Heart Metab. (2018) 76:23-26

Trimetazidine in the frail patient

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Abstract

Frailty encompasses a coexistence of medical factors that reduce resistance to endogenous and exogenous stressors and increase morbidity and mortality. The prevalence of frailty increases with age and in females. Frailty is an important factor to consider in the management of cardiovascular disease (CVD). Patients with CVD often have several overlapping chronic conditions that often require medical therapies, which may negatively affect concurrent diseases. To prioritize treatment strategies, it is necessary to recognize frailty and unnecessary polypharmacy early. Some cardiac medications should be used cautiously in frail patients with CVD as their use may increase the risk of serious adverse events. β-Blockers are associated with an increased risk of cognitive decline and a reduction in the ability to independently perform activities of daily living. Therefore, in frail and highly vulnerable elderly patients, it is best to avoid prescribing β-blockers, especially when they are not strictly needed. Ivabradine is well tolerated in frail elderly patients with comorbidities and is a sound alternative to β-blockers. ACE inhibitors and indapamide can also be used in frail patients and patients with multimorbidities. Trimetazidine is effective and safe in elderly patients with CVDs and multimorbidities; it also significantly reduces the frequency of angina attacks and contributes to the positive dynamics of the indicators of quality of life in elderly frail patients. Therefore, for treating frail patients with CVD, priority should be given to drugs that have a positive effect on functional capacity and quality of life. ■
Heart Metab. 2018;76:23-26

Keywords: cardiovascular disease; frailty

Introduction

Frailty refers to older adults who are at an increased risk of poor clinical outcomes, such as increased mortality, hospitalization or rehospitalization, disability, cognitive decline, and falls. The term comprises a compendium of medical factors that negatively influence the physiological state (physical capability, mobility, cognitive function) and reduces resistance to endogenous, exogenous, acute, and chronic stressors, thereby facilitating increased clinical exposure to adverse outcomes. The term frail, from the Latin fragilis (easily broken), is no longer confined to geriatrics and gerontology, but now extends to all domains of medicine, particularly cardiovascular medicine.

Epidemiological studies indicate that the prevalence of frailty increases with age, resulting in with nearly 7% of people >65 years old and more than 45% of people >85 years old being frail. In addition, the prevalence of frailty is greater in females and in residents of long-term care facilities.[1] As patients with

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Abbreviations

ACE: angiotensin-converting enzyme; **CVD:** cardiovascular disease; **NYHA:** New York Heart Association

cardiovascular disease (CVD) age, it is easy to understand why frailty has become an important factor to consider in the management of CVD. Indeed, the increased life expectancy of the general population and the reduced mortality from acute cardiac events have changed the epidemiology of CVD, with an increasing number of patients with chronic heart diseases. Since the prevalence of most chronic diseases increases with age, many older patients now suffer from a higher number of overlapping chronic conditions, which is also known as multimorbidity. Multimorbidity is not the only contributor to frailty, with age-related loss of muscle mass (sarcopenia), reduced nutritional intake, low physical activity and disability (defined as difficulty or dependency in carrying out activities necessary for independent living), and cognitive impairment all playing key roles in determining the frailty phenotype.[2-3]

Although the concept of frailty is well accepted, there is still a lack of standardized instruments for its assessment. In addition, many older adults are not frail, meaning that chronological age, in most cases, neither provides a reliable estimate of biological age nor of how the prevailing underlying disease may affect frailty. Therefore, different frailty models may differently identify frailty as multimorbidity, polypharmacy, and nutritional status. In the frail cardiac patient, the underlying CVD is often the main disease leading to unfavorable outcomes and disability, but, in some instances, other diseases may be more prevalent; therefore, identifying the disease associated with an unfavorable outcome is the key to prioritizing treatments in frail patients.[4-5]

Frailty influences the effect of drugs, as drugs used to treat a given disease may negatively affect other concurrent diseases. Therefore, frail patients are also vulnerable to clinically important drug-to-drug interactions and adverse drug reactions. Frail cardiac patients are often hospitalized due to adverse drug reactions or interactions between cardiac and noncardiac medications. Polypharmacy is associated with a higher incidence of frailty and with increased rates of mortality, incident disability, hospitalization, and emergency department visits in frail and prefrail older adults, but not in nonfrail adults.[6] Since most of these events are often preventable,[7-10] early recognition of frailty and unnecessary polypharmacy is warranted. However, if the cardiac disease is prevalent, the potential negative effects of cardiac medications on other metabolic or neurologic diseases should be taken into account without discontinuing the cardiac medications because they are, in many instances, the only drugs favorably influencing prognosis. It is, therefore, important to include the assessment of frailty in the clinical evaluation of older adults in order to guide their management and coordinate better care.

