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Secondary cardiovascular prevention in older adults: an evidence based review

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1 Background

In the United States, life expectancy is rising, particularly among the older population (≥ 65 years), with projected estimates approaching 20% by year 2050.[1] Despite improved survival estimates, cardiovascular diseases remain the leading cause of morbidity and mortality resulting in substantial increase in health care cost.[2] For younger adults, the evidence for secondary cardiovascular prevention is well established and corroborated by robust data. However, the application of risk reduction strategies in older populations remains an area of active debate. Many assume that vulnerability to chronic cardiovascular diseases is an inexorable part of aging such that the risks attributable to prevention outweigh potential benefits. Yet, while aging is associated with greater predisposition to disease, the onset and progression of cardiovascular disorders may still be modified by effective risk reduction strategies, which may ultimately improve survival as well as symptoms, quality of life, and functional independence. If such improvements are achieved, it may potentially offset the rising healthcare costs associated with cardiovascular morbidity as well as related vulnerabilities to frailty, disability, and enfeeblement. In this review, we will discuss current available evidence for secondary cardiovascular prevention in the elderly.

2 Obesity

In industrialized nations, obesity [defined as body mass index (BMI) > 30 kg/m^2] is a public health problem, particularly among the elderly.[2] Based upon the National Health and Nutrition Examination Survey, 40.8% of adults aged 65 years or older had a BMI > 30 kg/m^2. Among adults aged 75 years or older, 27.8% were obese and 33% were found to be overweight.[3] Lower metabolic rates, decreased physical activity, and difficult-to-change dietary habits are potential risk factors that contribute to the development of obesity among the elderly. Although obesity can theoretically compound the risk of atherosclerotic disease and worsen co- existing co-morbidities like diabetes and hypertension, it also begets other comorbid conditions, such as arthritis, restricted respiratory function, urinary incontinence, and can even increase the risk of certain cancers among older adults.[4]

Despite these associations, there is lack of strong evidence suggesting that weight reduction among the elderly decreases all-cause-mortality. In fact, controversies exist regarding whether elevated BMI may be associated with lower mortality rates, which formed the basis for the "obesity-survival paradox".[5] Further, the appropriateness of using BMI in older adults remains uncertain, especially given predictable changes in height as well as reduced muscle mass in the aging population.[3] A systematic review of cohort studies showed that there was no increased (all-cause or cardiovascular) mortality in older adults with obesity or severe obesity (defined as BMI > 35 kg/m^2).[6] Despite such lack of mortality benefit, weight reduction strategies and increased physical activity among older adults with obesity were associated with improvement in quality of life and functional independence. Thus, for severely obese elderly patients, modest weight reduction in addition to exercise for maintenance of lean body mass were recommended by the American Society for Nutrition and the North American Association for the Study of Obesity (Table 1).[7]

3 Hypertension

Of the multiple modifiable risk factors, hypertension is

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Table 1. Summary of secondary prevention and risk reduction therapies in the elderly.

