

Overview of cardiovascular risk in older people with diabetes: Basic pathophysiology, risk factors and management

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Increasing age is a risk factor for diabetes; consequently, diabetes is prevalent in older people. Older people with diabetes are at high risk of cardiovascular disease (CVD) and cardiovascular events, such as myocardial infarction and heart failure. Multiple pathological processes underlie CVD, including inflammation, oxidative stress, endothelial dysfunction, thrombosis and angiogenesis. These pathological processes are influenced by age, ethnicity, genetic makeup, obesity, hyperglycaemia, insulin resistance, dyslipidaemia, hypertension, renal disease, inappropriate diet and inactivity, which are components of the metabolic syndrome and CVD risk factors. The more risk factors present, the higher the risk of CVD. Significantly, vascular damage occurs slowly; therefore, it is essential to undertake a comprehensive vascular risk assessment and manage the risk early in life to improve the individual's outcomes. Management strategies must be negotiated with the individual and appropriately tailored to their CVD risk and functional status, life expectancy and safety.

Ageing is associated with progressive decline in many physiological processes that affect health status and contribute to inflammatory changes and oxidative stress that contribute to diabetes, CVD and other complications. Atherosclerosis causes 80% of deaths in people with diabetes and 75% of hospital admissions are related to CVD (Huxley et al, 2006). CVD-related mortality is 3–10-fold higher in type 1 diabetes, and 2-fold higher in men and 4-fold higher in women with diabetes than those who do not have diabetes. Significantly, women have a 50% higher CVD risk than men and CVD develops 7–10 years later in women than men (Huxley et al, 2006; Maas and Appelman, 2010).

As older people are highly individual, management needs to be individualised to be effective. Generally, older age refers to people

older than age 60 but chronological age is not a good indicator of health status or functional capacity (International Diabetes Federation [IDF], 2013; Dunning et al, 2014). Therefore, it is important to consider functional status when planning care for older people. The IDF functional categories are outlined in *Box 1* (overleaf). These functional categories can be used with a CVD risk screen and thorough assessment.

This article gives an overview of the basic changes in cardiac physiology associated with diabetes, the risk factors for CVD and outlines management strategies.

Overview of age-related changes in the cardiovascular system

A healthy cardiovascular system is important to transport oxygenated blood, nutrients and

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Article points

1. CVD is a common cause of morbidity and mortality in older people with type 1 and type 2 diabetes and is responsible for 44–65% of diabetes-related deaths.
2. Primary prevention might not be possible, nor indicated, in older people with established diabetes, functional and cognitive impairments and limited life expectancy. It is important to control symptoms to promote comfort and quality of life.
3. Older people usually have several concomitant CVD risk factors. It is important to determine the individual's absolute CVD risk (the probability of a CVD event occurring over 5 years) to guide care planning.
4. Management consists of discussing the CVD risk profile with the individual to develop care goals and a care plan to manage the risk status and life expectancy.

Key words

- Cardiovascular disease
- Diabetes
- Older people

Author

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Page points

1. The risk of recurrent myocardial infarction, stroke and death is high, occurring 12–36 months after the initial event. Older age and multiple risk factors are strong predictors of adverse outcomes.
2. Recent research suggests high-calorie diets and little exercise might suppress the “longevity genes” that promote cellular defence mechanisms against ageing and age-related disease, including cardiovascular (CVD).

Box 1. International Diabetes Federation functional categories (IDF, 2013).

- Category 1:** Functionally independent, generally self-caring and living in the community. They may have other comorbidities besides diabetes.
- Category 2:** Functionally dependent but requires assistance with activities of daily living and diabetes self-care. Individuals living in the community are at risk of admission to a care home. There are two subcategories:
- a. Frailty, which occurs in up to 75% of older people with diabetes.
 - b. Dementia, which is associated with diabetes and severe hypoglycaemia.
- Category 3:** End of life, which generally refers to life expectancy <12 months.

often medicines to tissues and to remove waste products (North and Sinclair, 2012). Age-related changes in cardiovascular tissues include cardiac hypertrophy, changed left ventricular (LV) function and LV reserve, arterial stiffness and impaired endothelial function, which compromises the transport system. There may be few or no changes in overall resting cardiac function up to age 80; however, unstable age-associated changes are usually present in specific aspects of heart function and structure, and these changes can be exacerbated by “lifestyle factors” (North and Sinclair, 2012).

Arterial stiffness often induces myocardial compensatory mechanisms, such as LV hypertrophy and fibroblast proliferation, reduced cardiac output and increased fibrosis. These changes slow the electrical impulses within the heart, and reduce heart rate, variability and capacity to respond to beta-adrenergic receptor activation. This compromises cardiac function in the long term.

