Care of the Aging Patient: From Evidence to Action

Polypharmacy in the Aging Patient
Management of Hypertension in Octogenarians

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IMPORTANCE Hypertension treatment is beneficial for most hypertensive patients. The benefits for patients who are very old and frail, especially those taking numerous medications, are less certain.

OBJECTIVE To provide recommendations for the evaluation and treatment of hypertension among patients aged 80 years and older.

EVIDENCE ACQUISITION MEDLINE, PubMed Central, and the Cochrane Database of Systematic Reviews were searched from inception through April 2015, with an emphasis on 2010-2015. Manual cross-referencing of review articles and meta-analyses was also performed to identify randomized controlled trials (RCTs) examining antihypertensive use in octogenarians. The search strategy included the following Medical Subject Headings: *hypertension* or *high blood pressure* and *trials* and *oldest old* or *very old* or *very elderly*.

FINDINGS Six post hoc analyses of the previously published Hypertension in the Very Elderly Trial (HYVET) met the inclusion criteria. In the only placebo-controlled RCT on hypertension management in patients older than 80 years (HYVET; N = 3845), the treatment was associated with lower total mortality and key cardiovascular end points but the effect on stroke (fatal and nonfatal), which was the primary outcome, failed to reach the significance level (P = .06). Post hoc analyses of HYVET suggested that active hypertension treatment in very elderly patients was beneficial by reducing blood pressure in individuals with white coat hypertension, showed moderate benefits of the active treatment for cognition, a possible effect for fractures prevention, and sustained differences in reductions of total mortality and cardiovascular mortality in those receiving active treatment. However, patients were community dwelling and less disabled than individuals of the same age in general.

CONCLUSIONS AND RELEVANCE Hypertensive patients who are healthy, functionally independent, and aged 80 years and older should be treated according to current recommendations for people older than 65 years. There is insufficient evidence regarding the benefits of hypertension treatment for frail polymedicated octogenarians, for whom treatment should be individualized.

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High systolic blood pressure (SBP) is caused by arterial stiffness[1,2] that develops during the aging process. Because increases in SBP and pulse pressure were formerly considered to be part of normal aging, it was thought that hypertension in elderly patients did not require treatment. However, older patients with high SBP and high pulse pressure, vs older patients without, have greater cardiovascular morbidity and mortality[1-3] and exhibit a higher prevalence of other age-related diseases,[4,5] loss of autonomy, and shorter life expectancy.[6,7] However, this association between high SBP, morbidity, and mortality is not observed in very old frail individuals with muliple morbidities. Older patients with multiple morbidities, frailty, and low SBP may have malnutrition and/or comorbidities (such as heart failure, neurological disorders) that are associated with poor prognosis. Most evidence regarding the risks of hypertension and the benefits from its treatment are extrapolated from the study evidence of younger populations and in select groups of robust older individuals.[3]

We reviewed the evidence supporting blood pressure treatment in patients who were very old and frail. We also reviewed the literature for comprehensive geriatric assessment and its effect on polypharmacy as it relates to the use of statins, anticoagulants, and antidiabetic drugs in older patients.

Box. Frailty: Concept and Clinical Assessment

Frailty is the increased susceptibility to adverse outcomes resulting from diminished reserve and resistance to stressors; this is caused by degradation in physiological systems that accumulate with age

The prevalence of frailty substantially increases after the age of 80 years and is much higher among nursing home residents; this is partly due to age-related diseases such as heart failure, stroke, sarcopenia, arthritis, osteoporosis, fear of falling, confusion, cognitive decline, depression, incontinence, chronic pain, and iatrogenic complications

Frailty is assessed with a 2-step approach:

1. Simple and rapid (<10 minutes) assessment[10] with one of the following tools: the Fried Frailty Scale[11] (frail if presence of ≥3 of the following: weight loss, exhaustion, weakness, decreased gait speed, diminished physical activity), gait speed,[12] the Geriatric 8 (G8),[13] the Groningen Frailty Indicator,[6] or the SHARE-FI75+[14] scale
2. Patients found to be at risk for frailty in the previous step 1 should undergo comprehensive geriatric assessment[15]

Detection of frailty by comprehensive geriatric assessment is useful in order to

1. Evaluate the risks for functional decline, morbidity and mortality
2. Determine the risks and benefits for proposed treatments based on a patient's physiologic capacity rather than on age alone
3. Propose specific actions to slow loss of autonomy

Methods

The current review emphasizes the management of hypertension in individuals 80 years and older. Although this age threshold is arbitrary, our choice of selecting it is based on 4 considerations: (1) the proportion of the population older than 80 years is expanding faster than any other segment[8,9]; (2) life expectancy at the age of 80 has increased by 50% between 1970 and 2010[9]; (3) there is scant evidence regarding the management of hypertension in this age group; and (4) the prevalence of age-related diseases, frailty, and loss of autonomy greatly increases after 80 years of age (**Box**). Our principal aim is to review these uncertainties in the management of hypertension in complex geriatric patients with too high or too low blood pressure levels, various degrees of comorbidity, frailty, polypharmacy, and loss of autonomy.

Search Strategy

MEDLINE, PubMed Central, and the Cochrane Database of Systematic Reviews were searched. In addition, manual cross-referencing of review articles and meta-analyses was also used to identify randomized controlled trials (RCTs) examining antihypertensive use in octogenarians. Randomized, controlled clinical trials were included if they were published up to the end of April 2015 and the language of publication was English. We focused our search on 2010-2015. Before 2010 only 1 RCT, the Hypertension in the Very Elderly Trial (HYVET), had been published.

Study Selection Criteria

Efficacy measures, number of patients, and percentage of responders had to be mentioned. To be included in this review, studies had to report randomization of patients, having a placebo or active comparator control group, study duration of 4 weeks or longer, and inclusion of patients aged 80 years and older with diagnosis of hypertension.

The search strategy included the following Medical Subject Headings: *hypertension* or *high blood pressure* and *trials* and *oldest old* or *very old* or *very elderly*.

Results

Treating Hypertension in Adults Older Than 80 Years

Between 2010 and 2015, there were 6 post hoc analyses from the 2008 HYVET study.[16-22] HYVET is the only placebo-controlled RCT on hypertension management in community-dwelling patients older than 80 years. In HYVET, 3845 patients from Europe, China, Australasia, and Tunisia who were 80 years or older and had a chronic SBP of 160 mm Hg or greater were randomly assigned to receive either the diuretic indapamide or matching placebo. The angiotensin-converting enzyme (ACE) inhibitor perindopril, or matching placebo, was added, if necessary, to achieve the target blood pressure of 150/80 mm Hg.[16]

In HYVET, the intention-to treat analysis showed that active treatment was associated with a 30% nonsignificant reduction in the primary outcome of fatal or nonfatal stroke (95% CI, −1% to 51%; $P = .06$), a 39% reduction in the rate of death from stroke (95% CI, 1% to 62%; $P = .05$), a 21% reduction in the rate of death from any cause (95% CI, 4% to 35%; $P = .02$), a 23% reduction in the rate of death from cardiovascular causes (95% CI, −1% to 40%; $P = .06$), and a 64% reduction in the rate of heart failure (95% CI, 42% to 78%; $P < .001$).[16] However, the primary outcome of reduced fatal or nonfatal stroke by hypertension treatment in very elderly patients was not statistically significant. HYVET was terminated early and as a result, underpowered. The trial was stopped early because results from

a second interim analysis found an unexpected decrease in all-cause mortality (a secondary outcome) in the hypertension-treated group (relative risk [RR], 0.76 [95% CI, 0.62-0.93]; *P* = .007). This interim analysis also showed that stroke rates were reduced in the active treatment group (RR, 0.59 [95% CI, 0.40-0.88]; *P* = .009).[23] However, because the trial was terminated early, the study is underpowered to yield information about its many secondary outcomes.

