

## Primary prevention of cardiovascular disease in older adults in China

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### Abstract

Over the past two decades, the percentage of Chinese

who is 60 years or older has increased from 5.2% in 1995 to 10.5% in 2015. Approximately 16% of the population in China was 60 years old and above in 2015. Since 1990, cardiovascular disease (CVD) has been the leading cause of death in China. Cardiovascular medications of older adults are usually more complicated than younger age groups due to polypharmacy, the presence of comorbidities and more susceptible to treatment-related adverse outcomes. Therefore, effective primary prevention of CVD for older adults is important in sustaining the health of older adults and reducing the burden of the healthcare system. Proper management of CVD-related risk factors, such as hypertension, dyslipidemia, diabetes and obesity, can remarkably reduce risks of CVDs in older Chinese. These risk factors can be modified by managing blood pressure, glucose and lipids *via* lifestyle modifications or receiving medications. Smoking cessation, healthy diets, strict alcohol intake and moderate physical exercise are examples of recommended lifestyle changes for remarkably recovering health conditions of older adults who have hypertension, dyslipidemia, obesity, diabetes or complications. Treatment prescriptions of older adults, in general, are recommended to be individualized and to be initiated at a low dose. The future directions for better primary CVD prevention in older adults include establishing guidelines for primary prevention of CVD for different older adults and further research on better management strategies of CVD risks for elderly Chinese.

**Key words:** Cardiovascular disease; Primary prevention; Adults; China; Aged

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**Core tip:** Cardiovascular disease (CVD) is the leading cause of death in China. More than half of the Chinese  $\geq 60$  years old have been exposed to at least one risk factor for CVD. This review aims to highlight the

primary CVD prevention in Chinese who are 60 years old and above. The management of common risk factors and future directions of primary CVD prevention for elderly population are described in this review.

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## INTRODUCTION

Cardiovascular diseases (CVDs) have been shown to aggravate the impairment of cognitive, pulmonary, renal, gastrointestinal, and hepatic functions<sup>[1]</sup>. Since 1990, CVD has been the leading cause of death in China<sup>[2]</sup>. The percentage of the Chinese population who were 65 years old or older has gradually increased from 5.2% in 1995 to 10.5% in 2015, approximately 16% of the people in China were 60 years old and above in 2015<sup>[3]</sup>. Although studies over the past two decades have provided relevant information on CVD treatments, the prescription of medications to older adults with CVDs remains challenging to clinicians and governments because older adults usually have polypharmacy, multiple comorbidities, and are vulnerable to adverse effects of treatments<sup>[1,4]</sup>. Furthermore, the clinical evidence of CVD treatments for older adults is limited, especially adults who are  $\geq 75$  years old<sup>[1,5-7]</sup>. Numerous studies have suggested that primary CVD prevention for older adults is crucial in sustaining the quality of life of older adults and in reducing the health care burden<sup>[8-10]</sup>. Therefore, there has been an increasing interest in primary CVD prevention in older adults.

A considerable amount of literature has been published on the primary prevention of CVD for older adults<sup>[1,9-11]</sup>. Since older adults across the world could vary in many aspects, such as physiological conditions, medical history, prior and concomitant medications, lifestyles and environments, the risk factors of each type of CVD and the definition of "elderly" could also differ across older adults worldwide. In China, a person who is 60 years old or above is considered older adults<sup>[5-7]</sup>. The primary CVD prevention strategies available in China are for ages, which lacks specific considerations for older adults. Older adults are in general different from younger adults regarding physiological, pharmacokinetics and pharmacodynamics, the susceptibility of adverse drugs effects, and the presence of multiple comorbidities and polypharmacy. Fortunately, there are expert consensuses for the management of common risk factors for CVD such as hypertension, dyslipidemia, and diabetes in older or very old people in China. This

review highlights the current primary CVD prevention strategies by briefly describing the management of common risk factors of CVD in China and providing suggestions for future directions, for better primary CVD prevention of Chinese who are 60 years old or above.