Cardiovascular medications in frail patients with CVD

Caution must be taken with the use of certain cardiac medications in frail patients as they may lead to negative effects on cognitive or functional decline and may result in an increased risk of serious adverse events *(Table I)*. Indeed, recent studies have shown that, among older patients in nursing homes, β-blocker

Drug	Adverse events
ACE inhibitors / ARBs	Hyperkalemia Hyponatremia Renal Failure
Antiplatelets / anticoagulants	Increased bleeding risk
β-Blockers	Confusion Decrease in functional capacity Decrease in mental function Lethargy Postural hypotension Autonomic dysfunction Depression
Calcium channel blockers	Postural hypotension Flushing Headache Edema Constipation
Digoxin	Confusion Toxicity
Diuretics	Gout Hypokalemia (thiazide and loop)
Nitrates	Postural hypotension Decreased baroreflex function Headache Dizziness Weakness or fainting Nausea and vomiting
Ivabradine / ranolazine / trimetazidine	No significant adverse events in multimorbid elderly. Adjust the dose of ranolazine and trimetazidine in impaired renal function

Table I *Possible negative effects of certain types of medications on cognitive or functional decline in frail patients.*
Abbreviations: *ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.*

therapy was associated with a 33% increased risk of cognitive decline and of having a major decline in the ability to independently perform activities of daily living.[11] Steinman et al studied 15 720 patients aged 65 and older (mean age, 83 years; 71% women) who lived in nursing homes and had a previous myocardial infarction. Nearly one-third (30%) of the patients had intact cognition, 52% had mild-to-moderate cognitive impairment, and 18% had dementia. Of these, 8953 patients (60%) were initiated on a β-blocker and 6767 patients (40%) did not receive a β-blocker. Patients on β-blockers were more likely to experience a major functional decline and they had similar rates of rehospitalization, as did patients not on β-blockers. In the subgroup of patients with moderate-to-severe cognitive impairment, patients who received β-blockers were more likely to experience functional decline (OR, 1.34; 95% CI, 1.11-1.61), with a number needed to harm of 36. Similarly, patients with severe functional dependence were also more likely to experience functional decline after receiving β-blockers (OR, 1.32; 95% CI, 1.10-1.59), with a number needed to harm of 25.

Therefore, although β-blockers improve outcomes in patients with a previous myocardial infarction and reduced ejection fraction, it is best to avoid prescribing β-blockers to frail and highly vulnerable elderly patients due to the negative effects on cognitive function. Another potential problem associated with the use of β-blockers is the deterioration of the autonomic responses, favoring the occurrence of orthostatic hypotension and associated falls, despite not having chronic hypotension or fulfilling orthostatic hypotension criteria during clinical examination.

Therefore, to preserve functional status, independence, and quality of life, therapeutic alternatives to β-blockers should be used. Ivabradine is well tolerated in the elderly with comorbidities and is a sound alternative to β-blockers. The recent UK multicenter LIVE:LIFE prospective cohort study showed that ivabradine improved quality of life, functional status, and New York Heart Association (NYHA) class in typical older patients with heart failure, comorbidities, and polypharmacy.[12] Angiotensin-converting enzyme (ACE) inhibitors and indapamide can also be used in frail patients and in patients with multimorbidities.[13-18]

The PROGRESS study (Perindopril pROtection aGainst REcurrent Stroke Study) showed that perindopril improves cognition in patients with a previous ischemic event. Indapamide is the only diuretic that has been prospectively studied in the elderly. The HYVET study (HYpertension in the Very Elderly Trial), although not primarily aimed at frail patients, reported a significant reduction in mortality, stroke, and occurrence of heart failure in elderly hypertensive patients (again not frail).

Trimetazidine in elderly and frail patients

Among antianginal medications, trimetazidine is effective and safe in elderly patients with CVDs and multimorbidities. Early reports of an increased risk of falls with trimetazidine have not been confirmed. Several studies have reported an improvement in left ventricular function, exercise capacity, and muscle strength in elderly patients with ischemic heart failure, most of whom had multimorbidities and were frail. More recently, our group reported that trimetazidine improves muscle performance and reverses the negative effect of aging in animals and humans.[19-24] Our group has also shown that trimetazidine improved left ventricular function and exercise capacity in elderly patients, especially in frail patients with heart failure. We have also shown that, in these patients, trimetazidine improved quality of life and functional capacity.[23-24] The effect of trimetazidine on quality of life parameters seems to be related to the improvement in left ventricular function and to an increase in skeletal muscle strength. The effects seen in patients receiving trimetazidine are most probably related to an improved efficiency of myocardial cells that often suffer from chronic hypoperfusion due to anatomic and metabolic derangements present in elderly patients.

Trimetazidine is an effective antianginal drug in elderly frail patients. In the elderly frail patients included in the TRIMPOL-I study (TRIMetazidine in POLand), trimetazidine significantly reduced the frequency of angina attacks. In the TRIMER study (TRIMEtazidine in eldeRly people), a 3-month treatment with trimetazidine reduced the frequency of angina attacks, reduced the frequency of ST-segment depression on ECG, and contributed to the positive dynamics of the indicators of quality of life. Trimetazidine is well tolerated and improves angina and myocardial ischemia in elderly and frail patients with coronary artery disease. Since trimetazidine is devoid of any significant effect on heart rate and blood pressure, it is extremely well tolerated in most subsets of patients with multimor-

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bidities. Therefore, trimetazidine represents an ideal treatment for elderly and frail cardiovascular patients.

Conclusion

Although the role of frailty in determining the therapeutic decision and patient outcomes is clear, the assessment of frailty is not included in the management of patients with CVD or in most contemporary models of outcome assessment. The reasons for noninclusion are not certain, but could relate to concerns about the complexity of measurements or to the lack of widely accepted and standardized approaches. Cardiovascular drugs may impair quality of life and functional capacity in frail patients with CVD. Therefore, drugs that have a positive effect on functional capacity and quality of life in elderly and frail patients are warranted. Trimetazidine is an effective antianginal drug that has been shown to improve myocardial ischemia, exercise capacity, quality of life, and prognosis in elderly patients, most of whom are either frail or multimorbid and either with or without heart failure. ■

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