Post hoc analyses of HYVET suggested that active hypertension treatment in very elderly patients was beneficial by reducing blood pressure in individuals with white coat hypertension[17] and was able to reduce pulse pressure.[18] Other post hoc analyses of HYVET showed moderate benefits in the active treatment group for cognition[19] and a possible effect for fractures prevention.[20] A 1-year open-label extension of HYVET showed sustained differences in reductions of total mortality and cardiovascular mortality in the active treatment group.[21]

HYVET had several important limitations. First, the trial was negative for its primary outcome of stroke. Second, only patients with SBP greater than 160 mm Hg were enrolled. Treating SBP in the 140 to 160-mm Hg range is beneficial for younger patients (<60 years). It is not known if there is a benefit for treating patients older than 80 years in this same SBP range (grade 1 hypertension). European guidelines recommend treating "younger old" hypertensive patients (aged 60-80 years)[3] for SBP values greater than 140 mm Hg if the patients are fit. The US JNC 8 guidelines[24] propose initiating treatment when SBP is greater than 150 mm Hg for "old people," as defined by age 60 years or older in the general population.

Another limitation is that patients requiring nursing care or having severe cardiovascular disease, renal failure, dementia, and other clinically significant comorbidities were excluded from HYVET, which was conducted in relatively healthy community-dwelling older patients who had little comorbidity. No association or greater morbidity and mortality was associated with lower blood pressures in very old patients with several morbidities and frailty.[25-30] In a post hoc analysis of the Systolic Hypertension in the Elderly Program (SHEP), the greatest benefits in terms of lowering stroke risk were observed in patients with SBP of less than 150 mm Hg but not in those with SBP of less than 140 mm Hg.[31] These findings might be explained by low blood pressure in older people being associated with several comorbidities predisposing to decreased tissue perfusion, which results in a higher mortality risk. A recent trial showed that the association between blood pressure and mortality was related to the frailty marker walking speed: in faster walkers, SBP was positively correlated with mortality. Among slower walkers, blood pressure was not associated with mortality. In those unable to complete the walk test, blood pressure was negatively associated with risk of death.[29]

Polypharmacy and drug-related adverse effects are also major problems for older patients and may contribute to morbidity, higher rates of hospitalizations, and mortality.[29,30,32,33] An analysis from HYVET[22] showed no firm evidence that frailty modified any potential benefits of antihypertensive treatment in older patients. Frailty indices were calculated in approximately two-thirds of the HYVET population. Although many of the HYVET patients had a relatively high frailty index, very frail patients with loss of autonomy, significant cognitive decline, major cardiovascular comorbidities, medications for cardiovascular disease, significant orthostatic hypotension, and several other morbidities were excluded from the study. Outcomes from hypertension management in these patients are not known.

Other Clinical Trial Results

As shown in the PARTAGE study (Predictive Value of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population), the benefits of hypertension treatment observed in middle-aged patients are not necessarily seen in older (≥80 years) nursing home residents[34] (ie, the frailest older patients). The aim of the longitudinal PARTAGE study was to determine the predictive value of blood pressure and arterial stiffness on overall mortality (primary end point) and major cardiovascular events in patients older than 80 years who were living in nursing homes. The highest mortality was observed in patients with SBP of less than 130 mm Hg. The high mortality associated with SBP of less than 130 mm Hg persisted even after adjusting for confounders such as age, sex, history of previous cardiovascular disease, comorbidity index (Charlson), cognitive function, and activities of daily living. A meta-analysis of randomized clinical trials[35] comparing an antihypertensive treatment in general to placebo or no treatment in patients older than 80 years, including the HYVET pilot and HYVET trial, showed no decrease in total mortality (overall relative mortality risk of 1.06 (95% CI, 0.89-1.25; *P* = .54). However, mortality results were heterogeneous and were best explained by higher mortality in trials in which the intensity of antihypertensive treatment was higher or the achieved SBP reductions were greater. However, the authors acknowledged that their results were not sufficiently robust to conclude that overtreatment and excessive blood pressure lowering increased mortality.[35]

Paradoxically, a higher SBP was strongly and independently associated with a lower risk of death.[29] A more recent analysis of the PARTAGE study showed a higher mortality in patients with SBP of less than 130 mm Hg when patients were treated with 2 or more antihypertensive drugs but not in patients treated with no or 1 antihypertensive drug.[36]

At present, based on the existing evidence, it remains unknown whether increased mortality rates in older patients with very low blood pressure are due to low blood pressure and/or polypharmacy, or reflect an overall declining health status.

Blood Pressure Management Guidelines for People Older Than 80 Years

Most international guidelines (**Table 1**) recommend treating robust patients older than 80 years who have SBP greater than 160 mm Hg to less than 150 mm Hg. However, there are at least 3 unclear aspects in these guidelines:

Because older individuals with frailty and multimorbidities are generally excluded from clinical trials, guideline recommendations based on those trials may not apply to them.[41] Moreover, clinical guidelines advocating standardized treatments do not account for complex older patients' unique symptom presentations, the patients' view of their clinical state and circumstance, and their individual preferences for care.[3,42]

Treating each disease an elderly patient may have as a single entity (ie, the single-disease approach) results in polypharmacy with concomitant increased risk of adverse drug events. Polypharmacy should be considered as a medical condition like any other that has adverse effects and complications.[42,43]

Table 1. Blood Pressure Management for People Older Than 80 Years as Recommended by Various National and International Expert Groups