## MANAGEMENT OF COMMON RISK FACTORS OF CVDs IN CHINA

In China, hypertension, dyslipidemia, diabetes, smoking, and overweight are common high-risk factors of CVDs in older adults<sup>[1,4,12,13]</sup>. The 2011-2012 China Health and Retirement Longitudinal Study (CHARLS)<sup>[14]</sup> reported that the prevalence of hypertension, dyslipidemia, diabetes, smoking and overweight in Chinese whose age was between 65 to 74 years old were 50%, 64.2%, 19.5%, 25.9% and 30.1% respectively; in Chinese whose age was between 75 years old or above were 65.2%, 59.7%, 28.3%, 17.4% and 22.5%, respectively. Proper managements of these risk factors have been shown to reduce risks of CVDs considerably<sup>[15,16]</sup>. A recent study demonstrated that the use of blood pressure and lipids-modulating therapies on hypertension and dyslipidemia patients could potentially prevent 10 to 20 million acute myocardial infarctions<sup>[8]</sup>. In 2013, a study on Chinese population reported that managements of blood pressure, lipid and glucose have remarkably reduced risks of CVDs in diabetic patients<sup>[15]</sup>.

### Hypertension

Hypertension has predominantly increased the risk of ischemic heart disease, stroke, kidney failure and aortic diseases in older adults, which are the leading causes of death in older adults<sup>[17]</sup>. According to the guidelines of World Health Organization (WHO) in 1999, elderly hypertension is defined as subjects who are aged 60 years or older, systolic blood pressure continuously or 3 measurements of different days at 140 mmHg or higher and/or diastolic blood pressure of 90 mmHg or higher; isolated systolic hypertension (ISH) is defined as systolic blood pressure is at least 140 mmHg and diastolic blood pressure is less than 90 mmHg<sup>[18]</sup>.

Unlike the younger age groups, the systolic blood pressure of older adults usually increases, and the diastolic blood pressure decreases as they age<sup>[19]</sup>. A China survey of 500223 adults over 10 regions in 2013 to 2014 reported that 33.3% of the older adults between 60 years old to 69 years old and 43.7% of the older adults  $\geq 70$  years old had ISH<sup>[20]</sup>. Other types of blood pressure that are also common in older adults in China include high pulse pressure, high fluctuation in blood pressure, masked hypertension, susceptible to secondary hypertension or orthostatic hypotension, and unusual pattern of blood pressure change in day and night<sup>[21,22]</sup>.

**Target blood pressure**

An expert consensus for the management of hypertension in the elderly recommended using personalized medicine and setting intermittent goals to treat elderly subjects with hypertension and other diseases such as heart, brain, and kidney functions<sup>[21]</sup>. According to the expert consensus, the target of blood pressures for older adults is recommended to begin at < 150/90 mmHg and gradually lowered to < 130/80 mmHg. For patients above 80 years old, their blood pressure is recommended to be under 140/80 mmHg.

The J-curve phenomenon of blood pressure has been increasingly recognized<sup>[23]</sup>. Although high blood pressure increases the risk of damaging target organs, excessively lowering blood pressure can influence the blood flow to target organs, which is also harmful to patients<sup>[24,25]</sup>. The degeneration of vascular elasticity and autonomic nervous system have been associated with higher risk of organ damage and stroke<sup>[1,12,21]</sup>. For older adults who had ISH and ischemic heart diseases, intense blood pressure reduction medications are not recommended to be used in lowering blood pressure<sup>[12,21,22]</sup>. Antihypertensive treatments are more effective in patients with higher baseline blood pressure level than those with lower baseline blood pressure<sup>[10,16]</sup>. Since anti-hypertensive treatments are usually much effective in reducing systolic blood pressure than in reducing diastolic blood pressure, antihypertensive medications can reduce the blood pressure of older adults with ISH<sup>[12,16,21]</sup>.

The ideal blood pressure targets for older adults with high cardiovascular risks (such as elderly with coronary artery disease, diabetes, kidney disease and stroke) remain unclear. Most guidelines suggest the blood pressure targets of diabetic older patients should be under 130/80 mmHg, which lacks support from large clinical studies<sup>[5,21]</sup>. Chinese expert consensus for the management of hypertension recommended<sup>[21]</sup> the optimal blood pressure targets for patients who had kidney disease is recommended to be 130/80 mmHg; for patients who were also  $\geq$  80 years old, blood pressure is recommended to be under 140/90 mmHg. In patients without contraindications, preferred treatments are ACEI or ARB because these medications can reduce proteinuria, ameliorate kidney functions, and delay the development of kidney dysfunction, decrease the risk of end-stage kidney diseases<sup>[26]</sup>. Loop diuretics are recommended for patients with severe kidney functions. Hypertension in the Very Elderly Trial (HYVET)<sup>[16]</sup> is the only large study so far that aimed to study patients who have hypertension and are 80 years old or older. That study had 3845 subjects, in which 1526 of them were Chinese patients. That study showed that reducing blood pressure < 150/80 mmHg is beneficial to reduce cardiovascular outcomes. The Chinese expert consensus for the management of hypertension in older adults<sup>[21]</sup> suggests that blood pressure can further reduce to < 140/90 mmHg if patients do not

have orthostatic hypotension, fainting, angina, cardiac and cerebral vascular perfusion deficiency, or other abnormal clinical manifestation. Further studies are recommended to assess the benefit of reducing blood pressure down to 140/90 mmHg<sup>[21]</sup>.