	Recommendation or target of therapy	Recommended therapy	Level of evidence	Scientific Society
Obesity	Moderate weight loss to improve: (1) Physical function (2) Quality of life (3) Muscle and bone loss	Lifestyle modification with change in diet and regular physical activity	Expert consensus	American Society of Nutrition North American Association for the Study of Obesity, The Obesity Society
Hypertension	(1) AHA/ACCF: SBP < 140 mmHg (Age < 79 years) SBP 140-145 mmHg (Age > 80 years) (2) JNC 8: BP < 150/90 (Age > 60 years) (3) ASH/ISH: BP < 140/90 (Age < 80 years) BP < 150/90 (Age: > 80 years)	Mild hypertension Non-pharmacologic approach with lifestyle modification, such as a DASH diet Moderate hypertension May require more than one medication but should be started at lowest doses and increased in gradual increments	Expert consensus/RCTs	(1) AHA/ACCF (2) JNC 8 (3) American Society of Hypertension/International Society of Hypertension
Dyslipidemia	Patients with known ASCVD should be on statin for secondary prevention, if tolerated (Age > 75 years)	Moderate-intensity statin	RCTs	ACC/AHA Blood Cholesterol Guidelines
Aspirin use	Aspirin is recommended for older adults with known ASCVD, if tolerated	Low-dose (81 mg) aspirin: monitor closely for bleeding	Expert consensus	
Diabetes mellitus	Lenient $HgbA_{1c}$ Goal: 7%–7.9% (Age > 65 years)	(1) Lifestyle modification with carbohydrate-consistent diet and structured exercise program. (2) First-line pharmacotherapy: biguanides (monitor closely for hypoglycemia)	Expert consensus	American Diabetes Association
Tobacco cessation	Complete cessation has shown to have survival benefits and improved quality of life at all ages	(1) Assess willingness to quit at every visit (2) Develop a plan for quitting (3) Choice of pharmacotherapy (4) Referral to smoking cessation programs	Expert consensus/ RCTs	AHA/ACCF Secondary Prevention and Risk Reduction Therapy Guidelines
Physical activity	Regular, moderate-intensity aerobic activity (3.0–6.0 METs) Muscle-strengthening activities with resistance training to improve flexibility and balance	(1) Reduce sedentary behavior (2) Increase moderate activity rather than placing emphasis on vigorous activity (3) Increase physical activity gradually in order to minimize risk of injury	Expert consensus	ACSM/AHA

ACC/AHA: American College of Cardiology/American Heart Association; ACSM: American College of Sports Medicine; AHA/ACCF: American Heart Association/American College of Cardiology Foundation; ASH/ISH: American Society of Hypertension/International Society of Hypertension; ASCVD: atherosclerotic cardiovascular disease; DASH: dietary approaches to stop hypertension; $HgbA_{1c}$: Hemoglobin A1c; JNC-8: eighth joint national Committee; MET: metabolic equivalent; RCTs: randomized controlled trials; SBP: systolic blood pressure.

the most prevalent, least likely to be adequately controlled, and carries the highest cardiovascular risk among older adults. In the Framingham Heart Study, approximately 90% of seniors eventually developed hypertension despite having a normal blood pressure at age 55 years. Additionally, isolated systolic hypertension accounted for 65% of hypertension cases among those age > 60 years and 90% among those aged 75 or older.[8] Increased arterial stiffness related to accumulation of arterial calcium, physical inactivity, and a very high-sodium diet are suggested risk factors that may contribute to the disorder in the older population.[3]

Large randomized controlled trials involving treatment of isolated systolic hypertension in older adults have resulted in reduction in stroke, coronary heart disease (CHD) events, kidney disease, atrial fibrillation, heart failure, and dementia.[8] In HYVET (Hypertension in the Very Elderly Trial), primary investigators demonstrated that isolated systolic hypertension [defined as systolic blood pressure > 160 mmHg]

was an independent cardiovascular risk factor even among patients over 80 years of age and that treatment with a target blood pressure of < 150/80 mmHg significantly reduced the risk of all-cause mortality, fatal stroke, and heart failure.[9] It is important to note that in older individuals a widened pulse pressure has also been shown to be an independent predictor of cardiovascular disease (CVD) risk and represents a measure of decreasing vascular compliance.[8]

With mild hypertension, lifestyle modification may be adequate.[8] In the trial of non-pharmacologic interventions in elderly (TONE) study, older adults demonstrated greater improvement in blood pressure with sodium restriction [i.e., the dietary approaches to stop hypertension (DASH) diet] and weight reduction than younger adults.[10] Moreover, interventions such as smoking cessation, increased exercise, and decreased alcohol intake have also shown to be effective in blood pressure control. For more severe hypertension, the initiation of pharmacologic therapy is logical, but the optimal therapeutic blood pressure goals remain an area of ongoing debate. For adults age 60 years or older, the Eighth Joint National Committee (JNC 8) recommended a blood pressure goal of < 150/90 mmHg for both primary and secondary prevention.[11] In contrast, the AHA/ACCF (American Heart Association/American College of Cardiology Foundation) expert consensus on hypertension in older adults recommended a systolic blood pressure goal of < 140 mmHg for patients ≤ 79 years of age and a blood pressure goal of 140–145 mmHg for patients ≥ 80 years of age, if tolerated.[8] Similarly, the American Society of Hypertension and the International Society of Hypertension both suggest a goal blood pressure of < 140/90 mmHg for those < 80 years of age and < 150/90 mmHg for those > 80 years of age.