Source	Specific Recommendations		No Specific Recommendations for Patients >80 y, Initial Pharmacological Treatment for Older Patients
	Patients >80 y	Frail Patients	
Eighth Joint National Committee (JNC 8),[24] 2014	None	None	Age description: ≥60 y In the general population of patients, initiate pharmacological treatment for SBP ≥150 mm Hg and DBP ≥90 mm Hg Treatment goal: SBP <150 mm Hg and DBP <90 mm Hg For patients who are not black: thiazide-type diuretic, ACE inhibitor, ARB, or CCB For black patients: thiazide-type diuretic or CCB
American Society of Hypertension and the International Society of Hypertension,[37] 2014	Some recent trials suggest that in patients ≥80 y, achieving an SBP of <150 mm Hg is associated with strong cardiovascular and stroke protection, and thus a target of <150/90 mm Hg is now recommended for patients in this age group (unless these patients have chronic kidney disease or diabetes, whereby <140/90 mm Hg can be considered)		Age description: 55-80 y For patients who are not black: age >60-<80 y; blood pressure goal, <140/90 mm Hg; CCB or thiazide diuretic (although ACE inhibitors or ARBs are also usually effective) For black patients (African ancestry): all ages; CCB or thiazide diuretic
European Society of Hypertension and the European Society of Cardiology,[3] 2013	In individuals >80 y with an initial SBP ≥160 mm Hg, it is recommended to reduce SBP to 150-140 mm Hg if they are in good physical and mental health condition Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual is >80 y	In frail older patients, it is recommended to leave decisions about antihypertensive therapy to the treating physician and based on monitoring of the clinical effects of treatment	Age description is not defined All hypertensive agents are recommended and can be used in older people, although diuretics and calcium antagonists may be preferred in treating isolated systolic hypertension
French Society of Hypertension,[38] 2014 (2013 guidelines)	When >80 y, it is recommended to target a SBP <150 mm Hg without orthostatic hypotension Do not use >3 antihypertensive drugs Assess cognitive function (using the Mini Mental State Examination [MMSE])	None	Age description not prespecified Any of the 5 antihypertensive drugs may be used regardless of age
National Institute for Health and Care Excellence,[39] 2011	Aim for a target clinic blood pressure of <150/90 mm Hg in patients ≥80 y with treated hypertension Offer patients ≥80 y the same antihypertensive drug treatment as people aged 55-80 y, taking into account any comorbidities When using ambulatory or home blood pressure monitoring to observe response to treatment (eg, in patients having a "white coat effect" and those who choose at-home blood pressure monitoring), aim for a target average blood pressure during the person's usual waking hours of <135/85 mm Hg for persons <80 y and <145/85 mm Hg for persons ≥80 y	None	Age description: >55 y For patients >55 y and for black patients of African or Caribbean family origin of any age, offer step 1 antihypertensive treatment If a CCB is not suitable, (eg, because of edema, intolerance, or evidence or high risk of heart failure, offer a thiazide-like diuretic
American College of Cardiology Foundation and the American Heart Association,[40] 2011 (expert document)	Individuals with SBP >150 mm Hg are candidates for antihypertensive drugs with a target SBP of 140-145 mm Hg if tolerated (ie, somewhat more conservative target than in individuals <80 y) There is less evidence of benefit in patients approaching 90 y or >90 y Initiate treatment with a single drug followed by addition of a second drug if needed; low-dose thiazides, CCBs, and renin-angiotensin-aldosterone system blockers are preferred; concomitant conditions will often dictate which drugs are appropriate; all drugs (alone or in rational combinations) may be used provided that they have a suitable safety profile and no excessive effect on orthostatic blood pressure; in starting or continuing treatment, use precautions even more stringent than those used in younger patients; octogenarians should be seen frequently and the medical history accurately updated at each visit; standing blood pressure should always be checked for excessive orthostatic decline Although blood pressure values below which vital organ perfusion is impaired are not known, SBP <130 mm Hg and DBP <60 mm Hg should generally be avoided if possible; drug treatments for concomitant diseases should be carefully monitored to prevent adverse interactions with antihypertensive drugs	Drug treatment should not indiscriminately involve all patients with hypertension who are >80 y of age In deciding whether to initiate treatment, physicians should consider the general health condition of their patients Treatment may be withheld in more frail or medically compromised patients	

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; CCB, calcium channel blocker; DBP, diastolic blood pressure; SBP, systolic blood pressure.

There are no specific recommendations for withdrawing drugs in the presence of excessively low blood pressure levels. The ESH/ESC (European Society of Hypertension and the European Society of Cardiology)[3] guidelines recommend continuing treatment "even if SBP is <140 mm Hg if the individuals are fit and treatment is well tolerated." JNC 8 guidelines[24] state that "if pharmacologic treatment for high blood pressure results in lower achieved SBP (for example, <140 mm Hg) and treatment is not associated with adverse effects on health or quality of life, treatment does not need to be adjusted (Expert Opinion-Grade E)"; ie, there is insufficient evidence or evidence is unclear or conflicting.[24] However, this recommendation concerns all patients older than 60 years and may not apply at all to octogenarians with pronounced frailty.

Discussion

Polypharmacy, Altered Drug Metabolism, and Multimorbidity in Older Patients

Polypharmacy is the concurrent use of multiple drugs. A distinction can be made between minor (2 drugs) and major (>4 drugs) polypharmacy. Polypharmacy is also described as (1) the use of more drugs than are clinically indicated or too many inappropriate drugs; (2) two or more medications to treat the same condition; and (3) the use of 2 or more drugs of the same therapeutic class. Polypharmacy is common among frail older adults. Patients aged 75 to 84 years have the highest number of medications used, (ie, 5-9 drugs per day in more than 50% of patients).[44-46]

Drug metabolism differs in older patients, and several features of the aging process should be considered when prescribing medications for this population. Pharmacokinetics are different in older patients and include reduced renal and hepatic clearance of drugs and an increase in volume of distribution for lipid-soluble drugs. End-organ responses to drugs at receptor or postreceptor levels are different in old patients and result in altered sensitivity to several drug classes such as cardiovascular, anticoagulant, and psychotropic drugs. Likewise, reduced homeostatic mechanisms make older persons more vulnerable to adverse effects (eg, orthostatic hypotension is more likely to occur at a usual dose of a vasodilating drug in an older person, based on a slow baroreceptor response).[47-51]

The appropriateness of medication use can be assessed in a variety of ways. There are explicit (criteria-based) or implicit (judgment-based) approaches or a combination of both.[52,53] Explicit instruments include the Beers list in the United States and the STOPP/START (Screening Tool of Older People's Prescriptions and the Screening Tool to Alert to Right Treatment) criteria in Europe. The Beers list[54] identifies 53 potentially inappropriate medications or medication classes divided into 3 categories: medications to avoid in general, medications to avoid under certain circumstances, and medications to be used with caution.[54,55] These medication classes used for treating hypertension are included in the list: central α-adrenergic receptor agonists, peripheral α-adrenergic receptor blockers, and nondihydropyridine CCBs. In addition, immediate-release nifedipine and high doses of spironolactone (>25 mg/d) are considered as inappropriate in older adults.[54] STOPP/START, endorsed by the European Union Geriatric Medicine Society (EUGMS), identify 80 and 34 criteria, respectively, for minimizing inappropriate prescribing and underprescribing in older people.[56,57] More than two-thirds of STOPP/START criteria emphasize avoidance of medication duplication in pharmacotherapy, avoiding long-term benzodiazepine use, rational application of cardiovascular prevention in older patients, treatment of osteoporosis, and initiating anticoagulation in atrial fibrillation.[58] These instruments are useful for identifying problematic medications that might require reconsideration, although these lists cannot substitute for good clinical judgment when treating older patients.

Strategies for Avoiding Overtreatment

Most international guidelines (Table 1) recommend initiating antihypertensive treatment in people older than 80 years who have an SBP of greater than 160 mm Hg, and targeting to an SBP of less than 150 mm Hg for the more robust patients. The low level of evidence underlying these recommendations is widely emphasized by both national and international expert groups. The lack of evidence guiding hypertension treatment for frail patients is especially problematic.

In practice, most hypertensive patients older than 80 years are treated with more than 1 antihypertensive drug.[59-64] International guidelines generally propose initiating treatment with monotherapy or low-dose combination therapies (mostly favoring a CCB or a thiazide-like diuretic in the absence of a disease-specific compelling indication). These recommendations are in addition to lifestyle changes when lifestyle modification is insufficient to control blood pressure. There is little evidence from controlled studies comparing different drug regimens in very old hypertensive patients. Lifestyle changes[40] including weight reduction, DASH (dietary approaches to stop hypertension) dietary sodium reduction, physical activity, and moderate alcohol consumption have little evidence regarding their efficacy in improving outcomes for patients older than 80 years. Some of the recommendations regarding lifestyle may not be appropriate or relevant or may even be detrimental. For example, weight reduction alone, without exercise,[65,66] might induce muscle mass loss or cause cachexia. Excessive salt reduction might cause hyponatremia, malnutrition, or orthostatic hypotension resulting in an increased risk for falls. The existing recommendations for physical activity should be individualized for each older patient since these recommendations do not distinguish between younger and older patients and therefore may not be specific enough and appropriate for very old patients.[67] Excessive alcohol intake is often underestimated in older people and should be discouraged, not only because of its pressor effect but also because of increased risk for falls and confusion.