**Antihypertensive therapy**

The pharmacokinetics of drugs in older adults is usually different from younger adults<sup>[22,27]</sup>. Older adults with comorbidities are in general at high risk of treatment-related adverse events such as deterioration in renal function and excessive orthostatic blood pressure decline<sup>[22,27,28]</sup>. Therefore, the choice of antihypertensive medication in older adults should consider age-related physiological characteristics that are related to the pharmacokinetics of drugs and the presence of comorbidities<sup>[6,7,22,27,28]</sup>. In general, medications should be initiated at the lowest dose and be slowly titrated based on the blood pressure response of patients<sup>[21,22]</sup>. The blood pressure of older adults should be gradually reduced to below target level to prevent hypotension that usually causes older adults to have a higher risk of falling and fainting<sup>[21,22,24]</sup>. The assessment of blood pressure responses to drugs is recommended to include consideration of adherence to blood pressure medications, potential drug-drug interactions, secondary hypertension, appropriateness of drug choice and accuracy of blood pressure measurement<sup>[10,27]</sup>. Many older patients require at least two types of antihypertensive medications to reduce blood pressure<sup>[4,21,27]</sup>.

The five most common classes of anti-hypertensive treatments are calcium channel blockers (CCB), diuretics, angiotensin receptor blockers (ARB), beta-blockers and angiotensin-converting-enzyme inhibitors (ACEI) are used in treating older adults with hypertension<sup>[16,22]</sup>. Diuretics and long-term calcium antagonists are recommended as preliminary treatments for older adults without symptomatic complications because these medications are effective in reducing blood pressure and have little adverse effects<sup>[21]</sup>.

The recommended essential antihypertensive treatments for older adults currently are dihydropyridine (DHP) calcium channel blockers because they are reliable and effective in reducing blood pressure and can be concurrently used with other 4 classes of drugs<sup>[21]</sup>. CCB has the following characteristics<sup>[1,13]</sup>: (1) no adverse effect on metabolism, which is appropriate for older adults with diabetes and metabolic syndrome; (2) the effect of reducing blood pressure is not affected by salt intake, which is suitable for salt-sensitive hypertension; and (3) effective on older adults with low renin activity or low sympathetic activity.

The use of diuretics has been associated with the decreased number of cardiovascular events and the reduced risk of cardiovascular mortality<sup>[29]</sup>. Thiazide diuretics can be utilized with other anti-hypertensive treatments to reduce the blood pressure in older adults, including older adults with ISH, or heart failure

and edema. Long term usage of diuretics might cause electrolyte disturbance and renal blood perfusion, and increase the risk of glucose and lipid metabolic syndrome; therefore, the change of renal functions and electrolyte levels need to be carefully monitored to prevent the development of hypopotassemia and hyperuricemia<sup>[21]</sup>. The use of diuretics in older adults should start at low doses; for those older adults whom their Creatinine clearance rate < 30 mL/min per 1.73 m<sup>2</sup>, loop diuretics such as torasemide and furosemide are recommended<sup>[21]</sup>.

ACEI is effective in lowering blood pressure and protecting the renal function of older adults who have hypertension and high renin activity<sup>[27]</sup>. This drug is suitable for hypertensive older patients who also have coronary artery disease, myocardial infarction, angina pectoris, diabetes, left ventricular dysfunction, chronic kidney disease or proteinuria<sup>[22]</sup>. ACEI does not only affect glucose and lipid metabolism, heart rate and cardiac output, but it also leads to little adverse outcomes<sup>[1,13,21]</sup>. The main adverse outcomes include coughing, skin rashes; allotriogeusia, kidney function deterioration, angioneurotic edema, and fatality occur in rare cases<sup>[21]</sup>.

