Hyperglycemia, dyslipidemia and hypertension in older people with diabetes: the benefits of cardiovascular risk reduction

Diabetes mellitus is increasingly recognized as an essentially vascular disease, and a principal objective of diabetes care is prevention or reduction of cardiovascular risk. In this context, control of hyperglycemia, dyslipidemia and hypertension is at the heart of this care. As the combination of age and diabetes increases baseline vascular risk in older people, they stand to gain most from cardiovascular risk prevention. Although most of the clinical trials have excluded or included only few older people, there is now enough evidence to suggest that aggressive treatment of vascular risk factors in this age group is beneficial and could be cost effective. Current comprehensive mutifactorial risk reduction is suboptimal in older people with diabetes. Aggressive intervention is suitable in older people with diabetes who have reasonable life expectancy. Many older people with diabetes may not achieve recommended targets for risk factors reduction due to various reasons, including polypharmacy and comorbidities, but even a small reduction in these risk factors is beneficial. However, for frail older people with multiple disabilities, including cognitive and functional impairment, tight interventions may not be effective considering their short life expectancy and the risks associated with multiple medications, particularly hypoglycemia. Quality of life remains the primary target in the medical care of this group of patients.

KEYWORDS: diabetes mellitus • older people • vascular risk

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Aging and diabetes have a profound effect on cardiovascular system structure and function increasing the risk for cardiovascular disease (CVD). With increasing age there is increased stiffness and loss of compliance of major arteries, leading to the development of systolic hypertension and wide pulse pressure. This vascular aging could be genetic [1] or influenced by adverse growth patterns in early postnatal life [2]. On the other hand, the increased risk of CVD caused by diabetes is not fully explained by the traditional risk factors, and there is some evidence to suggest that abnormalities in insulin-like growth factor-1 occur in insulin-resistant states and may be a significant factor in the pathophysiology of CVD [3]. This may occur even before clinical diabetes is diagnosed, and affects individuals with impaired glucose tolerance [4]. The prevalence of coronary heart disease (CHD) is around 80% of elderly people with Type 2 diabetes [5], and the incidence is twice that in nondiabetic elderly patients [6]. As the combination of both diabetes and age places older people with diabetes at the highest baseline risk for CVD, this population stands to gain the most benefit from cardiovascular risk reduction. Although the evidence for cardiovascular risk reduction in diabetics is established for younger patients, there is still some uncertainty for how far we should go with risk reduction in older people, as most of the clinical trials have excluded or only included few of these patients [7]. We have performed a Medline review for the evidence of major cardiovascular risk reduction relevant to older people with diabetes using the following search terms individually and in combination: diabetes mellitus, hyperglycemia, blood glucose, elderly, older people, aged, vascular risk, cardiovascular risk, hypertension, hypercholestrolemia, hyperlipidemia, dyslipidemia.

Hyperglycemia

Hyperglycemia increases risk for CVD. In the United Kingdom Prospective Diabetes Study (UKPDS), data indicate that with each 1% rise in hemoglobin A1c (HbA1c) the incidence of myocardial infarction increases by 14% [8]. Moreover, the relationship between glycemia and cardiovascular risk seems to start within the normal blood sugar range [9]. A meta-analysis of ten studies involving individuals with Type 2 diabetes (n = 7435) demonstrated increased relative risk (RR) of CVD by 1.18 (95% CI: 1.10–1.26) for every 1% increase in HbA1c [10]. In addition, postprandial glycemia appears to have more pathogenic potential than fasting blood glucose [11]. Despite this clear association between hyperglycemia and cardiovascular risk, it is not very clear whether reducing blood sugar will result in