In older patients, in whom polypharmacy (including antihypertensive agents) is a frequent problem, drug-related problems (adverse drug reactions, drug-drug and drug-disease interactions, and nonadherence) are directly correlated with the number of drugs a patient is taking and therefore, starting hypertension treatment with a monotherapy should be pursued first. **Table 2** summarizes adverse effects for the most commonly used antihypertensive medication in older patients. Combination antihypertensive therapy to control blood pressure should be considered for older patients only if there is a clear benefit likely from the combination therapy relative to the risk of the drugs themselves or by exacerbating polypharmacy.

Before initiating or increasing treatment, blood pressure should be measured in both sitting and upright positions and confirmed by self-measurements (mainly for active older patients since in those living in nursing homes, standard blood pressure measurements and

Table 2. Adverse Effects Associated With Antihypertensive Drugs

Drug Class	Most Common Adverse Effects	Special Precautions and Considerations in Frail Older Individuals
Calcium channel blockers		
Dihydropyridine calcium channel blockers	Dizziness, flushing, headache, hypotension, peripheral edema, tachycardia	Very useful medications for older individuals Lower limb edema, which is relatively frequent with these drugs, can be erroneously interpreted as a clinical sign of heart failure; lower limb edema can contribute to the decrease in social and physical activities for practical reasons (difficulty walking with shoes)
Nondihydropyridine calcium channel blockers	Bradycardia, atrioventricular block, worsening heart failure, constipation (verapamil), hypotension, fatigue, dyspnea	Second-line selection; diltiazem can also cause lower limb edema With verapamil, lower limb edema is unusual but constipation may be a major problem in very old individuals because it can lead to fecal impaction with nausea, anorexia, delirium, and functional decline Never associate verapamil with β-blockers
Diuretics		
Thiazide	Hyponatremia, hypokalemia, hyperglycemia, hyperuricemia and gout attacks, hypotension, dehydration	First-line drugs for older individuals; indapamide has been tested in a randomized controlled trial in patients >80 y Small doses (up to 25 mg of hydrochlorothiazide) are safe and well-tolerated
Loop diuretic	Hyponatremia, hypokalemia, hypocalcemia, hypomagnesemia, hypotension, dehydration, hyperuricemia and gout attacks, hyperglycemia	Loop diuretics are not indicated for hypertension unless there is a severe renal insufficiency (estimated creatinine clearance <30mL/min/1.73 m^2) With hypertension and heart failure combined, loop diuretics can be used for both diseases, alone or in association with thiazides For thiazide and loop diuretics: diuretic doses should be titrated (ie, down-titrated in case of dehydration) according to the patient's volemic status; the latter may be difficult to assess in very old and frail individuals (eg, edema due to malnutrition vs fluid overload; a dry tongue may be multifactorial in this setting); creatinine and electrolyte monitoring is warranted after each dose change Association with selective serotonin reuptake inhibitor antidepressants increases the risk of severe hyponatremia Think about aggravation of urine incontinence; for this reason, diuretics may have an effect on the social life of the patient and can contribute to isolation Other patients often do not take their treatment if they want to have outdoor activities
Potassium-sparing diuretics that are aldosterone antagonists	Hyperkalemia, hyponatremia, and gastrointestinal disturbances including cramp and diarrhea; gynecomastia	Aldosterone antagonists should not be given in case of severe renal insufficiency, estimated creatinine clearance <30mL/min/1.73 m^2 or hyperkalemia Creatinine and electrolyte monitoring is warranted after each dose change
ACE inhibitors	Dry cough, hyperkalemia, rash, angioedema, hypotension, dizziness, fatigue, acute renal failure	ACE inhibitors can be useful in very old individuals Tested in a randomized controlled trial in patients >80 y Avoid if dehydration is suspected Do not simultaneously increase diuretics to avoid worsening renal function
Angiotensin II receptor antagonists	Hyperkalemia, rash, angioedema, hypotension, dizziness, fatigue, acute renal failure	The same as for ACE inhibitors Do not combine angiotensin II receptor blockers with ACE inhibitors or aldosterone antagonists
β-Adrenoreceptor antagonists (β-blockers)	Bradycardia, heart failure, peripheral vasoconstriction, bronchospasm, fatigue, depression, dizziness, confusion, hypoglycemia, hyperglycemia	Second-line drugs for older individuals with hypertension unless indicated for cardiovascular disease Fatigue, which is multifactorial in older patients, can be accentuated Nightmares, sleep disturbances, depression, and confusion may be present, especially for the β-blockers crossing the blood-brain barrier Cardiac conduction problems can also be aggravated Caution when used in association with acetylcholinesterase inhibitors (for Alzheimer disease): risk of major bradycardia
α-Adrenoreceptor antagonists (α-blockers)	Dizziness, fatigue, nausea, urinary incontinence, orthostatic hypotension, syncope	Usually not indicated Risk of hypotension (orthostatic, post-prandial) and syncope
Central α-adrenoreceptor agonists	Drowsiness, dry mouth, dizziness, constipation, depression, anxiety, fatigue, urinary retention or incontinence, orthostatic hypotension, confusion, delirium	High risk for delirium and confusion Depression, which is atypical and very frequent in older patients (and difficult to diagnose vs cognitive disorders), can be aggravated

Abbreviation: ACE, angiotensin-converting enzyme.

self-measurements are very similar)[62] or by blood pressure measurements at home to rule out anxiety reactions related to white coat hypertension. NICE (National Institute for Health and Care Excellence) guidelines[39] propose a home blood pressure target of less than 145/85 mm Hg for patients older than 80 years. In contrast, for patients who are younger than 80 years, the target is 135/85 mm Hg. In general, patients older than 80 years should not be given more than 3 hypertensive medications.[38]

Treatment of hypertension should be reassessed in patients with declining functional status. Increasing frailty, loss of autonomy, and institutionalization often lead to a decrease in an individual's activities, loss in body weight, and consequently a decrease in blood pressure. Therefore, an individualized, patient-tailored treatment, one in which the benefits of the therapy outweigh the risks vs a single disease-centered approach, should be adopted. Patient preferences, function, life expectancy, and quality of life should be considered.

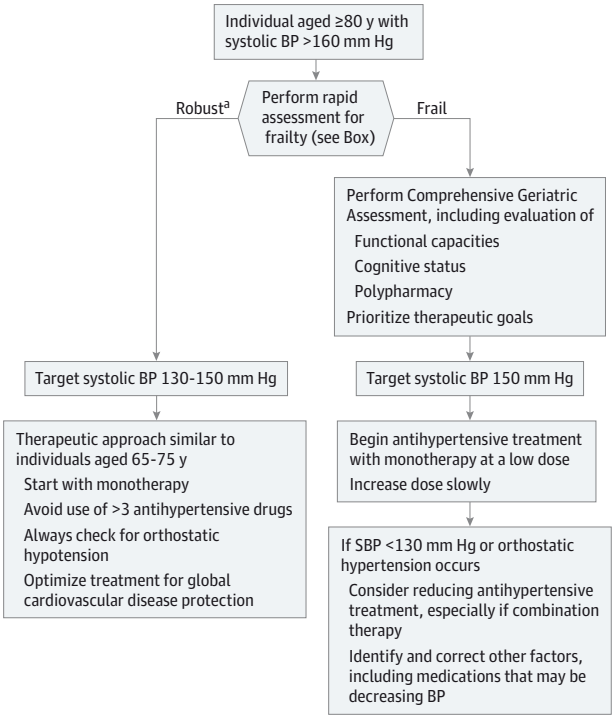
Tailored Approach: Comprehensive Geriatric Assessment