The effect of ARB on lowering blood pressure and protecting kidney function are very similar, lead to fewer adverse outcomes such as coughing, angioneurotic<sup>[27]</sup>. This drug is particularly useful in subjects who are susceptible to ACEI-related adverse outcomes<sup>[22]</sup>. While using ACEI or ARB medications in older adults, close monitoring their blood potassium and serum creatinine levels are recommended<sup>[21]</sup>.

Beta-blockers are the pre-ferred choice recommended to hypertensive older adults with coronary artery disease, chronic kidney failure, and without contraindication<sup>[12,21]</sup>. Prescribing beta-blockers to older adults with sick sinus syndrome, second degree or higher atrioventricular block or bronchial asthma is prohibited because its long term usage will result in glucose and lipid metabolic disorder<sup>[12,21]</sup>. Since bradycardia and atrionector disorder are common in older adults, the usage and dose of beta-blockers should be determined according to their indications<sup>[12,21]</sup>.

Alpha-blockers are usually not considered as the first choice for hypertensive older adults unless they have benign prostate hyperplasia<sup>[13,16,21,22]</sup>. The main adverse outcome is orthostatic hypotension. Therefore, such treatment should be initiated at low doses and eaten before sleep; the orthostatic blood pressure should be monitored to prevent orthostatic hypotension<sup>[21]</sup>.

### Dyslipidemia

Dyslipidemia, including hypercholesterolemia, hypertriglyceridemia, combined hyperlipidemia and low HDL-C, has been associated with increased risks of CVDs<sup>[1,6,13]</sup>. The elevation of plasma cholesterols, especially low-density lipoprotein cholesterol (LDL-C) and non-high-density lipoprotein cholesterol (non-HDL-C), are main risk factors for arteriosclerotic vascular disease (ASCVD)<sup>[30,31]</sup>. The decrease in

LDL-C has been shown to improve cardiovascular health significantly<sup>[15]</sup>. Numerous guidelines, including China, have suggested that modulating LDL-C levels or non-HDL-C can considerably reduce CVD risk<sup>[6,32-34]</sup>. Therefore, the guidelines of many countries including China have selected LDL-C as the primary target of lipid-lowering therapy<sup>[32-34]</sup>. The guideline of dyslipidemia prevention for Chinese adults<sup>[34]</sup> has established target levels of LDL-C and non-HDL-C for different risk groups. Table 1 shows the target lipid levels for older Chinese (men  $\geq$  45 years old or women  $\geq$  55 years old). According to that guideline, if high LDL-C or HDL-C levels cannot be safely reduced to the target level, 50% reduction from baseline is also acceptable.

### Lipid-modulating therapy

Over the past decade, a considerable amount of literature has shown that statin is effective in reducing risks of CVDs through modulating blood lipids<sup>[35,36]</sup>. For an example, Heart Outcome Prevention Evaluation-3 trial (HOPE-3)<sup>[37]</sup> found that the use of rosuvastatin (10 mg, QD) can reduce the risk of cardiovascular events in an intermediate-risk population, regardless of the baseline LDL-C levels. Open Label Study of Long Term Evaluation Against LDL-C Trial (OSLER)<sup>[38]</sup> and ODYSSEY<sup>[39]</sup> have shown that the use of Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitor in addition to statin can further reduce 50% of LDL-C level, leading to 50% reduction in risk of developing CVDs. A systematic review<sup>[40]</sup> in 2013 has demonstrated that statin, in comparison to placebo, significantly reduced the risk of myocardial infarction and stroke in elderly subjects without previous CVD by 39.4% and 23.8%, respectively. Furthermore, the HPS2-THRIVE<sup>[41]</sup> trial showed that although statin is more effective in lowering LDL-C of Chinese than in Europeans, statin-related adverse effects is also more noticeable in Chinese than in Europeans. Therefore, statin has been suggested as the first line lipid-modulating therapy<sup>[10,35,42]</sup>. Statin-related adverse events include cognitive dysfunction, myopathy, increased risk of developing diabetes and cognitive impairment<sup>[32,33]</sup>. Whether older adults are more susceptible to adverse effects of statin therapy and whether effects of statin therapy in younger population can be extrapolated to Chinese who are 80 years and above remain unclear<sup>[43]</sup>. Hence, statin therapy for older adults has been recommended to be initiated at a low dose and gradually titrated according to the response of patients, especially in Chinese who are 80 years old and above<sup>[2,3,6,27,34,35]</sup>. Non-statin therapies can be considered for older adults who cannot tolerate statin or cannot attain target LDL-C level after taken maximum tolerated statin therapy<sup>[44]</sup>.