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reduced cardiovascular events. Three multicenter trials investigating whether reducing HbA1c to near-normal levels in patients with Type 2 diabetes will reduce the risk of cardiovascular events were recently published. They are the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial [12], the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [13], and the Veterans Affairs Diabetes Trial (VADT) [14]. Data from these trials, in addition to the UKPDS post-trial study (UKPDS follow-up) [15], are summarized in Table 1. In the ADVANCE, ACCORD and VADT studies, populations included were at high risk of cardiovascular events. In the ADVANCE study, the reduction of HbA1c to 6.4% in the intensive therapy versus 7.0% in the standard therapy group resulted in lower primary outcome (combined major macrovascular and microvascular events, 18.1 vs 20.0%, p = 0.01) in the corresponding groups, respectively. This was mainly due to a significant reduction in new or worsening nephropathy (4.1 vs 5.2%, p = 0.006). For major macrovascular events, all-cause or cardiovascular deaths there was no significant differences between both groups. In the ACCORD study, a reduction of HbA1c to 6.4% in the intensive therapy versus 7.5% in the standard therapy group resulted in higher mortality in the intensive therapy group (hazard ratio [HR]: 1.22; 95% CI: 1.01–1.46, p = 0.04) and early termination of the study after a mean of 3.5 years of follow-up. There was no significant reduction in major cardiovascular events (HR: 0.90; 95% CI: 0.78–1.04; p = 0.16). However, the results of this study were not consistent, as there was a significant reduction in nonfatal myocardial infarctions in the intensive treatment group (3.6 vs 4.6%, p = 0.004) compared with standard treatment. In the VADT study, a reduction of HbA1c to 6.9% in the intensive therapy versus 8.4 in the standard therapy group resulted in no significant differences in the occurrence of first major cardiovascular event or mortality of any cause (HR: 0.88; 95% CI: 0.74–1.05; p = 0.14 and HR: 1.07; 95% CI: 0.81–1.42; p = 0.62, respectively). Hypoglycemic events were significantly higher in the intensive therapy arms among the three studies in comparison to standard therapy (Table 1). In the original UKPDS study, a reduction of HbA1c to 7.0% in the sulfonylurea/insulin intensive therapy group vs 7.9% in the conventional treatment group resulted in a nonsignificant reduction of myocardial infarction by 16% (p = 0.052) [16]. After a further 10 years of follow-up, significant cardiovascular protection starts to emerge, despite the fact that differences in HbA1c between therapy arms have disappeared (Table 1). The increased mortality in the ACCORD study was not clearly explained. In the intensive therapy group a median HbA1c of 6.4% was rapidly achieved after only 4 months of randomization. The increased mortality could be related to multiple factors, including the speed of glucose lowering and the treatment used to achieve such a level. Of note, after approximately 3 years, a nonsignificant reduction of the primary outcome (nonfatal myocardial infarction, nonfatal stroke or death from cardiovascular events) starts to emerge in the intensive therapy group. This pattern may suggest that if there is any benefit associated with intensive glucose lowering, it may take several years to emerge. This has been shown in the UKPDS follow-up study, which has demonstrated the benefit of intensive glucose control on cardiovascular events only after a long duration in newly diagnosed younger patients with Type 2 diabetes. The study demonstrated extended effects of improved glycemic control – the so called legacy effect – after a long period of follow-up, reaching up to 30 years in some patients, despite the fact that the difference in HbA1c between intensive and standard therapy arms had disappeared. Those patients included in the ACCORD, ADVANCE and VADT studies were older and had longer duration of diabetes. This may suggest that their cardiovascular disease has already been established prior to intervention, minimizing the benefit of tight glucose control compared with the lower-risk, younger patients with newly diagnosed diabetes included in the UKPDS study. It is also possible that the multiple interventions with blood pressure control, statins and antiplatelet therapy in these three trials have reduced the rate of end point events and, hence, the power of the studies, minimizing the effect of tight glucose control on outcome. The legacy effect or glycemic memory effect was also demonstrated in the Epidemiology of Diabetes Interventions and Complications (EDIC) study [17], which is a follow-up of the Diabetes Control and Complications Trial (DCCT) [18]. In the DCCT study, which included younger patients (13–39 years) with Type 1 diabetes and no history of cardiovascular disease, intensive insulin therapy resulted in a nonsignificant reduction of macrovascular events (41%, 95% CI: -10–68) after a mean of 6.5 years follow-up. However, after 11 years of follow-up, intensive therapy had significantly reduced the risk of cardiovascular events by 42% (95% CI: 9–63, p = 0.02). In summary, older

Table 1. Summary of data from recent trials.

	UKPDS-follow-up [15]	ADVANCE [12]	ACCORD [13]	VADT [14]
Baseline characteristics				
Location and year published	23 centers in UK, 2008	215 centers across Asia, Australia, Europe and North America, 2008	77 centers across USA and Canada, 2008	20 centers in USA, 2008
Inclusions criteria	Newly diagnosed DM with fasting blood sugar >6 mmol/l but <15 mmol/l	Diagnosis of Type 2 DM at ≥30 years of age or age ≥55 years or history of major macro- or micro-vascular disease	HbA1c ≥ 7.5%, age 40–79 years with history of CVD, age 55–79 years with evidence of atherosclerosis, albuminuria, LVH or two additional risk factors for CVD (smoking, hypertension, obesity, dyslipidemia)	Type 2 DM with inadequate response to maximum dose of an oral agent or insulin therapy
Exclusion criteria	Significant CVD (previous MI, current angina or HF, more than one major CV event)	Definite indication for or contraindication to any of the study treatments or definite indication for long-term insulin therapy at time of entry	Recent or frequent serious hypoglycemia, BMI > 45 creatinine > 133 µmol/l, serious illness	HbA1c < 7.5%, CV events in previous 6 months, advanced HF, severe angina, life expectancy < 7 years, BMI > 40, creatinine > 141 µmol/l, ALT > 3× ULN
Number of patients	3277	11,140	10,251	1791
Mean (SD) age (years)	62 (8)	66 (6)	62.2 (6.8)	60.5 (9)
Race (%) Whites Blacks Hispanics Others	 76.1 9.4 13.7 (Asians) 0.8	 NR	 64.4 19.9 7.0 8.9	 62.0 16.7 16.3 5.0
Duration of DM on entry (years)	Newly diagnosed	8.0	10.0	11.5
Duration of study (median years)	16.8 for sulfonylurea/insulin 17.7 for metformin	5.0	3.5 (terminated early)	5.6
Intervention & outcome				
Intervention	Intensive therapy either with sulfonylurea/insulin or metformin versus conventional therapy	Intensive glucose control with gliclazide MR plus other agents as required to achieve HbA1c ≤ 6.5% versus standard therapy	Intensive therapy with target HbA1c < 6% versus standard therapy with HbA1c 7–7.9%	To compare intensive versus standard glucose control on cardiovascular events
HbA1c (%) intensive vs standard therapy	7.9 vs 8.5 for sulfonylurea/insulin and 8.4 vs 8.9 for metformin	6.5 vs 7.3	6.4 vs 7.5	6.9 vs 8.4

