measure of frailty in community-dwelling older women, and whether this relationship was modified by cardiovascular disease (CVD) status.	Mildly low and low-normal Hb levels were independently associated with increased frailty risk. This risk was synergistically modified by the presence of CVD.
Woods et al. [10]	Prospective study, the Women's Health Initiative Observational Study/40,657 women	Identified risk factors for frailty as targets for prevention. Investigated the predictive validity of this frailty classification for death, hospitalization, hip fracture, and activity of daily living (ADL) disability.	Community-dwelling older women with CVD and cardiovascular risk factors were at higher risk of developing incident frailty.

Table 1. Effect of cardiovascular disease on frailty.

Study	Study type/ number of patients	Objective	Outcome
Klein et al. [11]	Prospective cohort/2962 patients	Association of measures of frailty to disease outcomes and survival in a population-based study of Midwestern adults.	Greater frailty was significantly associated with cardiovascular disease and hypertension.
Cacciatore et al. [12]	Prospective cohort/1259 patients	This study aimed to examine the predictive role of frailty on long-term mortality in elderly subjects with CHF.	Frailty represents a new independent variable for predicting long-term mortality in elderly subjects with CHF.
Purser et al. [13]	Observational cohort/309 patients	To characterize physiological variation in hospitalized older adults with severe coronary artery disease (CAD) and evaluate the prevalence of frailty in this sample, to determine whether single-item performance measures are good indicators of multidimensional frailty, and to estimate the association between frailty and 6-month mortality.	Gait speed frailty was the strongest predictor of mortality in a population with CAD and may add to traditional risk assessments when predicting outcomes in this population.
Boxer et al. [14]	Prospective cohort/60 patients	To assess the distance on the 6-min walk test (6MWT) as a measure of frailty in 60 older HF patients (ejection fraction \leq 40%) compared with frailty phenotype (FP).	The 6MWT may be useful to identify frailty and those in transition to frailty.
Dumurgier et al. [15]	Prospective cohort study/3208 men and women	Study the relation between low walking speed and the risk of death in older people, both overall and with regard to the main causes of death.	Slow gait speed was associated with a threefold increase in cardiovascular mortality over 5 years but no difference in death due to cancer or death due to other causes, implying a specific effect of frailty on CVD.
Ekerstad et al. [5]	Prospective cohort/307 patients	To analyze how frailty predicts short-term outcomes for elderly non-ST-segment elevation myocardial infarction patients.	Frailty is strongly and independently associated with in-hospital mortality, 1-month mortality, prolonged hospital care, and the study's primary composite outcome which included endpoints like all-cause mortality, reinfarction, revascularization, and even dialysis in older patients after non-ST elevation myocardial infarction (NSTEMI).

Table 2. Effect of frailty on cardiovascular disease.

A scoring system easily used on an inpatient basis highlights the interplay of CVD and frailty [16]. Sanchis et al. described seven independent predictors of frailty: age \geq 75 years, female sex, prior CHD, admission for heart failure (HF), hemoglobin \leq 12.5 g/dL, vitamin D \leq 9 ng/mL, and cystatin-C \geq 1.2 mg, which could be measured on an inpatient basis. Defining frailty as positive when there were \geq 3 had a good correlation with the Fried score of frailty.

In this chapter, we delve into a basic understanding of the underlying pathophysiology of CVD in relation to frailty and how it is worsened by the latter, inflammatory markers that have proven significant in CVD and frailty, and how frailty affects a vast spectrum of CVD, ranging from lipid dysregulation to outcomes in VHD.

2. Pathophysiology

The pathophysiology of CVD and frailty relates to a baseline chronic inflammatory state [17–20]. This phenomenon is caused by a metabolic imbalance in the body, hereby systemic demand is not met by metabolic supply, and consequently the body becomes primarily catabolic, oxidative stress increases, and ultimately a low-level inflammatory phenotype is established [18, 21–28].

Multiple diseases place systemic stress demands on the body [1] that in turn leads to the inability of the body to keep pace with the demands of daily living, such as thermoregulation, aerobic respiration, glycolysis, and oxidative phosphorylation [17, 22, 29]. As a consequence of this baseline mismatch between the body's demand and its ability to supply, the body enters a pro-catabolic state and begins to metabolize itself for nutrient utilization [17, 25]. During this state, more inefficient systems are used to produce energy, and weakness and weight loss occur [30]. A pro-catabolic state is frequently seen in both CHD and frailty and leads to, as we already know exists in frailty, a pro-inflammatory state [18, 24].

The aforementioned pro-inflammatory state is highlighted by the presence of elevated inflammatory markers. There are markers specific to frailty and others that are common between CVD and frailty. Interleukin (IL)-6 is the most consistently seen inflammatory marker in patients with frailty, and is thought to be central to the pathogenesis of the phenotype [18, 21, 24, 26–28]. Studies have reported seeing elevated plasma uric acid, D-dimer, white blood cells (WBCs), erythrocyte sedimentation rate (ESR), triglycerides, homocysteine, glucose, hemoglobin A1C (HbA1c), creatinine, cystatin C, insulin-like growth factor (IGF)-1, fibrinogen, von Willebrand factor, factors VIII and IX, oxidized proteins, protein carbonylation, as well as decreased vitamin D and testosterone in patients with frailty [31]. In order to highlight the common role inflammation plays in both CVD and frailty, we can appreciate that elevations of C-reactive protein (CRP), factor VIII, and D-dimer are commonly seen even after correction of CVD [32]. Particularly, D-dimer, CRP, IL-6, and tumor necrosis factor (TNF)-alpha will be discussed where pertinent.