### Diabetes

Type II diabetes is the most common types of diabetes among older adults in China<sup>[4]</sup>. Postprandial hyperglycemia is more noticeable in Chinese patients

**Table 1 Target lipid level across different risk groups of older Chinese (men  $\geq$  45 years old or women  $\geq$  55 years old)**

Current lipid level (mmol/L)	Risk level	Target lipid level (mmol/L)
TC $\geq$ 7.2 or LDL-C $\geq$ 4.9	High	Primary target
4.1 $\leq$ TC < 7.2 or 2.6 $\leq$ LDL-C < 4.9 (hypertension + smoking or low HDL-C)		LDL-C < 2.6
3.1 $\leq$ TC < 7.2 or 2.6 $\leq$ LDL-C < 4.9 (hypertension + smoking + low-HDL-C)	Moderate	Secondary target
3.1 $\leq$ TC < 7.2 or 1.8 $\leq$ LDL-C < 4.9 (diabetes)		Non-HDL-C < 3.4
5.2 $\leq$ TC < 7.2 or 3.4 $\leq$ LDL-C < 4.9 (smoking or low HDL-C)		Primary target
4.1 $\leq$ TC < 7.2 or 2.6 $\leq$ LDL-C < 4.9 (hypertension, or smoking + low HDL-C)		LDL-C < 3.4
3.1 $\leq$ TC < 4.1 or 1.8 $\leq$ LDL-C < 2.6 (hypertension + smoking or low HDL-C)	Low	Secondary target
3.1 $\leq$ TC < 7.2 or 1.8 $\leq$ LDL-C < 4.9		Non-HDL-C < 4.1
3.1 $\leq$ TC < 5.2 or 1.8 $\leq$ LDL-C < 3.4 (smoking or low HDL-C)		Primary target
3.1 $\leq$ TC < 5.2 or 1.8 $\leq$ LDL-C < 3.4 (smoking or low HDL-C)		LDL-C < 3.4
3.1 $\leq$ TC < 4.1 or 1.8 $\leq$ LDL-C < 2.6 (hypertension or smoking + low HDL-C)		Secondary Target
		Non-HDL-C < 4.1

LDL-C: Low-density lipoprotein cholesterol; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol.

with early type 2 diabetes than in other population because they have significant  $\beta$ -cell deterioration<sup>[45]</sup>. Chinese is at high risk of developing diabetes with BMI relatively lower than non-Asian patients<sup>[46]</sup>. Older adults with diabetes are usually complicated by other metabolism disorders such as high LDL-C, high HDL-C, and hypertriglyceridemia<sup>[7]</sup>. Moreover, older adults with diabetes usually have poor treatment adherence and tolerance, and at high risk of hypoglycemia due to the following main reasons<sup>[7,28,47]</sup>: (1) damaged autonomic nervous system and sympathetic nervous system; (2) deteriorated compensatory mechanism of blood glucose hormone; and (3) malnutrition, irregular eating habits, reduced cognitive impairment, alcohol consumption, under-reserved hepatic glycogen, polypharmacy, and declined hepatic and renal functions.

### Management of diabetes

Higher risks of morbidity and mortality have been found in older adults with diabetes at both low and high glycated hemoglobin (HbA1c) levels<sup>[7]</sup>. As a consequence, the Chinese guideline for the management of diabetes<sup>[42]</sup> has recommended the control of HbA1c to effectively reducing the risk of morbidity and mortality (Table 2). The target of blood pressure and blood lipid for older adults with diabetes are shown in Table 3. Treatments that have little or no association with hypoglycemia are recommended to reduce blood glucose level of older adults<sup>[48]</sup>. Older adults are recommended to have fasting blood glucose level < 7.8 mmol/L and 2-h after fed blood glucose level < 11.1 mmol/L<sup>[48]</sup>. Treatment strategies are encouraged to avoid hypoglycemia, symptomatic hyperglycemia, orthostatic hypotension, and other drug-related complications<sup>[7,28,42,49]</sup>. Since postprandial hyperglycemia and  $\beta$ -cell deterioration are characteristics of Chinese patients with type 2 diabetes, considerations of anti-diabetic therapy for