Clinically, these changes manifest as increased systolic blood pressure, which is a significant risk factor for hypertension, atherosclerosis, stroke and atrial fibrillation (Lakatta and Levy, 2003). Tissue perfusion is compromised, leading to cardiac ischaemia, which compromises the capacity of endothelial cells to proliferate and migrate after tissues are injured. The

endothelium becomes porous, allowing vascular smooth muscle cells to migrate into the sub-endothelial spaces and deposit extracellular matrix proteins that cause intimal thickening. This contributes to major CVD events such as myocardial infarction (MI) and stroke. The risk of recurrent MI, stroke and death is high, occurring 12–36 months after the initial event. Older age and multiple risk factors are strong predictors of adverse outcomes (Jernberg et al, 2015).

Six main causal mechanisms are proposed that might all be driven by a single process – overproduction of superoxide in the mitochondria electron transport channels (Giacco and Brownlee, 2010):

1. Glucose and other sugars enter the polyol pathway and lead to sorbitol accumulation.
2. Increased production of advanced glycated end products (AGE).
3. Increased expression of AGE receptors and activating ligands.
4. Activation of protein kinase C (PKC) isoforms.
5. Overactive hexamine pathway.
6. Inactivation of two critical antiatherosclerotic enzymes (endothelial nitric oxide synthase and prostacyclin synthase).

Although reactive oxygen species contribute to CVD, the role of antioxidants, such as vitamin E, is unclear. A healthy balanced diet and regular exercise are important to prevent or manage obesity, maintain heart health and reduce the risk of diabetes and CVD. They are key aspects of primary prevention as well as essential management strategies. Recent research suggests high-calorie diets and little exercise might suppress the “longevity genes” that promote cellular defence mechanisms against ageing and age-related disease, including CVD (Sinclair, 2005).

Risk factors for CVD

Table 1 outlines the key CVD risk factors and management considerations for older people. CVD risk can be calculated using one of several recommended CVD-risk calculators available on the Internet. Most modern risk calculators recommend calculating absolute risk to decide management goals and an individualised care

Table 1. Overview of key cardiovascular risk factors in older people and strategies to manage CVD risk.

Key CVD risk factors	Management strategies
<p>Hyperglycaemia Several studies showed the impact of hyperglycaemia on cardiovascular risk (King et al, 1999) and that reducing HbA_{1c} reduced CVD risk. Follow-up studies demonstrated that the beneficial effects were maintained for many years (metabolic memory/legacy effect; Hayward et al, 2015).</p> <p>Hyperglycaemia contributes to symptoms that compromise cognitive function, mood, comfort, quality of life and safety (e.g. falls and dehydration) in older people (Dunning et al 2014).</p>	<ul style="list-style-type: none"> ● Healthy eating and regular exercise are essential. ● Set an appropriate blood glucose target range and HbA_{1c}: <ul style="list-style-type: none"> -Functionally independent: 53–59 mmol/mol (7–7.5%). -Functionally dependent: 53–64 mmol/mol (7–8%). -Frail/dementia: up to 70 mmol/mol (8.5%). ● A safe recommended blood glucose range is 6–15 mmol/L, especially in aged care homes (Dunning et al, 2014). <p>Medication</p> <ul style="list-style-type: none"> ● More than one type of glucose-lowering medicine is often required and can reduce major CVD risk factors in people with a long duration of diabetes but do not necessarily improve survival over 12 years (Hayward et al, 2015). ● Consider contraindications to medicines, risk of polypharmacy, errors and adverse events and whether the person can self-manage their medicines. <ul style="list-style-type: none"> - Metformin is first-line therapy. Monitor renal function (serum creatinine might be more accurate than eGFR in older people) and gastrointestinal intolerance. - Sulphonylureas with low hypoglycaemia risk can be used but might not be useful for people with long-standing diabetes and significant beta-cell loss. - DPP-4 inhibitors and GLP-1 RAs can be considered providing they do not cause excessive weight loss and/or gastrointestinal problems (IDF, 2013). Sitagliptin does not appear to increase risk of major adverse CVD events over 3 years in people >50 years (Green et al, 2015). - Insulin therapy should not be unnecessarily delayed even though it has a high risk of hypoglycaemia. ● Some glucose-lowering medicines must not be crushed and liquid dose forms might be needed for older people with swallowing difficulties. ● Preventing hypoglycaemia is important. Severe hypoglycaemia can precipitate adverse CV events such as MI, ischaemia and cardiac arrhythmia secondary to autonomic activation, which results in haemodynamic changes, vasoconstriction, intravascular coagulability and viscosity (Chopra and Kewal, 2012).
<p>Dyslipidaemia Many studies show adverse lipid profiles predict micro- and macrovascular disease. People with diabetes usually have an adverse lipid profile with high LDL and very-LDL, which increases the risk of adverse cardiovascular events.</p>	<ul style="list-style-type: none"> ● The goal is to reduce vascular events by treating the underlying lipid abnormalities. Managing hyperglycaemia does not necessarily improve the lipid profile. ACCORD (2010) showed protocol-driven treatment can improve outcomes. <p>Targets</p> <ul style="list-style-type: none"> -LDL-C: <3 mmol/L -Non-fasting triglycerides: <4.0 mmol/L; fasting triglycerides <2 mmol/L -HDL-C: >1.0 mmol/L (Diabetes Australia and Royal Australian College of General Practitioners, 2014; NICE, 2014). <ul style="list-style-type: none"> ● Lipid targets can be less stringent in frail older people and those with dementia (IDF, 2013). <p>Medicines</p> <ul style="list-style-type: none"> ● Lipid-lowering drugs are often needed to reduce LDL-C and triglycerides, and increase HDL-C. ● Every 1-mmol/L reduction in LDL-C represents a 20% reduction in major CVD events. ● Medicine choice depends on the underlying lipid abnormality. ● Statins can be used alone or in combination, unless they are contraindicated. Lower doses should be used and the person monitored for side effects (e.g. muscular and liver abnormalities). ● Fibrates alone or with statins are used to increase HDL-C and reduce triglycerides, and can decrease relative risk by 31% (ACCORD, 2010). <p>Monitoring</p> <ul style="list-style-type: none"> ● The lipid profiles should be assessed as part of the CVD risk assessment and then annually.