3. Frailty and hypertension (HTN)

Though not all frail patients are hypertensive, there is some evidence to suggest that HTN is independently associated with frailty [33]. The mechanism behind this finding is further elucidated by the fact that frail patients have a decreased ability to use adenosine triphosphate (ATP) [23, 29, 34]. This leads to a decreased ability of smooth muscle to use ATP to pump calcium back into the sarcoplasmic reticulum, which is marked by a slower rate of decay of the calcium transit. In practical terms, this means the blood vessels of frail patients have decreased compliance and difficulty relaxing, which leads to HTN.

The renin-angiotensin-aldosterone system (RAAS) is one of the primary systems used by the body to regulate blood pressure (BP) (**Figure 1**) [35, 36]. Chronic inflammation directly stimulates RAAS, which causes HTN [37]. Since frail patients have persistently increased inflammation, stimulating RAAS, they are more likely to develop HTN. Thus, there is a direct link between the chronic inflammation phenotype and HTN in frail patients.

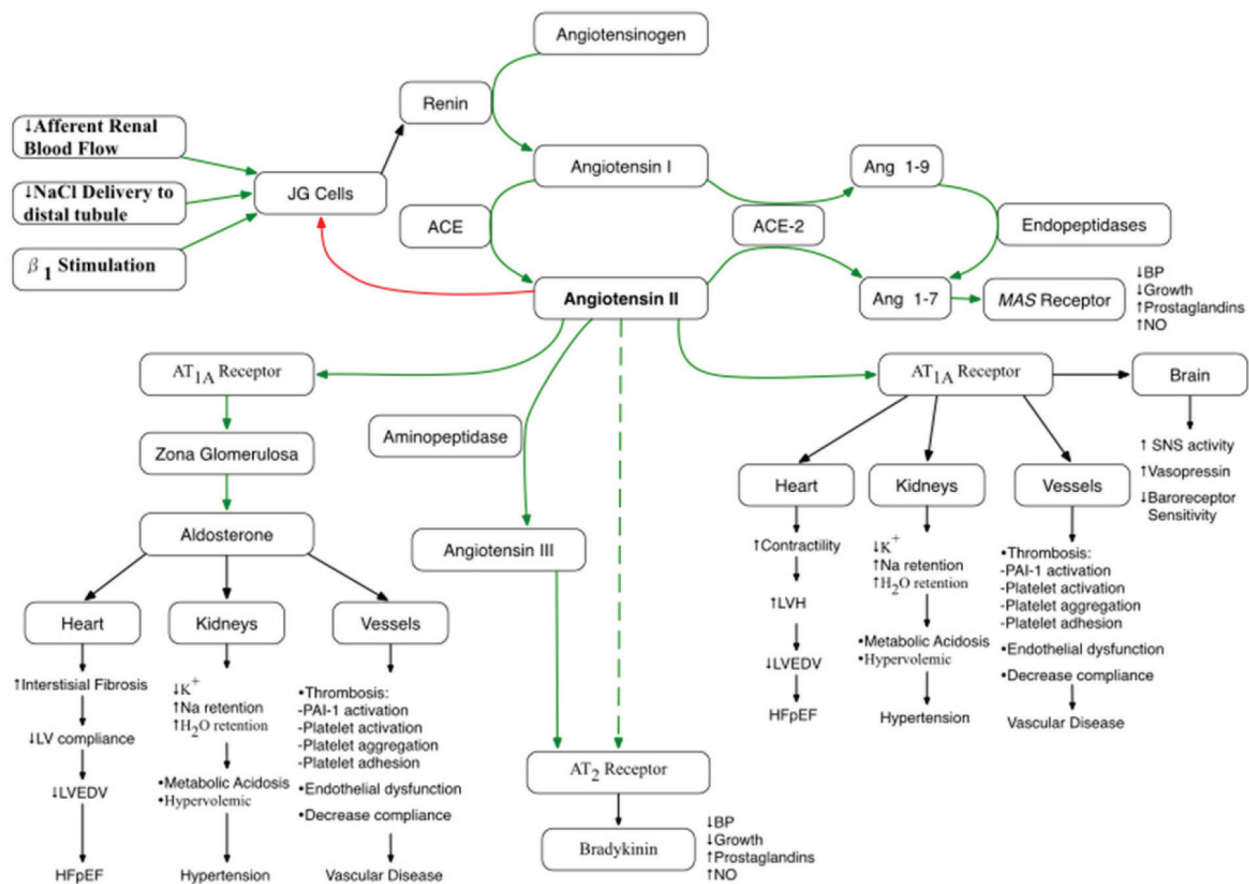


Figure 1. Renin-angiotensin-aldosterone system. ACE I, angiotensin-converting enzyme inhibitor; ACE-2, angiotensin-converting enzyme-2; Ang, angiotensin; BK, bradykinin; BP, blood pressure; HFpEF, heart failure with preserved ejection fraction; JG, juxtaglomerular; LV, left ventricle; LVEDV, left ventricular end diastolic volume; LVH, left ventricular hypertrophy; NO, nitric oxide; PAI-1, plasminogen activator inhibitor-1; SNS, sympathetic nervous system.