Comprehensive geriatric assessment (CGA) is a methodology for providing a global approach to the problems of complex care in older adults, facilitating the development of a specific customized care plan for each patient. CGA is defined as a multidimensional, multidisciplinary process for assessing an older person's medical (ie, disease severity, comorbidities, nutritional status, medication review), psychological (ie, cognitive and mood/depression testing), social (ie, informal support needs, care resource eligibility), environmental (ie, home safety, transportation), and functional (ie, mobility, activities of daily living, and instrumental activities of daily living) capacities. Older people most likely to benefit range somewhere between the functionally independent and terminally ill patients or those without residual autonomy, eg, patients having severe dementia. Although there is no standard to evaluate each domain, there are a variety of clinical screening tests for each component[68] and comprehensive instruments including sets of clinical assessment protocols (eg, the interRAI[69]) that are applicable to patients at high risk of frailty (Box). Comprehensive geriatric assessment is most effective when conducted by a multidisciplinary team, which usually includes a geriatrician, a coordinating or specialist nurse, a social worker, a physiotherapist, an occupational therapist, a psychologist, and optionally a clinical pharmacist. The geriatrician may direct and advise a multidisciplinary team in a patient's treatment, rehabilitation, and long-term care plan.[70]

The medical complexity of older patient care plays an important role in the onset of drug-related problems and should always be considered before prescribing any pharmacological treatment. CGA facilitates a complete assessment of pharmacotherapy, with the goal of recognizing and preventing potential drug-related problems and improving the quality of prescribing. CGA accounts for issues that may adversely affect a drug's benefit/risk ratio and reduce its efficacy. A medication review in the context of a multidisciplinary team, in addition to approaching the subject of complex clinical and therapeutic problems of geriatric patients, with a global review of different domains that includes assessing each patient's clinical and functional parameters before tackling the pharmacological issues, is likely to succeed better than merely reviewing pharmacotherapy by itself. Moreover, CGA can evaluate the appropriateness of medication use in complicated cases of older patients, aligning treatments with clinical guidelines recommendations, functional (ie, risk of falls) and cognitive impairment (ie, dementia, risk of delirium), geriatric syndromes, and limited life expectancy.[71,72]

CGA results in greater diagnostic accuracy, improved functional and mental status, less institutionalization, fewer discharge medications, and greater satisfaction with care.[73] Moreover, several studies have assessed the effect of CGA and management on drug prescribing and drug-related illness, showing a substantial improvement in medication utilization.[74,75] A comprehensive CGA may help simplify drug prescriptions and help prioritize pharmacological and health care needs (**Figure**). These assessments can help with "de-prescribing" rather than prescribing medications in older patients who have many comorbid diseases. A practical approach to de-prescribing consists of the following 5 steps: (1) identification of all drugs the patient is presently taking and the indications for each drug; (2) consideration of the overall risk of drug-induced harm in individual patients in order to decide on the intensity of de-prescribing; (3) estimation of the potential benefits and harms of each drug; (4) prioritization of drugs to discontinue that have the lowest benefit-harm ratio and lowest risk of withdrawal reactions or disease rebound syndromes; and (5) implementation of a discontinuation regimen and monitoring the patient closely for improvement in outcomes or onset of adverse effects.[76]

Figure. Decisional Algorithm for the Management of Hypertensive Patients Older Than 80 Years



[a] Describes patients who are healthy in general with no or few comorbidities and functionally independent. SBP indicates systolic blood pressure.

Managing Polypharmacy: Consideration of Other Drugs Commonly Prescribed to Older Hypertensive Patients

Nonantihypertensive drugs are the most commonly used medications in hypertensive older patients (ie, statins, antiplatelets, anticoagulants, and antidiabetic drugs).

Statins

Statin treatment should not be discontinued on the basis of increasing age only. Statins are generally safe, even in frail older patients. The decision to discontinue statins should be made by judiciously taking into account life expectancy, serious adverse effects, and possible drug interactions. This must be especially considered if a statin has been prescribed for dyslipidemia in the absence of overt atherosclerotic disease.

The decision to initiate a statin in a patient older than 80 years should be made on an individual basis and usually for secondary prevention in a patient with arteriosclerotic cardiovascular disease (ASCVD) and with a life expectancy of more than 5 years.[77,78]

Aspirin and Other Antiplatelet Drugs

Antiplatelet drugs are indicated for secondary prevention and in hypertensive patients with clinical ASCVD.[3,79] Use of aspirin, clopidogrel, ticagrelol, prasugrel, dipyridamole, cilostazol, or a combination depends on the nature of the ASCVD and any individual patient's clinical presentation (eg, a combination is temporarily warranted after the implantation of a coronary drug-eluting stent).

There are no age-specific guidelines for antiplatelet therapy. Decisions to prescribe antiplatelet medications in elderly patients should be individualized to account for ASCVD risk, bleeding risk, and kidney function. To decrease the risk of bleeding, it is essential that blood pressure be well-controlled during antiplatelet therapy. Antiplatelet drugs are not indicated for primary prevention (ie, patients without ASCVD since the net benefit is minimal).[3,80]

Anticoagulants

Since hypertensive patients have a very high risk for atrial fibrillation and embolic stroke, anticoagulants (aspirin is not a substitute) should be given based on a balanced assessment of stroke vs bleeding risk. This can be done by calculating the CHA_2DS_2VASc score (congestive heart failure or left ventricular dysfunction, hypertension, age ≥75 years [×2], diabetes, stroke [doubled], vascular disease, age 65-74 years, sex category [female]) and the HAS-BLED scores (hypertension, abnormal renal and/or liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], old age, drugs or alcohol).[81]

When the risk for stroke in atrial fibrillation is high, anticoagulant is indicated even for frail, older patients who are at risk for falls. Patients with risk for bleeding, as determined by the HAS-BLED score, should have those risks minimized but, in general, because of the devastating consequences of stroke, anticoagulation therapy is recommended.[82] Good blood pressure control (systolic <160 mm Hg) is very important in patients receiving anticoagulants.

There is limited evidence supporting what medications to use for anticoagulation. Thus, which medication is best is determined from an individual patient's clinical condition. There are currently no age-specific guidelines for anticoagulation.[81,82]

Antidiabetic Drugs

Hypertension is frequently accompanied by diabetes,[83] a disease for which adequate control of blood pressure is important but more difficult to achieve. The association of hypertension with diabetes increases the risk for orthostatic hypotension, falls, heart and renal failure, as well as several other cardiovascular complications.

Although treatment with newer antihypertensive drugs in general does not influence blood glucose control, certain precautions should be taken when treating frail older patients with both diseases: β-blockers can mask signs of hypoglycemia; antihypertensive drugs can worsen orthostatic hypotension and diuretics can exacerbate dehydration.

Guidelines for treating patients with diabetes older than 80 years are available but their recommendations are not supported by the same quality weight of evidence that exists for younger patients. None of the guidelines specifically address frail patients.[84-87]

In older patients, functional status and frailty and the duration of diabetes are important when establishing glucose and HbA_{1c} goals; thus patient-tailored treatment regimens are favored. Maintaining HbA_{1c} above 8% in frail older patients with progressive functional and/or cognitive decline is recommended by the palliative and therapeutic harmonization guideline and any medication provided to lower the HbA_{1c} below 8% can be stopped.

