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Editorial

Use of Frailty in Deciding Clinical Treatment Goals for Chronic Disease in Elderly Patients in the Community

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Frailty is an important geriatric syndrome with a global prevalence of 4.9%-27.3%.[1] It is defined as an age-related decrease in the physiological reserve needed to maintain biological homeostasis and increased vulnerability to stressors. Recognition of physical frailty is important for clinicians because it poses a greater risk of adverse health outcomes including falls, increased morbidity, physical dependence, hospitalization, and death.[2] Rockwood et al have defined another form of frailty that is equivalent to multimorbidity.[3–5] This editorial will focus on persons with the physical frailty phenotype.

Frailty is an important consideration for geriatricians in the clinical setting, particularly with regard to treatment goals for chronic disease in elderly patients. In this study, we review the role of frailty in setting treatment goals for elderly patients. Highly prevalent and clinically important chronic diseases including hypertension, diabetes mellitus, hypercholesterolemia, and atrial fibrillation are considered.

Frailty and Hypertension

The incidence of hypertension increases with age, hence, hypertension is correlated with frailty.[6] In addition, systolic (SBP) and diastolic blood pressures (DBP) are associated with the risk of stroke. However, the association is not as great in the highest age category (80–89 years of age) based on meta-analysis of cohort studies.[7] There is an inverse association in the ≥85 years age group according to a high-quality prospective population-based cohort study.[8] In the latter study, men aged ≥85 years with SBP ≥180 mm Hg show significantly higher survival rates compared with those with SBP <130 mm Hg. The paradoxical finding could be explained as follows.

A large proportion of patients aged over 85 years have widespread vascular alterations, ranging from atherosclerosis and arterial stiffness to microvascular rarefaction. In the presence of lower blood pressure (BP) levels, regulatory mechanisms to preserve perfusion of vital organs may fail.[9] In addition, BP gradually decreases in the 3 years preceding death suggesting that lower BP levels are a risk factor for underlying comorbidity.[10] Patients aged >85 years with diastolic BP <70 mm Hg have a significant increase in mortality risk.[8]

Moreover, the high prevalence of frailty in the ≥85 years of age population may be another explanation. In a National Health and Nutrition Examination Survey study of the participants over 65 of age from 1999 to 2002, the authors divide participants into fast walkers (faster than 0.8 m/s), slower walkers (slower than 0.8 m/s), and noncompleter through gait speed measurement. In fast walkers, elevated systolic BP (>140 mm Hg) is associated with increased mortality, just as in the general population. Slower walkers show no association between elevated systolic or diastolic BP (≥90 mm Hg) with increased mortality. Noncompleters of the walking test show an inverse association between elevated BP and mortality even after adjusting for potential confounders.[11] This may be because low DBP contributes to high pulse pressure, which is a strong risk factor for coronary events in elderly adults and aggressive therapeutic interventions may have a higher risk in older frail adults.[12] In a prospective study on nursing home (frail) patients, an overtreatment group with target SBP <130 mm Hg and taking ≥2 antihypertensive drugs represent a 2.09 of hazard ratio for all-cause mortality.[13] However, whether frailty likewise affects antihypertensive treatment in real practice remains unclear. In a meta-analysis of randomized controlled trials (RCTs) for mortality on hypertensive patients aged ≥80 years, all RCTs, except for the Hypertension in the Very Elderly Trial (HYVET), fail to show a decrease in total mortality in response to hypertension treatment.[14]

The HYVET study shows decreased total mortality possibly because of selection of indapamide with or without low dose perindopril to target BP of 150/80 mm Hg and exclusion of patients with dementia and in nursing care, and consequently, most frail patients.[15] There is some evidence that perindopril increases strength,[16] and hip fractures were reduced in the HYVET trial.[17]