CVD=cardiovascular disease; DPP-4=dipeptidyl peptidase-4; eGFR=estimated glomerular filtration rate; GLP-1 RAs=glucagon-like peptide-1 receptor agonists; HDL-C=high-density lipoprotein cholesterol; IDF=International Diabetes Federation; LDL-C=low-density lipoprotein cholesterol.

Table 1 continued.

Key CVD risk factors	Management strategies
<p>Obesity Weight loss improves fitness and reduces morbidity and mortality. However, weight loss might lead to muscle and protein loss in older people and be detrimental to health and safety. Older obese people can be sarcopaenic. Obesity is associated with hyperlipidaemia, hypertension, insulin resistance and inflammatory changes that lead to CVD risk and actual events. In addition, it limits the individual's ability to exercise, compromises sleep and causes sleep apnoea.</p>	<ul style="list-style-type: none"> ● Weight reduction is controversial in older people (Halter et al, 2014). It exacerbates sarcopenia and can lead to stress and anxiety. <p>Nutrition</p> <ul style="list-style-type: none"> ● A comprehensive nutrition assessment should be undertaken, including any swallowing difficulties, and ability to shop and prepare meals. ● The meal plan should supply essential nutrients, energy, fluids and fibre. Consider supplements. <p>Medicines and surgery</p> <ul style="list-style-type: none"> ● Evidence base is lacking for weight-loss medicines. Use with caution, especially when the individual has gastrointestinal problems, and is frail and inactive. ● Bariatric surgery in older people leads to more modest benefits than in younger people (Sugerman et al, 2004). Benefits are largely unknown for frail older people. ● Surgical and infection risk must be taken into account (Pearse et al, 2006). <p>Monitoring</p> <p>Monitor nutritional status at least annually but also when the person's condition changes or they suddenly lose weight.</p>
<p>Hypertension Most people with prediabetes and diabetes are hypertensive. Hypertension is a risk factor for micro- and macrovascular disease. Every 20 mmHg increase in systolic and 10 mmHg diastolic blood pressure increases CVD risk in 20–70-year olds. Antihypertensive medicines, especially those that act on the renin–angiotensin–aldosterone system, have protective effects and are recommended to manage albuminuria, even when the blood pressure is normal (Demir and Cooper, 2015). People with diabetes often require three or more antihypertensive agents. Kidney function should be assessed regularly.</p>	<ul style="list-style-type: none"> ● Blood pressure targets need to be carefully considered. <ul style="list-style-type: none"> -Functionally independent: 140/90 mmHg -Frail: 150/90 mmHg -Dementia: 140/90 mmHg but avoid strict control (IDF, 2013). ● Diet and exercise can be combined with antihypertensive medicines. ● Renal disease is diagnosed when eGFR <30 mL/min/1.73 m² and influences medicine choices. <p>Medicines</p> <ul style="list-style-type: none"> ● Antihypertensive medicines, especially ACE inhibitors, have protective effects and are recommended to manage albuminuria, even when the blood pressure is normal. ● ARBs can be used if the individual cannot tolerate ACE inhibitors; diuretics and CCBs can be used as add-on therapy to ACE inhibitors. ● Antihypertensive medicines should be started at low doses and slowly titrated up. Medicines might need to be titrated down or stopped if renal function declines. ● Often three or more antihypertensive agents are required; however, the benefits need to weighed against the risks associated with polypharmacy, postural hypotension and falls. <p>Monitoring</p> <ul style="list-style-type: none"> ● Measure blood pressure at least biannually, when an antihypertensive medicine is commenced or stopped and if function declines. ● Dietitian assessment and advice about diets, weight management and restricting protein, if renal function declines.
<p>Other factors Smoking, alcohol and knowledge deficits</p>	<ul style="list-style-type: none"> ● Encourage smoking cessation and reducing alcohol intake. ● Stress management can also be helpful. ● Regular screening for associated risks, such as vision and hearing problems, and neuropathic changes. ● Cognitive and sensory changes, and changes in the way older people learn must be considered when providing diabetes education. ● Given the high risk of sudden MI, preferences for resuscitation and end-of-life care should be discussed.