The lack of consensus could be partly explained by the special patients' characteristics of the elderly, including the potential for poly-pharmacy and the greater risk for iatrogenic effects associated with changes in drug metabolism and absorption. Compared to the Seventh Joint National Committee (JNC 7) recommendations, the new blood pressure goals outlined in JNC 8 reclassified approximately one in every six older patients with hypertension, leading to an increased percentage of patients at goal blood pressure.[12] These less aggressive goals for treatment have raised significant concerns given the association between increased age and the incidence of CVD events; however, further studies are needed to determine the effect of these new guidelines on CVD outcomes in the older population.[12] Overall, blood pressure should be lowered to at least <150/90 mmHg in adults aged ≥ 60 years, and management should likely be individualized and tailored towards patient's specific health status and comorbidities. It should also be noted that all anti-hypertensive medications should be initiated at the lowest possible dose to avoid rapid changes in hemodynamics and perfusion pressures. In certain individuals, two or more anti-hypertensive medications may be necessary to meet the target blood pressure goals specified in these recommendations (Table 1).[3]

4 Dyslipidemia

In recent years, there has been cumulative evidence regarding the safety and efficacy of statin use for secondary CVD risk reduction in older adults. In the SHEP (Systolic Hypertension in the Elderly Program) trial, elevations in total cholesterol levels were associated with increased coronary artery disease risk, suggesting that cholesterol management is an important modifiable risk factor with no age limits.[13] In HPS (Heart Protection Study) and a subsequent meta-analysis with more than 19,000 patients (> 65 years), treatment with statins showed a decrease in all-cause mortality, coronary heart disease, non-fatal myocardial infarction, need for revascularization, and stroke, as well as a similar number needed to treat for both young and old patients.[14] Furthermore, due to the high prevalence of CVD in older adults, this population may potentially derive more clinical benefit with statin treatment than younger adults.[3] Despite these findings, current prescribing practices consistently reveal that patients > 65 years of age are less likely to receive statins.[15]

The 2013 AHA/ACC (American College of Cardiology/American Heart Association) Guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults emphasize that the use of statin therapy should be individualized in patients > 75 years of age, even in people with clinical CVD or disease equivalents, taking into consideration life expectancy, functional status, goals of therapy, and comorbidities. For adults age 75 years or older with atherosclerotic cardiovascular disease, moderate-intensity statin therapy is recommended for secondary prevention if they are able to tolerate the treatment.[16] Despite these recommendations, under-treatment is common in older adults and may be related to their higher propensity for: (1) statin-induced adverse events, (2) polypharmacy, (3) lack of knowledge of statin efficacy, or (4) perceived decrease in benefits due to reduced life expectancy and other comorbidities.[15] The most common side effect of statin therapy is dyspepsia, but statin-associated myopathies create an additional challenge due to difficulty of differentiating these from other musculoskeletal symptoms in this age group.

Of the more serious adverse events associated with statin use, the incidence of fatal rhabdomyolysis is low in older adults. In one systematic review and meta-analysis of randomized control trials with statin therapy in the aging population, the incidence of myopathy did not differ between placebo and treatment groups with statins.[17] This data significantly contrasted with prior multinational observational studies, especially those in Asian populations, which showed that statin-induced myopathy was one of the most commonly reported side effects in older adults. Myalgias appear to be dose-dependent in aging individuals, emphasizing the need to start statins at low doses and increase as tolerated. Benefits derived from secondary risk reduction must always be balanced with medication adverse effects and drug-drug interactions. Such approach should help guide individualized therapy decisions in the elderly (Table 1).