Recently, the Systolic Blood Pressure Intervention Trial (SPRINT) shows that among ambulatory adult aged ≥75 years, intensive treatment of hypertension (an SBP target of <120 mm Hg compared with an SBP target of <140 mm Hg) results in significantly lower rates of fatal and nonfatal major cardiovascular events and death from any cause. However, the SPRINT trial includes only ambulatory, community-based persons, therefore, the results may not be relevant to frail individuals and those restricted to their homes or institutions. In the SPRINT, intensive hypertension control in the frail group by frailty index slightly

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reduces cardiovascular disease events and mortality (P = .06, .05, respectively). In addition, intensive hypertension control in the low gait speed group (<0.8 m/s) does not reduce cardiovascular disease events and mortality (P = .05, .28, respectively).[18] The SPRINT study design also does not include a specific assessment of frailty phenotype.

Guidelines from the European Society of Hypertension and the European Society of Cardiology recommend leaving decisions on antihypertensive therapy in frail older patients to the treating physician and considering treatment based on monitoring of the clinical effects of treatment and individual tolerability.[19] Some experts do not recommend initiating antihypertensive medications for frail elderly aged ≥80 years, except for those with SBP >160 mm Hg or 180 mm Hg, recent stroke, or congestive heart failure.[20]

Frailty and Diabetes Mellitus

Frailty is more common among elderly patients with diabetes than with peers without diabetes.[21,22] Many studies report that frail individuals with diabetes have a higher mortality than nonfrail individuals with diabetes. Also, elderly patients with diabetes may have increased risk for functional dependency and frailty.[23,24] Frailty prevalence of 32% to 48% in persons with diabetes >65 years is much higher than the 5% to 10% seen in the general population of the same age.[25] Thus, elderly patients with diabetes require screening for frailty. Despite several RCT studies to evaluate optimal hemoglobin (Hb)A1c level in elderly patients with diabetes, the oldest patients and frail older patients with diabetes are not addressed. Hence, how best to address diabetes in the frail elderly group remains unclear.

Hypoglycemia is a very important issue in managing diabetes among frail elderly. Hypoglycemia and frailty have a reciprocal correlation. Hypoglycemia causes recurrent hospital admissions because of syncope or fracture and eventually leads to frailty. Hypoglycemia also leads to cognitive dysfunction, and subsequently physical frailty. Frailty, in turn, is associated with undernutrition, leading to hypoglycemia. Therefore, hypoglycemia and frailty work in a vicious cycle.[26] Nevertheless, hypoglycemic symptoms tend to be less specific with increasing age.[27] Avoiding hypoglycemia should be at the core of therapeutic goals in frail elderly. In a 2-year prospective cohort study among community-dwelling, nursing home eligible patients with diabetes, HbA1c levels between 8% and 8.9% appears to be associated with less functional decline or death at 2 years, compared with HbA1c levels between 7% and 7.9%.[28] Mortality findings in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial and subgroup analyses of the VADT (Veteran's Affairs Diabetes Trial) suggest that the potential risks of intensive glycemic control may outweigh its benefits in some patients with advanced age and frailty.[29]

Modern guidelines set a target HbA1c at around 8% for frail elderly patients with diabetes. AGS (American Geriatrics Society) consensus panels (2003) recommend HbA1c between 7.5% and 8.0%[30]; the Veterans Affairs/Department of Defense (2004) HbA1c between 8% and 9%[31]; European Diabetes Working Party for Older People (2011) HbA1c between 7.6% and 8.5%[32]; and the American Diabetes Association and European Association for the Study of Diabetes (2012) HbA1c between 7.5% and 8.0%.[33] The IAGG (International Association of Gerontology and Geriatrics) also supports a level of HgbA1C of 7.5-8.5%[34] Most recently, the International Diabetes Federation (2014) indicate target HBA1c of up to 8.5% for frail elderly patients with diabetes.[35] However, these guidelines are based on expert consensus, not on accumulated evidence. Future research is needed on frail patients or those with dependent living situations to establish evidence-based guidelines.