Chinese patients with type 2 diabetes include control of postprandial hyperglycemia and  $\beta$ -cell preservation. Older adults usually have lower metabolism rate, malnutrition and multiple comorbidities<sup>[7,28]</sup>; therefore, their diets are recommended to limit calorie intake and balance diet nutrition for the prevention of deteriorating other comorbidities<sup>[50]</sup>. Older adults with diabetes should avoid high-intensity exercise to prevent hypoglycemia and injury<sup>[28,42]</sup>. Intense blood-glucose-lowering therapy such as glyburide should be avoided as treatment options to prevent hypoglycemia<sup>[28,42]</sup>. Initial therapy should start at low doses, and insulin therapies must be used with caution. Older adults with diabetes and high risk of CVD are not encouraged to use glycemic agents to lower blood glucose levels<sup>[7,27,50]</sup>.

In comparison to older adults who had diabetes at a younger age, older adults who developed diabetes at later age secrete more insulin resistance and insulin compensation<sup>[7,28,50]</sup>. A Chinese expert consensus for the management of diabetes in the elderly<sup>[42]</sup> has proposed an overall treatment strategy for management of diabetes in the elderly, including the four principles: (1) early prevention; (2) early diagnosis; (3) early treatment; and (4) early target attainment. Glycemic target management is encouraged to be personalized<sup>[42]</sup>.

### ntidiabetic therapy

The choice of type II diabetes medications has been explicitly suggested in Expert Consensus on Diabetic Diagnosis and Treatments for Elderly<sup>[42]</sup>. In brief, first-line antidiabetic therapy includes metformin,  $\alpha$ -glucosidase and insulin secretagogues. Metformin has been effective and safe in lowering HbA1c levels.  $\alpha$ -glucosidase and insulin secretagogues (glinides and sulfonylurea) are alternatives for older adults who cannot tolerate metformin or who have postprandial

**Table 2 Glycemic goals across different clinical conditions of older Chinese (men ≥ 45-year-old or women ≥ 55-year-old)**

Clinical conditions	Glycemic goals
> 10 yr of life expectancy Good medical support	HbA1c < 7% Fasting plasma glucose < 7 mmol/L
High expected benefit from treatment	Postprandial blood glucose < 10.0 mmol/L
Low hypoglycaemia risk	Stable blood glucose level
> 10 yr of life expectancy New diagnosed and relatively young No syndromes or complications Low risk of treatment-related hypoglycaemia Not using glycaemic-lowering medications or only use one type of non-insulin secretagogues Good treatment adherence	HbA1c = 7%
> 10 yr life expectancy Type I or type II diabetes Mild syndromes or complications Moderate risk of treatment-related hypoglycaemia Receiving insulin secretagogues or insulin therapy	HbA1c < 7.5%
< 5 yr of life expectancy Moderate syndromes or complications Moderate risk of hypoglycaemia Receiving insulin secretagogues or primarily multiple insulin injections	HbA1c < 8%
< 5 yr of life expectancy Incapable to self-manage	HbA1c < 8.5% Avoid acute diabetic complications or refractory infections caused by severe hyperglycaemia Blood glucose < 11.1 mmol/L

**Table 3 Target levels of blood pressure, low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol for older Chinese with diabetes**

Risk group	Target blood pressure level (mmol/L)	Target lipid level (mmol/L)
Diabetes	< 130/80 mmHg	Primary target LDL-C < 2.6 Secondary target Non-HDL-C < 3.4
Diabetes with hypertension and another risk factor	< 130/80 mmHg	Primary target LDL-C < 1.8 Secondary target Non-HDL-C < 2.6

LDL-C: Low-density lipoprotein cholesterol; Non-HDL-C: Non-high-density lipoprotein cholesterol.

hyperglycemia at healthy weights. New diagnosed type 2 diabetic patients who have HbA1c above 9% or FPG above 11.1 mmol/L are recommended to use short-term intensive insulin therapy, including basal and prandial insulin therapy, continuous subcutaneous insulin infusion or premixed insulin for sustaining β-cell function. Chinese patients with type 2 diabetes, who usually have poor early-phase insulin secretion, are recommended to use insulin secretagogues for

lowering blood glucose by stimulating the pancreatic β cell to release insulin. Although sulfonylurea is one of the first-line antidiabetic treatments in China, results of randomized controlled trials on Chinese patients are needed for a better guideline of its use in Chinese patients. Acarbose, a type of α-glucosidase inhibitor, has found to be more effective in lowering postprandial glucose and less useful in fasting plasma glucose than metformin<sup>[51]</sup>.