Evidence from randomized controlled trials over the past decade indicates there is benefit to treating hypertension in older patients [38, 39]. This is inconsistent with earlier observational and subgroup analyses of previous randomized control trials which were inconclusive [40, 41]. The HYVET trial in 2008 specifically focused the treatment of hypertension in elderly patients and found that antihypertensive treatment in patients older than 80 was beneficial [39]. In 2015, the Systolic Blood Pressure Intervention Trial (SPRINT) was undertaken. This trial should not be confused with the Sarcopenia and Physical Frailty in Older People: Multicomponent Treatment Strategies (SPRINTT) trial, which aims to provide a clear operational definition of physical frailty and assess the impact a multi-component intervention has on its progression [42]. The SPRINT trial showed that among patients >50 years old, lowering BP to <120 mmHg, particularly in the elderly, was associated with a significant decrease in mortality compared to a target of less than 140 mmHg at 5 years (5.2% vs. 6.8%; hazard ratio (HR): 0.75; 95% confidence interval (CI): 0.64–0.89, $p < 0.001$) [38]. Of note, patients who were >75 years old tended to fare better than younger patients. Taken together, this suggests that all elderly patients benefit from antihypertensive treatments, but there is an important caveat to both of these studies: enrolled patients tended to be relatively healthy patients and specifically excluded patients with heart failure, stroke, and end-stage renal disease [35, 38].

The exclusion criteria for HYVET and SPRINT raise concern that their findings may not be generalizable to frail patients [43]. A subgroup analysis of patients enrolled in HYVET addressed this concern [44]. Participants in both the control and treatment groups were given a frailty index according to 60 different variables. The impact of the frailty index on subsequent risk of stroke, mortality, and cardiac events was found to be non-significant, suggesting that benefits associated with BP lowering were conserved in frail patients. A frailty index was calculated for SPRINT participants using a similar set of 36 variables [45]. The frailty index distribution among the participants was comparable to general population cohorts. This suggests the heterogeneity of frailty among participants is similar to the general population.

Another 2015 report as a part of the Zwolle Outpatient Diabetes Project Integrating Available Care-34 (ZODIAC-34) cohort study, this time including all-comers, confirmed what observational studies had shown: for all-cause mortality (especially frail patients), there was an inverse relationship between blood pressure and all-cause mortality with a hazard ratio for systolic blood pressure of 0.92 (95% CI: 0.87–0.98) and 0.83 for diastolic blood pressure (95% CI: 0.73–0.93) [46]. This suggested that among all patients >75 years of age, this time including those with less than 1 year life expectancy and DM, lower BP was associated with an increase in mortality. Contiguously, intensive lowering of BP in patients with low gait speed (a commonly used proxy for frailty) did not reduce mortality and the rate of CVD events ($p = 0.05, 0.28$, respectively) [47].

4. Frailty and lipids

The metabolism of lipids has been shown to affect aging, such that having a high-density lipoprotein (HDL) level above 70 mg/dL is referred to as longevity syndrome. The *Invecchiamento e Longevità nel Sirente (iLSERENTE)* study showed that the HDL levels of the patients in their study who died during follow-up were significantly lower than the levels of the survivors. This finding contributed to the understanding of the effect of HDL on lifespan, highlighting the role of lipid metabolism in decreasing mortality in the frail, elderly patient [48]. Another study of the same group of patients showed that, among frail patients, those with the highest HDL levels had the best functional states [49]. To further support this idea, another study done in 2015 supported frailty as an independent risk factor for various diseases along the CVD spectrum. A low HDL level was one of the parameters [50]. As a part of the Longitudinal Aging Study Amsterdam, it was described that a lower total cholesterol was related to a higher rate of decline on information-processing speed indicating, ultimately, that lower total cholesterol may be considered to be a marker of frailty and predictive of lower cognitive function in the elderly [51]. As described earlier, there has been significant study regarding the relationship between frailty, HDL status, and its effect on mortality. Conversely, the relation between low-density lipoprotein (LDL) levels and frailty has yet to be established. Also, whereas the effect of lipids in the frail patient has been studied, the effect of frailty on the patient with a lipid disorder has yet to be established.

There has been speculation upon the metabolism of lipids in the frail patient. As there is a pro-inflammatory milieu in the frail patient, this inflammation may affect lipid metabolism and, hence, lipid profiles in those who are frail. There may also be some correlation between

dysfunctional lipid metabolism due to endocrine dysregulation evidenced by lower IGF-1 and growth hormone levels in frail patients, lower HDL levels, and resultant poorer outcomes in CHD [52, 53]. A study on metabolic syndrome and disability showed a correlation between high triglycerides and a limitation in mobility and activities of daily living [54]. Overall, the effect of frailty, its pro-inflammatory state, and the collective effect on lipids seems to be contiguous with an elevation in triglycerides (TGs) and a decrease in HDL likely contributing to the elevated CVD risk in the frail population.

5. Frailty and atrial fibrillation (AF)

The up-regulation of the RAAS system in frail patients, as mentioned earlier, mediates an up-regulation of endothelin-1, which in turn mediates an increase in cardiac fibrosis [55]. Cardiac fibrosis, in turn, increases the likelihood of AF by disrupting the cardiac neuroconduction pathways [23]. Additionally, frailty may be an independent risk factor for AF [46] due to a decreased ability to modulate heart rate, resulting in an increased likelihood of a patient developing AF [56, 57]. Additionally, an increased calcium influx, as discussed earlier, causes changes in the trans-cellular membrane potential, which in turn makes a patient more likely to develop AF [23].

Frail patients have a 4.4 times higher chance (95% CI: 2.104–9.080, $p < 0.001$) of having AF compared to the general population [57]. Additionally, Polidoro et al. found that even after adjusting for age, sex, CVD, and CVD risk factors, AF was associated with a fourfold increase in frailty highlighting the relation between frailty and AF [58]. Additional evidence supporting the link between frailty and AF is the impairment of autonomic control vis-à-vis decreased heart rate variability which often precedes episodes of paroxysmal AF [57]. Similarly, there is decreased heart rate variability in frail patients.