5 Aspirin use

In high-risk older adults with known CVD, aspirin is indicated as a secondary risk reduction therapy.[18] In order to lower bleeding risk, 81 mg of aspirin is the preferred dose over the regular 325 mg dose. Despite the perceived benefits of aspirin, there is scarcity of data for secondary prevention in adults age 85 years or older. In these patients with pre-existing ischemic heart disease or stroke, low-dose aspirin may reduce the recurrence of nonfatal myocardial infarction, stroke, or vascular events.[18] Close monitoring of aspirin-related adverse events (i.e., gastrointestinal irritability or bleeding risk) is indicated due to increased vulnerability of this subgroup, especially in the context of polypharmacy, multi-morbidity, and frailty.[3]

6 Diabetes mellitus

Based on projections from NHANES/NCHS (National Health and Nutrition Examination Surveys/National Center for Health Statistics) studies, the prevalence of diabetes mellitus in the United States is expected to double by 2050, with the largest increase among those over 75 years of age (about 450%).[2] Moreover, FHS/NHLBI (Family Heart Study/National Heart, Lung, and Blood Institute) data showed that patients with diabetes have a significantly increased risk of CVD and even higher mortality risk if CVD is already present. Diabetic men and women who are older than 50 years have lower life expectancy than their non-diabetic counterparts (average of 7.5 versus 8.2 years, respectively).[2] Despite growing prevalence, diabetes mellitus remains under-diagnosed and under-treated in older adults with a higher risk of progression to diabetes-associated complications, thus posing a significant burden on the healthcare system.[19]

The etiology of diabetes mellitus in older adults is likely related to two main reasons: (1) increased insulin resistance due to adiposity and sarcopenia, and (2) pancreatic islet cell dysfunction with decreased insulin production.[19] Because older diabetic adults are extremely heterogeneous in terms of their physical activity, independence, and comorbidities, management must be individualized for each patient, and the prevention of hypoglycemia should be prioritized. Lifestyle modifications including a carbohydrate-consistent diet and structured exercise training are first-line therapy, lowering the hemoglobin A1c (HbA_{1c}) by 0.5%–1%.[3] Pharmacological therapy for older adults with diabetes remains controversial. Whereas high glucose is associated with increased morbidity from the disease, trials testing aggressive treatment in older patients have not led to anticipated mortality benefits. In contrast, higher rates of hypoglycemia have been associated with adverse outcomes in this population. Therefore, while the American Diabetes Association recommends a pharmacological therapeutic goal of < 7% HbA_{1c} in adults age < 65 years, it cautions against generalizability to the elderly population.[3,19] For older adults, especially those with elements of frailty and multi-comorbidity, treatment goals are lenient, usually targeting HbA_{1c} between 7%–7.9% (Table 1). Other organizations that have developed guidelines recommend tailoring therapy based on life expectancy, number of co-morbidities, and functional status.[19]

First-line pharmacotherapy depends on the individual patient's risk of hypoglycemia, and therefore medications like biguanides (metformin) are usually recommended; however, renal clearance must be monitored closely. If insulin therapy is used, long-acting basal in combination with very short-acting prandial insulins are preferred over intermediate-acting insulin regimens.

7 Tobacco cessation

Despite the growing prevalence of anti-tobacco education, cigarette smoking is still the leading preventable cause of death in the world, irrespective of age.[2] Similar to young adults, smoking cessation in the elderly is associated with significant improvements in cardiopulmonary health and reduced cardiovascular risk.[2] While smokers who quit at younger ages have greater benefits in terms of longevity, those who quit at an older age still experience decreased mortality rates, cardiovascular events, and new or recurrent strokes.[3] In the Cancer Prevention Study II Trial, among smokers who quit at age 65 years, men gained 1.4–2.0 years of life, and women gained 2.7–3.7 years.[20] Therefore,

smoking cessation can provide meaningful survival benefits and improved quality of life, even if entertained at an older age (Table 1).[3]

8 Physical activity

A sedentary lifestyle is common among older adults. Reduced aerobic functional capacity, as measured by exercise testing or walking tests, is strongly associated with increased mortality risk, especially among older adults with cardiovascular disease.[21,22] The benefits of physical activity in older adults are multifold, including improvements in blood pressure, lipid profile, glucose control, osteoarthritis symptoms, neurocognitive function, quality of life, and independence.[3] Whereas many assert that increasing physical activity of any type is the therapeutic priority in old age (as compared to structured exercise training), in many instances a more structured exercise training program can help instill insight as well as confidence that, in turn, catalyzes increases in overall physical activity.