Clinical Cases: Managing Polypharmacy in Older Patients

These 4 clinical cases illustrate the principles of CGA to reduce polypharmacy.

Case 1

Mrs S is 85 years old, functionally independent, with office blood pressure of 168/90 mm Hg and no postural hypotension. She has been treated with a CCB for the last 5 years (10 mg of amlodipine, once daily); she also has dyslipidemia and asymptomatic carotid artery stenosis (75%), treated once daily with 40 mg of simvastatin and 80 mg of aspirin. Her blood pressure is too high and the pharmacotherapy should be optimized.

Consider Adaptation

To achieve an SBP of less than 150 mm Hg, another antihypertensive drug (eg, a hydrochlorothizide) should be recommended in addition to the 10 mg of amlodipine. Discontinuation of aspirin could be considered given that the patient has no clinical ASCVD; aspirin increases bleeding risk with poorly controlled blood pressure and if statin treatment has stabilized the plaques for years, aspirin may no longer provide extra benefit. Aspirin reintroduction could be considered once blood pressure is better controlled.

Consider Continuation

Statin treatment is recommended given the increased risk of stroke.

Case 2

Mrs A is 85 years old and has hypertension (165/85 mm Hg). She is functionally dependent, living in a nursing home, with moderate Alzheimer-type dementia (Mini Mental State Examination score, 17/30), depression, type 2 diabetes, osteoporosis, atrial fibrillation, cataract, history of falls, and urinary incontinence; and currently receives 9 chronic drugs: warfarin (dosed depending on international normalized ratio [INR] values), diltiazem (300 mg, once daily), metformin (850 mg, once daily), calcium/vitamin D (1000 mg/880 IU, once daily), paroxetin (20 mg, once daily), bromazepam (3 mg, once daily), donepezil (10 mg, once daily), alendronic acid (70 mg, once/week), and atorvastatin (40 mg, once daily). There is an increased fall risk and polypharmacy, which includes the use of benzodiazepines, SSRIs, and one antihypertensive drug. Consequently, polypharmacy should be reduced.

Consider Withdrawal

Bromazepam: gradual drug withdrawal should be considered because of prolonged sedation, confusion, impaired balance, falls.

Paroxetin: drug continuation should be reassessed. To prevent relapse and recurrence in cases of major depression, antidepressants should be continued for at least 6 months after a good initial response is shown. However, the effects of the treatment on geriatric outcomes (ie, social, functional, cognitive, comorbidities, malnutrition and falls) should be taken into consideration.

Alendronic acid: drug cessation may be considered if the treatment has continued for 5 years or more because there is little benefit to continue the treatment beyond 5 years.

Atorvastatin: drug cessation may be considered depending on life expectancy and the balance between drug indication vs adverse effects.

Consider Adaptation
Metformin: maintaining an HbA_{1c} level above 8% has been recommended and any medication lowering the HbA_{1c} below 8% can be stopped.

Consider Continuation
Donepezil should be continued in this patient with mild Alzheimer-type dementia since this drug can have a substantial positive effect in individual patients. Change to another preparation (rivastigmine, galantamine) or consider withdrawal if the drug is not well tolerated. Thus, individual judgment is important and careful supervision is needed in order to make a decision.

Calcium and vitamin D supplementation: drug continuation is recommended given its safe profile and positive effects on osteoporosis and falls. Calcium supplementation should be reconsidered if food intake is considered insufficient.

Warfarin: drug continuation is recommended with the target INR between 2.0 and 2.5 for optimal stroke prevention, although the benefit/risk ratio (especially increased bleeding risk associated with suboptimal INR control) should be repeatedly reassessed.

Diltiazem: drug continuation may be recommended if needed for blood pressure and rate control. At the same time, a tight blood pressure control may be problematic given the high risk for falls. Clinical and electrocardiogram control should be considered to detect any severe bradycardia (<50 bpm) and/or conduction problems.

Case 3

Mr P is 89 years old, without cognitive impairment, with limited mobility due to polyarthritis, and living at home with his wife, who is 10 years younger. He has been treated for hypertension with felodipine (5 mg, once daily) and a combination of bisoprolol and hydrochlorothiazide (5 mg/6.25 mg, once daily). Because of stable angina pectoris, he receives isosorbide dinitrate (20 mg, 2 times/day), aspirin (80 mg, once daily), and simvastatin (40 mg, once daily). SBP is 125/70 mm Hg when he is in a supine position and 105/65 mm Hg when upright and he has a history of peptic ulcer disease. Blood pressure is too low; there is orthostatic hypotension and associated risk of falls and consecutive fractures.

Consider Withdrawal
Isosorbide dinitrate: nitrate does not improve prognosis in ASCVD and drug withdrawal should be considered given the additive blood pressure–lowering effect in combination with bisoprolol, felodipine (both effective in case of stable angina), and hydrochlorothiazide, as well as the clinical picture of postural hypotension and consecutive risk of falls. Whether the patient needs nitrate for angina symptoms is revealed with gradual discontinuation.

Either bisoprolol or felodipine: withdrawal of one of the drugs should be considered in case the other drug is continued since both drugs are effective in cases of chronic angina but at the same time, lower blood pressure in the patient with postural hypotension and risk of falls.

Hydrochlorothiazide: drug withdrawal should be considered depending on blood pressure values and the presence of orthostatic hypotension after the previously mentioned adaptations given the additive blood pressure–lowering effect in combination with bisoprolol or felodipine.

Consider Continuation
Aspirin and statin: drug continuation is recommended given the risk reduction of ischemic heart events.

Either felodipine or bisoprolol: drug continuation of one of the drugs is recommended in case the other drug is withdrawn (both drugs are effective in the treatment of arterial hypertension and chronic angina).

Hydrochlorothiazide: drug continuation might be considered depending on blood pressure values and the absence of orthostatic hypotension after the previously mentioned adaptations.

The target SBP should be 150 mm Hg or less.

Consider Initiation
Add a proton pump inhibitor (history of peptic ulcer disease plus use of aspirin).

Case 4

Mrs T is an 89-year-old widow, functionally dependent, and living in a nursing home. She has hypertension, mild vascular dementia, osteoarthritis, and osteoporosis. She currently receives the following drugs: carvedilol (6.5 mg, 2 times/day), lisinopril (20 mg, once daily), hydrochlorothiazide (12.5 mg, once daily), aspirin (100 mg, once daily), paracetamol (1 g, 3 times/day), and calcium/vitamin D (1000 mg/880 IU, once daily). Her blood pressure while seated is 110/68 mm Hg. There is no orthostatic hypotension. Her blood pressure is too tightly controlled, which is associated with an increased risk of falls and subsequent fractures in a patient with underlying osteoporosis.

Consider Withdrawal
Carvedilol, lisinopril, hydrochlorothiazide: gradual withdrawal of 1 or more antihypertensive drugs should be considered depending on clinical evolution and judicious risk/benefit estimation. SBP of 140 to 150 mm Hg should be targeted.

Aspirin: withdrawal of antiplatelet therapy can be considered given an increased risk of bleeding and absence of clinically manifest ASCVD.

Consider Continuation
Vitamin D supplementation: drug continuation is recommended given its safe profile and positive effects on osteoporosis and falls. Calcium supplementation should be considered if food intake is considered insufficient.

Paracetamol: drug continuation can be considered depending on patient's reporting of pain.