ACE=angiotensin-converting-enzyme; ARB=angiotensin II receptor blockers; CCB=calcium channel blockers.

plan (Jenkins et al, 2015).

Gender-specific risk factors should also be considered, such as pre-menopausal hormonal dysfunction, hypertension and/or pre-eclampsia and gestational diabetes during pregnancy in women. The role that polycystic ovarian disease plays in CVD risk is unclear (Maas and Appelman, 2010).

Significantly, diabetes is an equivalent risk factor to previous MI among men aged 60–79 with early onset diabetes (Giacco and Brownlee, 2010). Over 30% of people admitted to hospital with acute MI have diabetes and 35% have impaired glucose tolerance (Giacco and Brownlee, 2010). Interestingly, the relative glucose-related risk of CVD appears to decrease with age; however, the overall absolute risk increases with age and is closely associated with congestive heart failure (Avery et al, 2012).

In addition, age-related risks include:

- Reduced insulin sensitivity and insulin resistance.
- Central obesity.
- Mitochondrial dysfunction.
- Reduced protein synthesis and protein quality, which compromises muscle quality and strength, especially in the presence of oxidative stress and DNA damage. Regular exercise helps reduce insulin resistance and maintains muscle strength and is important to preventing falls in older people (Ruas et al, 2012).
- Declining beta-cell function and beta-cell mass is evident before diabetes is diagnosed and is progressive, which suggests insulin might be required over time. Older people who are not obese can adapt to these changes but metabolic stress exacerbates deficits in glucose regulation and overwhelms adaptive mechanisms (Taichi et al, 2012).

In addition, some commonly used medicines such as corticosteroids, antihypertensive agents, thiazide diuretics and some antipsychotic agents are associated with disrupted glucose homeostasis and increased risk of diabetes and its most significant complication, CVD.

Managing cardiovascular risk

Most countries have guidelines for managing diabetes, CVD and CVD risk factors such as

dyslipidaemia, hypertension and hyperglycaemia (NICE 2010; Scottish Intercollegiate Guideline Network, 2014; American Diabetes Association, 2015). Strategies to manage key CVD risk factors are outlined in *Table 2*. A number of overarching considerations and clinical challenges influence management decisions. These include:

- Functional status, and the relative risks and benefits of guideline recommendations for individual older people in light of their absolute cardiovascular risk, life expectancy, care goals and preferences.
- Chronological age is not an appropriate indicator of health, function or self-care capacity.
- The importance of managing CVD-related symptoms such as dyspnoea, breathlessness, exertion angina, exercise tolerance, tiredness, depression and peripheral oedema. Thus, a palliative approach to managing symptoms to promote comfort and quality of life can be integrated into usual care.
- The potential influence of the legacy effect (metabolic memory). The legacy effect highlights the benefit of controlling hyperglycaemia and its associated metabolic derangements before the person becomes old, and the importance of identifying CVD and diabetes risk early in life.
- Managing CVD risk might be more important and relevant than focusing on optimal blood glucose control. The Veterans trial showed intensive blood glucose control in people with mean age 60.5 did not significantly reduce CVD risk (Hayward et al, 2015).
- Cognitive changes and the effects on self-care, the ability to problem-solve, make decisions and recognise symptoms.
- The presence of comorbidities, such as hyperthyroidism, which can be subclinical and lead to atrial fibrillation (AF). AF can be due to transient conditions, such as infection.
- Many older people have peripheral and/or autonomic neuropathy. The former is associated with risk of foot complications, such as ulcers and infections. The latter, combined with CVD, compromises sexual function. It also affects sensation and a person's ability to recognise important life-threatening events

“...some commonly used medicines such as corticosteroids, antihypertensive agents, thiazide diuretics and some antipsychotic agents are associated with disrupted glucose homeostasis and increased risk of diabetes and its most significant complication, CVD.”