The Zwolle Outpatient Diabetes Project Integrating Available Care cohort study with median follow-up for 14 years shows an inverse relationship between increase in BP and all-cause mortality in frail elderly patients with diabetes. In addition, the inverse relationship is more significant in the oldest frail elderly group and hazard ratios of SBP and DBP for all-cause mortality are 0.92 (0.87%–0.98%) and 0.83 (0.73%–0.93%), respectively.[36]

Frailty and Hypercholesterolemia

In general, the association between higher serum cholesterol level and increased cardiovascular disease risk is attenuated in old age and may be reversed.[37,38] An apparent increase in mortality associated with low cholesterol level in older people can be related to malnutrition, frailty, and chronic diseases, which simultaneously decreases cholesterol level and increases mortality risk.[39,40] Especially, people >80 years of age are at high risk for frailty, comorbid conditions, and polypharmacy; hence, the decision to treat with statins in the oldest patients must be individualized. Frailty also may exacerbate adverse effects of diabetic therapy.[41] The ACC/AHA (American College of Cardiology/American Heart Association) guideline indicates that patients of age ≥75 years should be administered moderate-intensity statin.[42]

A nursing home cohort study shows that statin therapy is associated with improvement in 1-year all-cause mortality for frail older patients with cardiovascular diseases. These associations are also true for age groups ≥85 years.[43] Pravastatin reduces coronary heart disease mortality according to a randomized controlled placebo trial on patients 70-82 years old with a history of, or risk factors for vascular diseases.[44] However, clinical trial data on treatment with statins in patients >75 to 80 years of age are scarce, especially for primary prevention.

The decision to administer statins to older patients with DM (diabetes mellitus) is also under debate, particularly in frail older patients with comorbidity and high mortality risk. A retrospective cohort study of community-dwelling frail older patients with DM requiring homecare services or nursing home admission (mean age 81.1 years) reports that statin use is associated with reduced mortality.[45]

Frailty and Atrial Fibrillation

Frailty is strongly related with atrial fibrillation (AF),[46] and frailty is an important factor for treating AF, as it is associated with immobility, nutritional status and swallowing disorders, and risk of falls. Factors such as cognitive impairment and frailty are common reasons for clinicians choosing not to prescribe thromboprophylaxis for elderly patients with AF.[47] Warfarin use requires clinical international normalized ration monitoring; and for immobile frail patients the new oral anticoagulants (NOACs) may be preferred to warfarin.

Frailty is frequently associated with polypharmacy and poor social support, resulting in anorexia and low food intake.[48,49] These poorly nourished patients may benefit from the use of NOACs, because, unlike warfarin, the effects of NOACs are not known to vary with changes in diet. In addition, frailty is associated with risk of falls and anticoagulation and may lead to an increased risk of intracranial bleeding. However, frailty should reportedly not preclude anticoagulant treatment in elderly patients with AF.

Most popular AF guidelines use CHADS2 and CHA2DS2VASc scale to assess thromboembolic risk in AF. However, these AF guidelines do not provide guidance for the management of elderly patients with characteristics of frailty.

Granziera et al[50] present a practical guideline. If an elderly patient diagnosed with nonvalvular AF has a low risk of thromboembolism or high risk of bleeding using the HAS-BLED score, then, no anticoagulation therapy is needed. Otherwise, they recommend classification into 2 groups according to 75 years of age. Oral anticoagulant is recommended for elderly patients <75 years of age. Patients >75 years of age, who are more likely to be frail, need an anticoagulation-focused frailty assessment. Such assessment includes evaluation of comorbidities, necessity of polypharmacy, adherence, cognitive impairment, mobility, nutritional status and, when appropriate, reduced patient life expectancy. Oral anticoagulation is

initiated if the elderly patient is fit for anticoagulants based on the assessments. For confirmed frail elderly patients, individual patient-based oral anticoagulation therapy is indicated. Clinicians might consider avoiding anticoagulation in cases with very high risk of poor adherence, dementia, inability to monitor drug intake by caregiver, or life expectancy of <6 months.

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