Conclusions

There is limited evidence to support recommendations for hypertension treatment of frail, very old patients. When treating hypertension in older patients, international guidelines and each patient's overall clinical condition should be considered. The guidelines suggest reducing SBP to between 140 and 150 mm Hg and avoiding having SBP lower than 130 mm Hg. This can be achieved by appropriate hydration and nutrition, reduction or cessation of other drugs that can decrease blood pressure and, if necessary, progressive reduction of antihypertensive treatment. All medications should be regularly reviewed to determine if they are necessary.

ARTICLE INFORMATION

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REFERENCES

1. Safar ME, Levy BI, Struijker-Boudier H. Current perspectives on arterial stiffness and pulse pressure in hypertension and cardiovascular disease. *Circulation*. 2003;107:2864-2869.

2. Franklin SS, Larson MG, Khan SA, et al. Does the relation of blood pressure to coronary heart disease risk change with aging? *Circulation*. 2001;103(9):1245-1249.

3. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension. *Eur Heart J*. 2013;34(28):2159-2219.

4. Alagiakrishnan K, Juby A, Hanley D, Tymchak W, Sclater A. Role of vascular factors in osteoporosis. *J Gerontol A Biol Sci Med Sci*. 2003;58(4):362-366.

5. Launer LJ, Ross GW, Petrovitch H, et al. Midlife blood pressure and dementia. *Neurobiol Aging*. 2000;21(1):49-55.

6. Franco OH, Peeters A, Bonneux L, de Laet C. Blood pressure in adulthood and life expectancy with cardiovascular disease in men and women. *Hypertension*. 2005;46(2):280-286.

7. Benetos A, Thomas F, Bean KE, Pannier B, Guize L. Role of modifiable risk factors in life expectancy in the elderly. *J Hypertens*. 2005;23(10):1803-1808.

8. National Institute on Aging, National Institutes of Health. *Global Health and Aging. NIH Publication no. 11-7737. Washington, DC: World Health Organisation; 2011.*

9. Organisation for Economic Cooperation and Development. Health at a glance 2009: OECD indicators. http://www.oecd.org/health/health-systems/44117530.pdf. Accessed April 19, 2015.

10. Berrut G, Andrieu S, Araujo de Carvalho I, et al. Promoting access to innovation for frail old persons. *J Nutr Health Aging*. 2013;17(8): 688-693.

11. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults. *J Gerontol A Biol Sci Med Sci*. 2001;56 (3):M146-M156.

12. Studenski S, Perera S, al Patelet K. Gait speed and survival in older adults. *JAMA*. 2011;305(1):50-58.

13. Baitar A, Van Fraeyenhove F, Vandebroek A, et al. Evaluation of the Groningen Frailty Indicator and the G8 questionnaire as screening tools for frailty in older patients with cancer. *J Geriatr Oncol*. 2013;4(1):32-38.

14. Romero-Ortuno R, Soraghan C. A frailty instrument for primary care for those aged 75 years or more. *BMJ Open*. 2014;4(12):e006645.

15. Abellan van Kan G, Rolland Y, Bergman H, et al. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. *J Nutr Health Aging*. 2008;12(1):29-37.

16. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med*. 2008;358(18):1887-1898.

17. Bulpitt CJ, Beckett N, Peters R, et al. Does white coat hypertension require treatment over age 80? *Hypertension*. 2013;61(1):89-94.

18. Peters R, Beckett N, Fagard R, et al. Increased pulse pressure linked to dementia. *J Hypertens*. 2013;31(9):1868-1875.

19. Peters R, Beckett N, Beardmore R, et al: Modelling cognitive decline in the Hypertension in the Very Elderly Trial [HYVET] and proposed risk tables for population use. *PLoS One*. 2010;5(7):e11775.

20. Peters R, Beckett N, Burch L, et al. The effect of treatment based on a diuretic (indapamide) +/- ACE inhibitor (perindopril) on fractures in the Hypertension in the Very Elderly Trial (HYVET). *Age Ageing*. 2010;39(5):609-616.

21. Beckett N, Peters R, Tuomilehto J, et al. Immediate and late benefits of treating very elderly people with hypertension. *BMJ*. 2012;344:d7541.

22. Warwick J, Falaschetti E, Rockwood K, et al. No evidence that frailty modifies the positive impact of antihypertensive treatment in very elderly people. *BMC Med*. 2015;13:78.

23. Kostis JB. Treating hypertension in the very old. *N Engl J Med*. 2008;358(18):1958-1960.

24. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults. *JAMA*. 2014;311(5):507-520.

25. Mattila K, Haavisto M, Rajala S, Heikinheimo R. Blood pressure and five year survival in the very old. *Br Med J (Clin Res Ed)*. 1988;296(6626):887-889.

26. Askari M, Kiely DK, Lipsitz LA. Is pulse pressure a predictor of cardiovascular complications in a frail elderly nursing home population? *Aging Clin Exp Res*. 2004;16(3):206-211.

27. Oates DJ, Berlowitz DR, Glickman ME, Silliman RA, Borzecki AM. Blood pressure and survival in the oldest old. *J Am Geriatr Soc*. 2007;55(3):383-388.

28. Molander L, Lövheim H, Norman T, Nordström P, Gustafson Y. Lower systolic blood pressure is associated with greater mortality in people aged 85 and older. *J Am Geriatr Soc*. 2008;56(10):1853-1859.

29. Odden MC, Peralta CA, Haan MN, Covinsky KE. Rethinking the association of high blood pressure with mortality in elderly adults. *Arch Intern Med*. 2012;172(15):1162-1168.

30. Rastas S, Pirttilä T, Viramo P, et al. Association between blood pressure and survival over 9 years in a general population aged 85 and older. *J Am Geriatr Soc*. 2006;54(6):912-918.

31. Perry HM Jr, Davis BR, Price TR, et al. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke. *JAMA*. 2000;284(4):465-471.

32. Muller M, Smulders YM, de Leeuw PW, Stehouwer CD. Treatment of hypertension in the oldest old? *Hypertension*. 2014;63(3):433-441.

33. Lipsitz LAA. A 91-year-old woman with difficult-to-control hypertension. *JAMA*. 2013;310 (12):1274-1280.

34. Benetos A, Gautier S, Labat C, et al. Mortality and cardiovascular events are best predicted by low central/peripheral pulse pressure amplification but not by high blood pressure levels in elderly nursing home subjects. *J Am Coll Cardiol*. 2012;60(16):1503-1511.

35. Bejan-Angoulvant T, Saadatian-Elahi M, Wright JM, et al. Treatment of hypertension in patients 80 years and older. *J Hypertens*. 2010;28(7):1366-1372.

36. Benetos A, Labat C, Rossignol P, et al Treatment with multiple blood pressure medicines, achieved blood pressure, and mortality in older nursing home residents. *JAMA Intern Med*. 2015;175 (6):989-995.

37. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. *J Hypertens*. 2014;32(1):3-15.

38. Blacher J, Halimi JM, Hanon O. Management of hypertension in adults: the 2013 French Society of Hypertension guidelines. *Fundam Clin Pharmacol*.2014;28(1):1-9.

39. National Institute for Health and Care Excellence. Hypertension: clinical management of

primary hypertension in adults, August 2011. http://www.nice.org.uk/guidance/cg127/resources/guidance-hypertension-pdf. Accessed January 25, 2015.

40. Aronow WS, Fleg JL, Pepine CJ, et al. ACCF/AHA 2011 expert consensus document on hypertension in the elderly. *J Am Soc Hypertens*. 2011;5(4):259-352.

41. Cherubini A, Oristrell J, Pla X. The persistent exclusion of older patients from ongoing clinical trials regarding heart failure. *Arch Intern Med*. 2011;171(6):550-556.