AF has a significant impact on outcomes, including mortality, in frail patients [59]. Nguyen et al. found that in patients with AF, there was a 2.69 times higher risk of death in frail patients over a 6-month period after hospitalization (HR: 2.69, 95% CI: 1.53–4.74). This relationship held even after correction for potential co-founders (HR: 2.33; 95% CI: 1.31–4.14). It may be plausible to infer that AF also causes significant risk for cognitive decline to these patients seeing as they are already at an increased risk for microbleeds as discussed subsequently in the section on cerebrovascular disease. Furthermore, the strong risk of stroke and TIA outlined in the subsequent text is indubitably linked with AF [60].

Despite the increased risk of death with AF, frail patients have an eightfold less likelihood of being discharged home on an oral anticoagulant after hospitalization [57]. In fact, frailty is the third most cited reason for not prescribing an oral anticoagulant. This makes the report by Granziera et al. more pertinent as the population ages [61]. In this study, he provides an approach to deciding if oral anticoagulation is appropriate in elderly frail patients (**Figure 2**).

Granziera et al. also discussed what factors should go into making the decision of whether to use warfarin or novel oral anticoagulants (NOACs) in frail patients [61]. Severe renal impairment, severe liver impairment, and poor adherence favored the use of warfarin. The exceptions

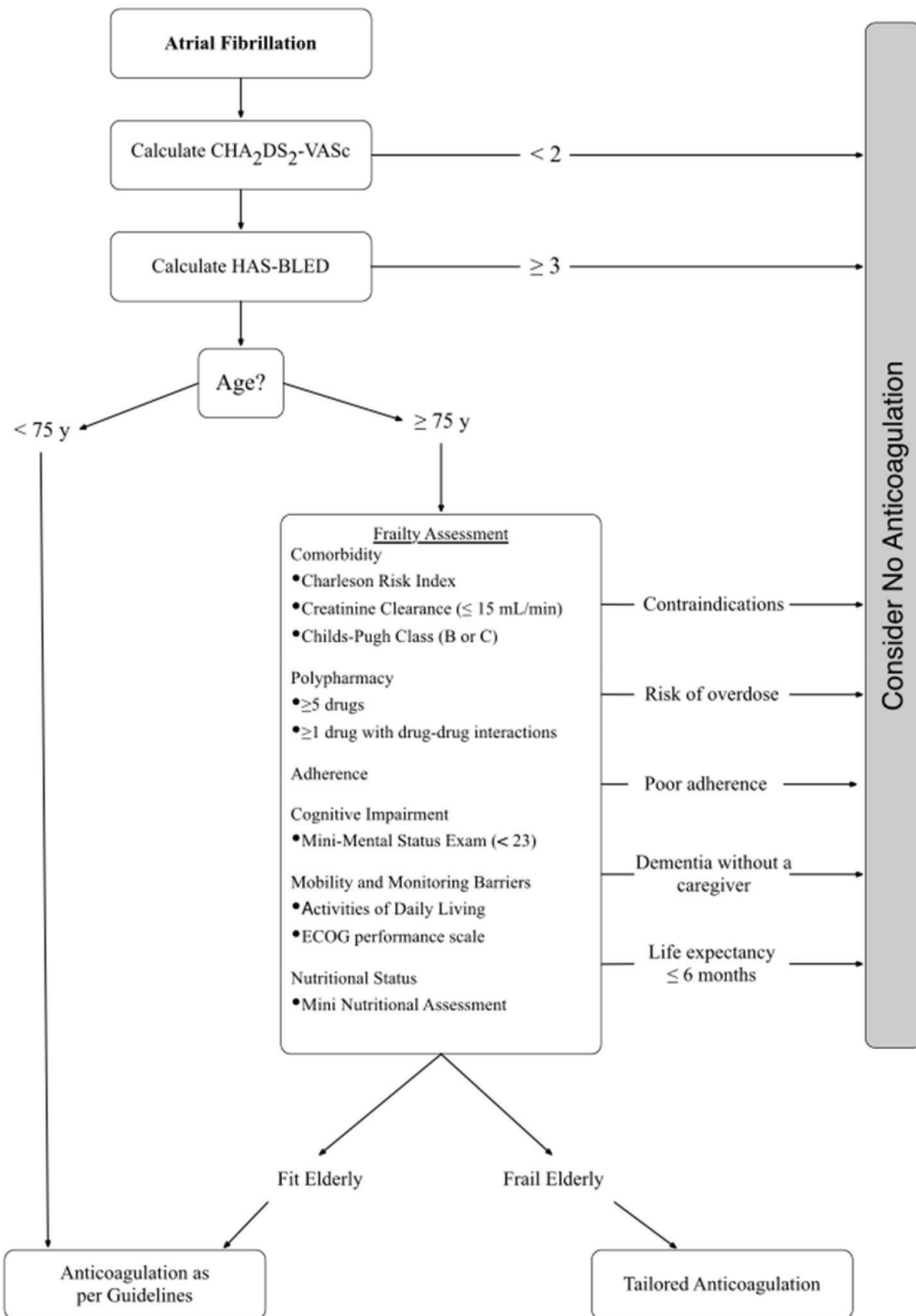


Figure 2. Decision algorithm for use of oral anticoagulants in elderly frail patients (<75 vs. ≥75 years). Adapted from Granziera et al. [61].

to favoring warfarin in renal impairment are apixaban and edoxaban, both of which may be prescribed in patients with compromised renal function. Decreased renal and hepatic clearances have minimal effect on warfarin. In patients at risk for poor compliance, their risk for stroke will not revert to baseline if a dose is missed. For patients with decreased mobility, they are less likely to comply with nutritional changes for warfarin and have polypharmacy; NOACs are the better choice for improved compliance.