Table 2. Important considerations when prescribing and monitoring cardiovascular medicines in older people.

Prescribing issue	Issues to consider
Decide and prioritise the goals of treatment.	<ul style="list-style-type: none"> ● Goals must be decided with the individual and family. ● Treatment must be safe and make clinical sense. ● Advise about diet and exercise, smoking cessation and alcohol in moderation. ● When starting cardiovascular medicines consider comfort and quality of life. Individual's preferences are a critical factor in determining outcomes.
Evidence for benefit and risk might not be available for older people, especially those who are frail, have dementia or are at the end of life.	<ul style="list-style-type: none"> ● Study participants may not be representative of older people in general or with regards to particular functional categories.
Need for pharmacovigilance to limit the risk of medicine errors and adverse events. Medicine errors and adverse events are significant causes of preventable hospital admissions, especially in people over the age of 80 (Naganathan, 2013).	<ul style="list-style-type: none"> ● Monitor medicines with a narrow therapeutic index. ● Consider whether the number of medicines can be reduced. Older people with CVD and diabetes usually have comorbidities, which increase the risk of medicine interactions. ● Hypoglycaemia may cause falls, short-term cognitive impairment and dementia (Chopra and Kewal, 2012; IDF, 2013; Dunning et al, 2014). ● Hypotension also contributes to falls. ● Falls risk is highest 1–14 days after commencing a new medicine class (Shimbo et al, 2015).
Consider using non-medicine options and whether evidence-based complementary medicines might be safe and beneficial.	<ul style="list-style-type: none"> ● Tai chi and weight training improve strength and reduce falls risk and confer other CVD benefits. Yoga reduces stress and diastolic blood pressure and increases HDL-C and reduces triglycerides (Holt, 2014). ● Red yeast rice, compared to placebo, reduced total and LDL cholesterol and triglycerides in people with a mean age of 60.5 years ($n=53$) who had dyslipidaemia and were statin intolerant (Chung et al, 2014). ● Ginkgo and gotu kola stabilise plaque (Bone, 2014). ● Research suggests that calcium supplements may increase CVD risk (Bollard et al, 2013).
Medicine adherence.	<ul style="list-style-type: none"> ● Side effects of antihypertensive agents, statins and diuretics can cause non-adherence. ● Adherence to statins reduces to 36% after 15 days (Shimbo et al, 2015).

CVD=cardiovascular disease; HDL-C=high-density lipoprotein cholesterol; LDL=low-density lipoprotein

such as MI and hypoglycaemia (Knopman et al, 2001). The latter can trigger MI in older people and is associated with dementia (Knopman et al, 2001).

- The need to manage surgical risk and risks associated with investigations (Pearse et al, 2006). Knowing the person's absolute CVD risk can be useful when emergencies, such as acute MI and foot problems that require surgical intervention, occur. Absolute risk can also be used to initiate conversations about documenting end-of-life care preferences.
- Accepting that health professionals' recommended care is likely to differ from the individual's goals and preferences and that of their families.
- The way older people learn and process information changes over time. Therefore, education strategies, written and other types of information, must be suitable to the individual older person. Significantly, the individual and their carers need education about how to recognise and act on atypical signs and symptoms of MI, and the importance of seeking advice early.
- The need for pharmacovigilance (Dunning and Sinclair, 2014), see *Table 2*.

Summary

Older people are at high risk of CVD. Identifying and managing CVD needs to occur as early as possible for prevention to be successful. This is before metabolic abnormalities and age-related factors lead to irreversible tissue damage. Changed pathophysiology and complications are often present approximately 10 years before CVD and diabetes manifest. A proactive comprehensive, individualised and person-centred approach to care, based on absolute cardiovascular risk, is essential.

This article made the following key points: CVD is common in older people with types 1 and 2 diabetes and is responsible for >50% of diabetes-related deaths. Older people are likely to have several concomitant CVD risk factors; however, it is important to determine the individual's absolute risk to guide care planning. Important management and prescribing issues were also presented. ■

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