42. Garfinkel D, Mangin D. Feasibility study of a systematic approach for discontinuation of multiple medications in older adults. *Arch Intern Med*. 2010;170(18):1648-1654.

43. Fried TR, O'Leary J, Towle V, . Health outcomes associated with polypharmacy in community-dwelling older adults. *J Am Geriatr Soc*. 2014;62(12):2261-2272.

44. Mannucci PM, Nobili A. Multimorbidity and polypharmacy in the elderly. *Intern Emerg Med*. 2014;9(7):723-734.

45. Onder G, Bonassi S, Abbatecola AM, et al. High prevalence of poor quality drug prescribing in older individuals. *J Gerontol A Biol Sci Med Sci*. 2014;69(4):430-437.

46. Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother*. 2007;5(4):345-351.

47. Petrovic M, van der Cammen T, Onder G. Adverse drug reactions in older people. *Drugs Aging*. 2012;29(6):453-462.

48. Van Pottelbergh G, Van Heden L, Matheï C, Degryse J. Methods to evaluate renal function in elderly patients. *Age Ageing*. 2010;39(5):542-548.

49. Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev*. 2009;41(2):67-76.

50. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics. *Br J Clin Pharmacol*. 2004;57(1):6-14.

51. Hutchison LC, O'Brien CE. Changes in pharmacokinetics and pharmacodynamics in the elderly patient. *J Pharm Pract*. 2007;20(1):4-12. doi: 10.1177/0897190007304657

52. Naugler CT, Brymer C, Stolee P, Arcese ZA. Development and validation of an improving prescribing in the elderly tool. *Can J Clin Pharmacol*. 2000;7(2):103-107.

53. Hanlon JT, Schmader KE, Samsa GP, et al. A method for assessing drug therapy appropriateness. *J Clin Epidemiol*. 1992;45(10):1045-1051.

54. American Geriatrics Society 2012 Beers Criteria Update Expert Panel. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012;60(4):616-631.

55. Beers MH, Ouslander JG, Rollingher I, et al. Explicit criteria for determining inappropriate medication use in nursing home residents. *Arch Intern Med*. 1991;151(9):1825-1832.

56. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment). *Int J Clin Pharmacol Ther*. 2008;46(2):72-83.

57. O' Mahony D, O'Sullivan D, Byrne S, et al. STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. *Age Ageing*. 2015;44(2):213-218.

58. Dalleur O. Screening tools for the assessment of prescribing in older patients. http://www.farm.ucl.ac.be/cfcl/Theses/Dalleur/Dalleur-Thesis-2013.pdf. Accessed April 19, 2015.

59. Thoenes M, Spirk D, Böhm M, et al. Treatment of hypertension in the elderly. *J Hum Hypertens*. 2013;27(2):131-137.

60. Aguado A, López F, Miravet S, et al. Hypertension in the very old. *BMC Geriatr*. 2009;8(9):16.

61. Hiitola PK, Enlund H, Sulkava RO, Hartikainen SA. Changes in the use of cardiovascular medicines in the elderly aged 75 years or older. *J Clin Pharm Ther*. 2007;32(3):253-259.

62. Benetos A, Buatois S, Salvi P, et al. Blood pressure and pulse wave velocity values in the institutionalized elderly aged 80 and over. *J Hypertens*. 2010;28(1):41-50.

63. Lloyd-Jones DM, Evans JC, Levy D. Hypertension in adults across the age spectrum. *JAMA*. 2005;294(4):466-472.

64. Bromfield SG, Bowling CB, Tanner RM, et al. Trends in hypertension prevalence, awareness, treatment, and control among US adults 80 years and older, 1988-2010. *J Clin Hypertens (Greenwich)*. 2014;16(4):270-276.

65. Amati F, Dubé JJ, Shay C, Goodpaster BH. Separate and combined effects of exercise training and weight loss on exercise efficiency and substrate oxidation. *J Appl Physiol (1985)*. 2008;105(3):825-831.

66. Thomas DR. Loss of skeletal muscle mass in aging. *Clin Nutr*. 2007;26(4):389-399.

67. Sparling PB, Howard BJ, Dunstan DW, Owen N. Recommendations for physical activity in older adults. *BMJ*. 2015;350:h100.

68. Abellan van Kan G, Rolland Y, Houles M, et al. The assessment of frailty in older adults. *Clin Geriatr Med*. 2010;26(2):275-286.

69. Hirdes JP, Ljunggren G, Morris JN, et al. Reliability of the interRAI suite of assessment instruments. *BMC Health Serv Res*. 2008;8:277.

70. Van Den Noortgate N, Petrovic M. The importance of a geriatric approach in medicine. *Acta Clin Belg*. 2009;64(1):7-10.

71. Fusco D, Lattanzio F, Tosato M, et al. Development of CRIteria to assess appropriate medication use among elderly complex patients (CRIME) project. *Drugs Aging*. 2009;26(suppl 1):3-13.

72. van der Cammen TJ, Rajkumar C, Onder G, Sterke CS, Petrovic M. Drug cessation in complex older adults. *Age Ageing*. 2014;43(1):20-25.

73. Ellis G, Whitehead MA, O'Neill D, Langhorne P, Robinson D. Comprehensive geriatric assessment for older adults admitted to hospital. *Cochrane Database Syst Rev*. 2011;7(7):CD006211.

74. Onder G, Lattanzio F, Battaglia M, et al. The risk of adverse drug reactions in older patients. *Curr Drug Metab*. 2011;12(7):647-651.

75. Lampela P, Hartikainen S, Lavikainen P, Sulkava R, Huupponen R. Effects of medication assessment as part of a comprehensive geriatric assessment on drug use over a 1-year period. *Drugs Aging*. 2010;27(6):507-521.

76. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy. *JAMA Intern Med*. 2015;175(5):827-834.

77. Strandberg TE, Kolehmainen L, Vuorio A. Evaluation and treatment of older patients with hypercholesterolemia. *JAMA*. 2014;312(11):1136-1144.

78. Kalyanasundaram A, Lincoff AM. Managing adverse effects and drug-drug interactions of antiplatelet agents. *Nat Rev Cardiol*. 2011;8(10):592-600.

79. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease. *Lancet*. 2009;373(9678):1849-1860.

80. Lip GY, Lane DA. Stroke prevention in atrial fibrillation. *JAMA*. 2015;313(19):1950-1962.

81. Camm AJ, Lip GYH, De Caterina R, et al. 2012 Focused update of the ESC guidelines for the management of atrial fibrillation. *Eur Heart J*. 2012;33(21):2719-2747.

82. Sardar P, Chatterjee S, Chaudhari S, Lip GY. New oral anticoagulants in elderly adults. *J Am Geriatr Soc*. 2014;62(5):857-864.

83. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes. *JAMA*. 2015;313(6):603-615.

84. Sinclair AJ, Paolisso G, Castro M, et al. European Diabetes Working Party for Older People 2011 clinical guidelines for type 2 diabetes mellitus. *Diabetes Metab*. 2011;37(suppl 3):S27-S38.

85. Sinclair A, Dunning T, Rodriguez-Mañas L. Diabetes in older people. *Lancet Diabetes Endocrinol*. 2015;3(4):275-285.

86. Benetos A, Novella JL, Guerci B, et al. Pragmatic diabetes management in nursing homes. *J Am Med Dir Assoc*. 2013;14(11):791-800.

87. Moorhouse P, Mallery LH. Palliative and therapeutic harmonization. *J Am Geriatr Soc*. 2012;60(12):2326-2332.