Frail patients may have less of a benefit from device therapy than healthy patients [57]. In a combined analysis of four clinical trials, the benefits of implantable cardioverter defibrillators were inversely proportional to the number of comorbidities. This line of thought was further supported by a retrospective study of 83,792 undergoing ICD implantation in which frail patients had a 22% risk of mortality at 1 year compared to 12% overall.

6. Frailty and cerebrovascular disease

Several studies have indicated that frailty is associated with low cognitive performance. This is attributed to multiple causes including increased rates of Alzheimer's disease (AD), mild cognitive impairment, and a distinct subtype of frailty—cognitive frailty [62, 63]. Cognitive frailty is a clinical syndrome found in elderly patients without AD or other dementias, and occurs concurrently with physical frailty [63]. The key feature differentiating this syndrome from AD and other dementias is its potential for reversibility. The proposed mechanism for cognitive frailty is similar to physical frailty—a decrease in physiological reserves for responding to systemic stressors that manifests as an erosion of homeostatic mechanisms. The erosion of homeostatic mechanisms seen in cognitive frailty is manifested as β -amyloid accumulation. These changes are independent other causes of dementia such as vascular and Alzheimer's dementia.

Frail patients were also more likely to have any form of dementia (HR 1.85; 95% CI: 1.01–3.40) and vascular dementia in particular (HF 2.68; 95% CI: 1.16–7.17) [62]. Frail patients are 3.38 times (95% CI: 2.37–4.81, $p < 0.001$) more likely to have a stroke or TIA than non-frail patients [60]. This association with cerebrovascular disease extends to include pre-frail patients, who have a 1.98 times greater risk of having a stroke versus non-frail patients (95% CI: 1.53–2.57, $p < 0.001$). Another manifestation of cerebrovascular disease, cerebromicrobleeds, is one of the primary lesions responsible for vascular dementia. When the number of lesions is low (only one or two), there is usually no clinical evidence of microbleed, but when there is a larger lesion burden, patients present with stroke or dementia [64]. Even when adjusted for age, sex, and presence of vascular risk factors (CHD, chronic kidney disease, and global cognitive impairment), the lesion number was positively correlated with the severity of physical frailty. Chung et al. also found that the severity of physical frailty was positively correlated with proportion of cerebromicrobleeds present in the deep and infratentorial regions of the brain.

Furthermore, a study performed on patients undergoing carotid endarterectomy (CEA) using the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database from 2005 to 2011 showed that frailty is a predictor of increased stroke,

mortality, myocardial infarction, and length of stay after CEA, further supporting the idea that CVD and frailty are strongly interlinked with frail patients suffering poorer outcomes postintervention [65].

6.1. Inflammatory markers in CHD

The relationship between frailty and CHD is one that has been extensively studied as well. Chronic inflammation is a shared mechanism between atherosclerosis and frailty [18, 66, 67]. In Libby et al.'s strong and well-cited review article, they show that, in addition to plaque characteristics, acute coronary syndromes are also caused by a chronic inflammatory state [59]. This link is most strongly seen by four markers of inflammation shared by both frailty and coronary vascular disease: IL-6, CRP, fibrinogen, and D-dimer [26, 27].

Hunter et al. made the strong case that IL-6 is a keystone mediator of systemic inflammation in multiple disease processes, especially CVD [28]. There have been numerous other studies linking IL-6 and CHD [18, 66, 67]. This suggests that IL-6 is central to the immunogenic dysregulation that accounts for the disease burden suffered by patients with both CVD and frailty [28]. Another significant marker of chronic inflammation shared between both CHD and frailty is CRP [26, 27]. Like IL-6, this marker is elevated in frailty even when CHD is accounted for [32].

Fibrinogen is an acute-phase reactant shown to be elevated with chronic inflammation and is strongly correlated with both frailty and atherosclerosis [26, 66]. Elevated fibrinogen is an independent risk factor for CVD events [66]. The mechanism is thought to be caused by fibrinogen affecting the plaque phenotype, causing it to be more permeable, able to accumulate oxidized LDL, increase platelet reactivity, and aggregation. A direct association between frailty and fibrinogen has been observed independent of chronic disease states [26].

Similar to fibrinogen, D-dimer fragments are an independent risk factor for CHD to the point where they are considered a biomarker for atherothrombosis [66]. Moreover, elevated D-dimers are also independently associated with frailty [32].

7. Frailty and CHD

A meta-analysis of 54,250 elderly individuals with a mean follow-up of 6.2 years showed that the presence of atherosclerotic CVD was associated with the coexistence of frailty syndrome with an odds ratio of 2.7–4.1 [6]. The relationship between CVD and frailty is significantly bidirectional [6, 60]. This is highlighted by the twofold increase in mortality among frail CHD patients compared to non-frail patients even when adjusted for age and comorbidities [68]. In the Women's Health Initiative Study, women with CHD were more likely to become frail over the subsequent 6 years; likewise, the Health, Aging, and Body Composition Study showed that older adults with frailty were more likely to develop CHD. This same study showed that the presence of frailty, assessed by gait speed, was associated with an increased risk of incident CVD. After adjustment for potential confounding factors, a slower gait was associated with an increased incidence of CVD events and all-cause mortality compared with individuals

having higher walking speed [69]. Furthering the complexity of this disease interplay is the fact that patients with both frailty and CHD have a higher frequency of multivessel disease and left main disease (74%) than non-frail patients (60%) and moderately frail (68%) patients ($p = 0.019$) [70]. These differences persisted even after correcting for age and gender ($p = 0.005$). The wealth of evidence clearly defines the effect of frailty upon CHD.