In research studies, aerobic exercise and strength training have also been demonstrated to ameliorate the typical decline in functional capacity and diastolic dysfunction that is typically associated with the aging process.[23] In fact, even low-intensity exercise regimens can lead to improvement in physiological and psychological function.[24]

For healthy adults aged 65 years or older, the American College of Sports Medicine (ACSM) recommends a total of 30 min of moderate-intensity aerobic-type exercise (e.g., walking, running, rowing) for at least 5 days per week or vigorous-intensity activity for at least 3 days per week. Strength activities (TheraBands™, free weights, or weight machines) should occur at least twice weekly and ideally include 8-10 exercises involving all major muscle groups. The ACC/AHA lifestyle guidelines recommend 150 min of moderate-intensity exercise per week for adults of all ages and also highlight that multiple episodes, as short as 10 min each, can have substantial cumulative benefits.[24] For deconditioned and frail patients, exercise training should start at less frequent intervals and be advanced as tolerated.[3] In general, as endurance improves, exercise duration should be increased first followed by the intensity of physical activity.

Advanced cardiac disease and/or comorbidities often add to the complexity of adhering to physical activity; however, these should not become reasons for older adults to become sedentary. For older adults who are sedentary and who are struggling amidst multi-morbidities (i.e., left ventricular systolic dysfunction, valvular disease, arrhythmia, hypertension, chronic obstructive pulmonary disease, arthritis) and geriatric syndromes (i.e., polypharmacy, incontinence), it is often helpful to seek guidance from clinicians who can help clarify safe and effective techniques to achieve a more active lifestyle.[24] While exercise testing or walking tests can often be useful to ensure relative safety prior to initiating exercise-training program, their application is often gauged relative to each person's individual circumstances.[3]

9 Opportunities for future research

Guidelines for primary and secondary prevention of CVD in the elderly are significantly limited by the lack of randomized controlled trials in this age group. In this capacity, some of the above recommendations are based on expert consensus. Some areas of potential research may include: (1) safety of diabetic pharmacotherapies in the elderly, (2) target blood pressure for adults > 75 years of age, (3) ideal body weight and body mass composition to balance cardiovascular health and frailty in the elderly, (4) aspirin use in adults > 80 years of age, (5) statin use in elderly patients without clinical atherosclerotic cardiovascular disease, (6) safety profiles of anti-hypertensive agents in the elderly, and (7) optimal exercise regimens for older adults who are frail.

Further, the value for secondary prevention for very old adults (above 85 years of age) or for those with multiple comorbidities and frailty requires research from experts in geriatric cardiology. Although applying effective secondary CVD risk reduction strategies in older adults may result in improvement in clinical events, other physical and functional outcomes should also be part of routine geriatric cardiology research evaluations. For instance, physical status, functional independence, quality-of-life, and health care cost efficacy may be essential parameters that could better define the benefits of secondary cardiovascular prevention in the elderly.

10 Clinical pearls

(1) Preventive strategies must be individualized for older adults depending on their clinical profile. (2) Exercise, including aerobic and strength training, attenuates age-related functional declines and preserves healthy cardiovascular physiology. (3) Healthy lifestyle behaviors including smoking cessation, improved physical activity, diet modification, and weight control can help increase longevity, physical function, and quality of life even in those who are very old. (4) Blood pressure control significantly decreases the risk of cardiovascular events as well as the incidence of heart failure, coronary heart disease, atrial fibrillation, and dementia. (5) Statin therapy can provide significant secondary risk reduction in all-cause mortality, coronary heart disease events,

ischemic stroke, and deep vein thrombosis. (6) For appropriate patients, exercise testing may serve as a tool to assess endurance, hemodynamic response, balance, and safety prior to physical exercise program. If an exercise stress test is needed, a low-intensity stress testing protocol may be best suited for older adults to assess symptoms and functional capacity.

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