Expert Consensus on Diabetic Diagnosis and Treatments for Elderly<sup>[42]</sup> also recommended DPP-4 inhibitor and GLP-1 receptor antagonist for treating type 2 diabetes. The effect of DPP4-inhibitors has been as efficacious as acarbose in treating drug-naïve patients with better gastrointestinal tolerability<sup>[52]</sup>. Some DPP-4 inhibitors<sup>[53,54]</sup> have been associated with improvement of β-cell function in non-Asian patients, but whether such benefit also occurs in Chinese remains unclear. In addition, long-term safety and cardiovascular outcomes of DPP-4 inhibitors in the Chinese population have not been reported<sup>[55]</sup>.

### LIFESTYLE INTERVENTION

Over the past two decades, the industrialization and urbanization of China have fundamentally improved the average standard of living of Chinese; on the other hand, the unhealthy eating patterns and sedentary lifestyles of Chinese have also increased as well<sup>[56]</sup>. The China Health and Nutrition Survey (CHNS) reported that the total physical activity and occupational, physical activity in men and women across nine provinces from 1991 to 2011 fell by 31% and 42%, respectively<sup>[57]</sup>. Urbanization has been associated with the decreased levels of occupational, physical activities<sup>[58]</sup>. Physical inactivity has been associated with increased risks of the five major CVDs in China, including coronary heart disease, stroke, hypertension, type 2 diabetes mellitus and cancer<sup>[59]</sup>. Over the past decade, several studies have shown that the food intake patterns of Chinese have dramatically changed as a result of urbanization; grain and vegetables consumptions are decreased, and meat and fats consumption have increased<sup>[56]</sup>. The average annual consumption of Chinese adults who were 15 years old or older has gradually increased from 2.5 L in 1978 to 6.7 L in 2010<sup>[60]</sup>.

Lifestyle modifications such as no smoking, healthy diets, strict alcohol intake and regular exercise, has been suggested by experts and studies worldwide as fundamental part of risk factor management to reduce the risk of CVDs<sup>[1,10,11]</sup>. Smoking and second-hand smoking are major risk factors for chronic diseases, including CVD and diabetes<sup>[4,5,9,21,61,62]</sup>. They deteriorate the vascular elasticity, accelerate the development of atherosclerosis, and increase the risk of developing CVDs and mortality<sup>[26,63,64]</sup>. Therefore, smoking cessation is crucial in reducing the risk of CVDs for both smoking and non-smoking older adults<sup>[10,62]</sup>. Effective smoking cessation interventions include

health promotion, nicotine replacement therapy and medication<sup>[65-67]</sup>.

Salt-sensitive hypertension is common in older adults in China<sup>[4,12,21]</sup>; therefore, reduction in salt intake is an essential part of hypertension management strategy<sup>[1,13]</sup>. The salt intake of subjects with hypertension is recommended to be < 5 g/d<sup>[21]</sup>. Older adults with hypertension are recommended to have high nutritional diets, which include intake of fresh vegetables, fruits, fishes, bean products, coarse grains, skim milk, other rich vitamins, high fiber and non-saturated fats food<sup>[10-12,21]</sup>. Of the total calories intake, the proportion of fats and saturated fats consumption are recommended to be less than 25% and 7%, respectively<sup>[21]</sup>.

Overweight has been associated with risk of elevated blood pressure and lipid levels, and diabetes, which are high-risk factors of CVDs<sup>[68-70]</sup>. Modest weight loss has shown improvement in health conditions<sup>[71,72]</sup>. In general, the BMI of older adults are encouraged to be under than 25 kg/m<sup>2</sup><sup>[21]</sup> because the reduction in BMI can alleviate the insulin resistance<sup>[73,74]</sup>, diabetes<sup>[48,75]</sup> and dyslipidemia<sup>[76,77]</sup>. Regular moderate exercise can control BMI and insulin resistance, improve systemic cardiovascular modulation and reduce high blood pressure<sup>[78-81]</sup>. However, weight-loss medications are in general not recommended to older adults because older adults are susceptible to adverse effects of medications<sup>[10]</sup>. Furthermore, excessively strict control of diet and salt intake in older adults often lead to malnutrition<sup>[82-84]</sup>. Food consumption is encouraged to be personalized based on individuals' clinical manifestation<sup>[1,12,21]</sup>. Rapid or extreme reduction in weight can lead to poor quality of life due to poor physical conditions or even susceptible to develop other systemic diseases<sup>[6,7,12,13,47]</sup>. Unlike the younger population, older adults should not have high-intensity exercise because that increases their risk of encountering fracture and fall<sup>[80]</sup>. These lifestyles modification factors are highly recommended for management of cardiovascular risk factors, such as obesity, hypertension, dyslipidemia, diabetes and chronic kidney disease<sup>[6,7,69,78,81]</sup>.