Interestingly, atherogenesis is also affected by sarcopenia. This effect is partially due to the replacement of muscle with adipose tissue, and partially to the neurohumoral dysregulation and decreased mobility brought on by sarcopenia [71–73]. Atherogenesis is worsened by the presence of sarcopenia and frailty in humans as evidenced by the association between carotid atherosclerosis, arterial stiffness, and sarcopenia [6]. It, therefore, seems natural that frail patients fare worse after an acute CHD event compared to non-frail patients. This notion was validated by Dodson et al., who found that at 1 year after an acute CHD event, older adults with slow gait speed (<0.8 m/s measured 1 month after the event) were more likely to die or be re-admitted to the hospital than those with faster speeds (35.4% vs. 18.5%; $p = 0.006$) [74]. However, it is important to note that the majority of these events were re-admissions—not death.

Regarding interventions, there has been an extensive amount of investigation into whether coronary artery bypass grafting (CABG) is better than percutaneous coronary intervention (PCI) in frail patients. Fifty-six percent of frail patients who underwent CABG had postoperative complications compared to seventeen percent of those who were non-frail ($p < 0.001$) [75]. Frailty was also an independent predictor of in-hospital mortality after CABG (OR 1.8; 92% CI: 1.1–3.0). Similarly, PCI also carried significant risks. Frailty was associated with a longer hospital stay (HR 4.8, 95% CI: 1.4–16.3; $p = 0.013$), higher 30-day mortality (HR 4.8, 95% CI: 1.4–16.3; $p = 0.01$), and higher 1-year mortality (HR 5.9, 95% CI: 2.5–13.8; $p < 0.001$) [76, 77]. Importantly, there is evidence that there is no significant difference in change in frailty at 30 months between CABG and PCI ($p = 0.090$) [78]. In patients ≥ 75 years old treated with either PCI or CABG, there was a significantly different trajectory in their frailty score at 30 months (0.188 vs. 0.247, respectively) and at baseline (0.164 vs. 0.189, respectively; $p = 0.041$). Including frailty as part of the three-tiered criterion in the assessment of a patient undergoing PCI improved the discriminatory ability of the Mayo Clinic risk score [79]. Of great importance is the decision as to which modality of intervention is most effective in the frail population with obstructive coronary artery disease (CAD). Although we suspect that being less invasive in frail patients may be preferable, a prospective, randomized trial in the frail population addressing this quandary, as well as whether revascularization impacts frailty, would be beneficial.

8. Frailty and peripheral arterial disease (PAD)

Clearly, PAD is a pandemic condition that could potentially lead to the literal loss of life and limb. It manifests as tissue hypoperfusion caused by acute insult upon a limb with preexisting underlying atherosclerosis. This disease process is a significant cause of morbidity and mortality in both the frail and non-frail populations [80, 81].

Frailty has been shown to be associated with and worsen outcomes in patients with PAD. A study of the participants >50 years of age in the National Health and Nutritional Examination Survey (NHANES) showed that, in multivariable multinomial logistic regression models, ankle brachial index (ABI) <0.9 predicted frailty and pre-frailty. A higher prevalence of frailty was seen in participants with ABI \geq 1.4. Frailty predicted general and CVD mortality in participants with ABI <0.9. Hence, this study suggested that frailty mediates increased morbidity and mortality in PAD [82]. A cross-sectional study was carried out in a geriatric population of \geq 65-year-old residents of Taichung, Taiwan, in June 2009 to assess the association between frailty and subclinical PAD. It reported findings suggesting that frail individuals had a significantly increased risk for subclinical PAD with an odds ratio of 3.168 [83]. In a study assessing gait in patients with PAD versus non-PAD both with and without frailty, the pre-frail group defined by the Fried Frailty Index had a diminished difference between study groups. This indicated that pre-frail patients have a poor functional status overall, which may overshadow the level of dysfunction imposed upon them by PAD alone [84].

Another study assessing the effect of frailty on outcomes after vascular surgery showed that frailty, assessed by the modified Frailty Index (mFI), predicted mortality in patients undergoing open procedures and Clavien-Dindo class IV (life-threatening) complications for both open and endovascular abdominal aortic aneurysm repairs [85]. Affecting disposition and, hence, patient wellness and health-care expenditure, frailty also increases the propensity of home-dwelling patients classified as frail to be discharged to a facility other than their home after elective vascular interventions [86]. There is also evidence to support the idea that frail females are potentially at the highest risk of death after vascular surgery, suggesting that female gender may be an additive risk factor [87].

9. Frailty and heart failure

The pathogenesis of HF has significant overlap with the processes leading to the frailty phenotype [17, 88]. With HF, much like frailty, the metabolic demands of the body outstrip physiologic reserves. The findings of Lavie et al. likewise show that a loss of fat (reserves) signals a worsening prognosis in HF [30].

Frail patients and patients with HF consistently have a similar biochemical profile of elevated CRP and interleukin-6, which in turn promote mitochondrial dysfunction [18, 22, 31]. Mitochondrial dysfunction produces excessive reactive oxygen species producing a pro-apoptotic intracellular environment. In the case of HF, apoptosis of cardiomyocytes fosters a local pro-inflammatory atmosphere, leading to cardiac fibrosis and ultimately decreased contractility. Likewise, when applied to skeletal muscle, this process causes sarcopenia, one of the hallmarks and precursors of frailty.

The likelihood of a frail patient to manifest HF is 8.76 times higher than that of a non-frail patient and, compared to any other element of CVD, HF is the most strongly linked with frailty [60, 89]. However, it should be noted that frailty is not limited to geriatric heart failure patient, and been observed in up to one-third of younger patients with HF [68]. The prevalence

of frailty among heart failure patients is important because frailty is an even stronger predictor of mortality than is HF per se [88]. Cacciatore et al. assessed the role frailty had on mortality in HF patients ($n = 1139$) over a 12-year period compared to patients without CHF ($n = 120$) and found that frailty was independently associated with mortality in HF (HR 1.48, 95% CI: 1.04–2.11; $p = 0.0032$) and control group patients (HR 1.36, 95% CI: 1.17–1.57; $p < 0.001$), proving that it indeed was a more important predictor of mortality than HF itself [12]. Lupon et al. found that among 622 outpatient HF patients, frailty was an independent predictor of mortality even after adjustment for HF (HR 2.09, 95% CI: 1.11–3.92; $p = 0.022$) [90].

Discerning which patients are frail versus non-frail also has an impact on clinic resources. Frail patients versus non-frail patients in one study had a 92% increase in Emergency Department (ED) visits (HR 1.92, 1.60; 95% CI: 1.30–2.83) and 65% increased risk for hospitalizations (HR 1.65; 95% CI: 1.17–2.35) [91]. Of note, there was no significant association between outpatient visits in HF patients and frailty. This raises the question as to whether or not more intensive outpatient management of frail HF patients would decrease ED and hospital utilization.

One possible intervention to decrease the amount of hospital utilization in frail patients and, moreover, improve their morbidity and mortality is specifically resistance exercise [92]. As noted by Lavie et al., there is compelling evidence that muscle mass and muscle strength are protective in HF patients [93]. Moreover, a lack of muscular fitness overall is a strong determinant of cardiac cachexia which, as mentioned earlier, may be seen as a classification of frailty. There is evidence to suggest that maximal aerobic power, a measure of frailty, decreases with age, due to a decrease in cardiac output, and is exacerbated by CVD. Importantly, this is a measure of frailty which could be addressed with an increase in muscle mass and anaerobic exercise [94]. It is important to note that resistance training is the most well-validated countermeasure to slow the decline of muscle mass and muscle strength, even in frail patients [92]. By slowing the decline in muscle strength, the decline into frailty is consequently retarded. Taken together, this evidence points to muscle bulk, or the lack thereof, as being a significant marker of disease progression in HF and element of CVD.

The choice of pursuing advanced therapeutic options in the frail population with HF is a difficult one. As Joyce points out, HF itself and its ensuing sequelae can simulate the frailty phenotype [95]. Discerning between frailty caused specifically by HF and frailty attributable to non-CVD causes has significant implications in this selection of patients for destination therapy with left ventricular assist devices (LVADs). In patients with HF as the primary driver of his or her frailty, implantation of an LVAD led to restoration of aberrant cardiac output and metabolism. Flint et al. sorted out frail patients receiving an LVAD into three groups: LVAD-responsive, LVAD-independent, and LVAD-intermediate. In the LVAD-responsive group, whose frailty was primarily due to HF, implantation of LVAD caused a significant decrease in post-LVAD frailty as measured by hand-grip strength compared to both the LVAD-intermediate and LVAD-independent patients. These LVAD-responsive patients may be more accurate representatives of cardiac cachexia versus frailty.

Frailty in the heart-transplant (HT) population has more significant and far-reaching importance. Frail patients who underwent HT in one study had a 1-year survival rate of $52 \pm 23\%$ versus 100% in the non-frail control arm. This has significant implications in the way HT

therapy is allocated. This is a realm that requires more study, though studies will be sparse given the requirements for HT approval, including appropriate performance on pre-HT cardiopulmonary testing, in which frail and pre-frail patient would likely have suboptimal results.

10. Frailty and valvular heart disease (VHD)

In industrialized countries, the prevalence of VHD is estimated at 2.5%. Degenerative calcification seems to augment the prevalence of VHD markedly after the age of 65 years, particularly regarding aortic stenosis (AS) and mitral regurgitation (MR). These two disease entities account for three in four cases of VHD. Also contributing to the incidence of VHD is infective endocarditis, the incidence of which is approximately 30 cases per million individuals per year worldwide. Finally, rheumatic heart disease (RHD) is another very significant contributor to the incidence of VHD and still represents a significant health burden with over 15 million cases of RHD worldwide, 282,000 new cases, and 233,000 deaths annually [96]. Health-care expenditure for these disease entities is substantial. In fact, US expenditure estimates close to \$2 billion annually for symptomatic and asymptomatic aortic VHD, and \$2.6 billion for symptomatic and asymptomatic mitral VHD [97, 98].