## FUTURE PERSPECTIVES

The increasing prevalence of CVD, hypertension, dyslipidemia, and diabetes are increasing in China, but clinical guidelines and expert consensus of primary CVD prevention for older adults or very old adults are currently lacking. Unlike management of a particular risk factor (e.g., hypertension, dyslipidemia) which considers treatment strategies that optimize a specific factor, primary CVD prevention strategies require treatment plans that simultaneously manage several risk factors. A systematic review in 2016 reported that many primary CVD preventions of clinical practice guidelines (CPGs) in other countries have inexplicit guidance to manage CVD risk factors of older adults<sup>[11]</sup>. Although that systematic review only reviewed English

articles, some limitations that were revealed in that review also applied to Chinese clinical guidelines and expert consensus of primary CVD prevention in older adults and very old adults: (1) limited discussion of primary prevention strategies for frail older people and older individuals with multiple comorbidities; (2) no recommendations on how to overcome problems that withhold the implementation of the CPG for older people such as treatment adherence; and (3) no specific guidance on how to prioritize treatments with consideration of multiple comorbidities, personal and family preferences, and vulnerability to adverse drug effects.

The development of CPG is recommended to be structured in ways that clearly outline primary CVD strategies for a wide variety of older Chinese. In addition, CPGs are recommended to include specific guidance to guide clinicians how to develop personalized primary CVD prevention strategies that take into consideration of clinical manifestations, tolerability, and multiple comorbidities.

In addition, with the increasing prevalence of diabetes, hypertension and dyslipidemia in Chinese elderly, better management of risk factors of CVDs for this growing population are needed. Better management of CVD risk factors includes additional research on optimizing the use of medications in the elderly and safer methods of administering medications to avoid treatment-related adverse outcomes. Personalize, analyze, and dynamically adjust treatment plans according to responses from patients are crucial as well. The awareness and treatments of hypertension, dyslipidemia, and diabetes remain low<sup>[4,14,50,85-87]</sup>; hence, more education and training and additional social services are also encouraged in China.

Multi-center large randomized trials of primary CVD prevention on older people (with the inclusion of the frail older people with comorbidities) in China are recommended to explore optimal treatment strategies and targets of blood pressure for older adults in China. Large double-blinded randomized controlled trials on very old people (age > 80 years old) are needed to assess the lipid-lowering effect and adverse effect of statin therapies and some non-statin therapies (Omega-3 fatty acid and bile acid sequestrants) on older adults with multiple comorbidities. More studies are needed to assess the antihypertensive effect of carvedilol and nebivolol and the long-term safety of DPP-4 inhibitors on Chinese elderly. Furthermore, additional studies are needed to evaluate the benefit and harm of lowering blood pressure targets of diabetic older patients to be under 130/80 mmHg<sup>[12,21]</sup>. The implementation of these suggestions may remarkably reduce the risk of CVDs in older adults *via* more effective management of CVD-related risk factors.

## CONCLUSION

In China, CVD has been the leading cause of death,

and the percentage of Chinese who are 60 years or older are increasing. Prescribing cardiovascular treatments to older adults are usually more challenging than younger adults due to polypharmacy, the presence of comorbidities and more susceptible to treatment-related adverse outcomes. Therefore, primary prevention of CVD for older adults is crucial to sustaining the health of older adults and reducing health care burden. Risks of CVDs in older adults can be remarkably reduced through appropriate management of CVD-related risk factors, such as hypertension, dyslipidemia, diabetes and obesity, by controlling blood pressure, glucose and lipids through lifestyle modifications or receiving medications. Lifestyle modifications such as smoking cessation, healthy diets, strict alcohol intake and moderate physical exercise have been recommended to effectively improve health conditions of older adults who have hypertension, dyslipidemia, obesity, diabetes or complications. Treatments for older adults, in general, are recommended to be personalized and to be initiated at low doses. The future direction for better primary CVD prevention in older adults include establishing guidelines for primary prevention of CVD across diverse older adults and further research on better management of CVD risks for elderly Chinese.

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