Patients who meet indications for VHD surgery are frequently not offered surgery due to prohibitive risk features. As an example in the mitral VHD population, among patients who meet the current indications for surgical treatment of MR, almost 50% are not offered therapy due to several factors, including high surgical risk from comorbidities and frailty associated with advanced age [99, 100]. Importantly, though some patients may tolerate a surgical procedure, meaningful functional recovery is not achieved if they demonstrate marked frailty prior to the intervention [101]. Unfortunately, such patients are left with few clinical options, resulting in frequent referrals to palliative care and hospice programs. Fortunately, as we now know, patients earlier deemed inoperable or high risk for conventional VHD surgery have minimally invasive options to address their comorbid state. These include transcatheter aortic valve replacement (TAVR), transcatheter mitral valve replacement (TMVR), and Mitraclip. These procedures may be the ones most suitable for the frail population as they are part of the aforementioned patient populations that would otherwise be left without options. Currently, of the interventions for VHD that are performed, the three mentioned earlier are the ones that have the most impact on the frail population.

In a study aimed at studying inflammatory markers in patients undergoing TAVR in an attempt to estimate preoperative risk, two inflammatory markers were studied. Neopterin, a pteridine synthesized by activated macrophages, and immune activation-mediated tryptophan and its subsequent degradation had both been shown prior to be associated with frailty and chronic disease. Ultimately, increased immune activation and associated tryptophan degradation underscored the prognostic role of baseline inflammation for outcome in patients with severe AS undergoing TAVR [102]. The aforementioned inflammatory markers like IL-6, TNF-alpha, D-dimer, and CRP have not yet been studied in the frail population in regard to outcomes in VHD but may prove to be valuable area of further research.

Frailty is well known in the VHD population to be associated with poorer outcomes when compared to non-frail patients. Patients with a moderate to severe degree of frailty (defined as requiring assistance to ambulate or attend to their own bodily needs, or a modified Rankin score 4) are generally considered high risk for valvular surgery [103]. In a study conducted by Sepeheri et al., frailty had a strong positive relationship with the risk of major adverse cardiovascular and cerebrovascular events (MACCE) (odds ratio, 4.89; 95% confidence interval, 1.64–14.60) [104]. Relationships were stronger in older patients undergoing TAVR than younger patients undergoing CABG and VHD surgery (hazard ratio for frailty in TAVR, 3.31–4.89 vs. hazard ratio for non-TAVR, 1.10–3.16). One single-center experience of all cardiac operations demonstrated frailty to be an independent predictor of in-hospital mortality, institutional discharge, and reduced midterm survival [105]. In a study assessing the effect of frailty on mortality, length of stay (LOS), and discharge destination in patients post-TAVR, Chauhan et al. showed that frailty portended an increase in LOS and mortality [106]. Additionally, a study assessing preoperative computed tomography (CT) scans that are done as part of the workup for transcatheter therapeutic interventions for VHD shows that these CTs have proven useful in measuring the patient's skeletal mass index (SMI) and, thus, preoperative sarcopenia. This correlated directly to length of stay more strongly than the frailty index [107].

Many of the frail patients afflicted with MR, however, tolerate MitraClip and are able to recover from the femoral venotomy and general anesthesia required for this procedure. In one study assessing effectiveness of transcatheter mitral valve repair with Mitraclip in 564 patients, frailty was noted in 57% of patients. The procedural success rate, nonetheless, was 91% defined as MR less than or equal to grade 2 and surviving the hospital stay. A majority of patients were discharged home with moderate or less MR than prior [108]. Patients with severe frailty who are bedridden and/or require constant nursing care may be too disabled to achieve meaningful benefit from MitraClip and may also be considered prohibitive for TAVR [101]. This, though, has yet to be assessed prospectively.

The interesting aspect of frailty in VHD is that the novel interventions in this field are generally aimed to treat non-operable or high, prohibitive risk individuals. Frail patients comprise a significant portion of this population indicating that understanding how best to treat these patients is of significant import for the field in its gestalt. As this field continues to develop more prolifically, addressing the frail patient will prove to be an area of in-depth study. Many practitioners share the belief that current interventions prove to reverse certain aspects of frailty but this has yet to be studied in a prospective trial.

11. Conclusions

Frailty is a significant disease entity affecting a myriad of clinical situations. How it affects the spectrum of CVD has been an area of interest and study for a number of years. With the advent of novel procedures in the realm of VHD and the expansion of patient populations now being considered as candidates for interventions, the topic of frailty, its interplay with CVD, and how it affects outcomes in patients with CVD are of the utmost import. As discussed earlier, current risk scores for patients undergoing cardiovascular surgery (STS and euroSCORE) have

yet to include frailty as official criteria in their scoring systems, yet many practitioners still note frailty to be a condition predisposing patients to unfavorable outcomes and, thus, precluding them from interventions.

That frail patient suffers poorer outcomes is significant. From postintervention mortality to disposition postdischarge, frail patients perform suboptimally when compared to their non-frail counterparts. The generalized debility to which frail patients are predisposed may make them less tolerant of therapeutic postintervention treatments that would otherwise improve their outcomes, such as physical therapy and progressive exercise training. Their subclinical inflammatory state may further prevent wound healing and resolution. Also, their comorbid conditions may prevent complete healing and recovery as well. These hypotheses have not yet been studied and warrant further investigation for the purpose of elucidating ways to counteract the aforementioned poorer outcomes experienced by frail patients.

Frailty can be treated, potentially, with specific modalities, such as exercise, protein-calorie supplementation, vitamin D, and reduction of polypharmacy [109]. This shows that, although frailty is incredibly significant and has undeniable impacts on morbidity and mortality, it is something that is potentially reversible. With further study and therapeutic interventions tailored specifically to the frail patient, we may be able to expand our indications and improve the quality of life for a patient population known to suffer with a disease process different from any other.

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