ALT: Alanine transaminase; BMI: Body mass index; CAD: Coronary artery disease; CI: Confidence interval; CV: Cardiovascular; CVD: Cardiovascular disease; DM: Diabetes mellitus; HF: Heart failure; LVH: Left ventricular hypertrophy; MI: Myocardial infarction; NR: Not reported; PVD: Peripheral vascular disease; SD: Standard deviation; ULN: Upper limit normal.

Table 1. Summary of data from recent trials.

	UKPDS-follow-up [15]	ADVANCE [12]	ACCORD [13]	VADT [14]
Intervention & outcome (cont.)				
Outcomes: relative risk reduction (95% CI)	Any DM-related end point: sulfonylurea/insulin = 9% (1–17) metformin = 21% (5–34) DM related death: sulfonylurea/insulin = 17% (4–27) metformin = 30% (8–47) Death any cause: sulfonylurea/insulin = 13% (4–21) metformin = 27% (11–41) MI: sulfonylurea/insulin = 15% (3–26) metformin = 33% (11–49) Stroke: sulfonylurea/insulin = 9% (-13–27) metformin = 20% (-27–50) PVD: sulfonylurea/insulin = 18% (-19–44) metformin = 37% (-27–32) Microvascular disease: sulfonylurea/insulin = 24% (11–36) metformin = 16%(-17–40)	Combined macro- and micro-vascular events: 10% (2–18) Major macrovascular events: 6% (-6–16) Major microvascular events: 14% (3–23) Death any cause: 7% (-6–17) Nonfatal MI: 2% (-23–22) Nonfatal stroke: -2% (-24–15) PVD: 6% (-9–19) All CV events: 1% (-7–9)	Combined nonfatal MI, nonfatal stroke and CV death: 10% (-4–22) Death any cause: -22% (-11 to -46) CV death: -35% (-4 to -76) Nonfatal MI: 24% (8–38) Nonfatal stroke: -6% (-50 to -25) HF (fatal or nonfatal): -18% (-49 to 7)	Time to occurrence of major CV event (MI, stroke, CV death, HF, surgical intervention for cerebrovascular, cardiac, or PVD, inoperable CAD and amputation of ischemic gangrene): 12% (-5 to 26) Death any cause: 7% (-42 to 19)
Hypoglycemia: intensive vs standard therapy (%)	NR	2.7 vs 1.5	10.5 vs 3.5	24.1 vs 17.6

ALT: Alanine transaminase; BMI: Body mass index; CAD: Coronary artery disease; CI: Confidence interval; CVD: Cardiovascular disease; DM: Diabetes mellitus; HF: Heart failure; LVH: Left ventricular hypertrophy; MI: Myocardial infarction; NR: Not reported; PVD: Peripheral vascular disease; SD; Standard deviation; ULN: Upper limit normal.

people with diabetes are heterogeneous in terms of age and duration of diabetes (early middle-life diagnosis or recent onset in later life), as well as their multiple comorbidities and life expectancy, suggesting avoiding tight glycemic control in those patients with established cardiovascular disease, especially those at risk of hypoglycemia, but tight glycemic control in those newly diagnosed with diabetes or those without established cardiovascular disease. Cardiovascular outcome may vary among different hypoglycemic medications independent of glucose reduction. An early clinical trial suggested that sulfonylureas are cardiotoxic and may exacerbate diabetic cardiomyopathy [19]. However, this was not confirmed in the UKPDS. In a retrospective cohort study, patients commenced on insulin had a higher incidence of heart failure hospitalization than those commenced on sulfonylureas (HR: 1.56; 95% CI: 1.00–2.45; p = 0.05) [20]. In addition, another retrospective cohort study demonstrated that there was no effect of sulfonylureas on mortality (HR: 0.99; 95% CI: 0.91–1.08) [21]. Although insulin therapy has been demonstrated to predict the development of heart failure and mortality in diabetes [22,23], this was not shown in the UKPDS. However, insulin use is likely to start late in Type 2 diabetes when macrovascular disease could have already been established. Treating hyperglycemia with metformin seems to have additional cardiovascular benefit above and beyond glycemic control. In the UKPDS, metformin decreased all-cause mortality, particularly mortality due to myocardial infarction, in a subgroup of overweight subjects with Type 2 diabetes mellitus, even though the difference in HbA1c between the metformin group and the conventional therapy group was similar to the difference between the sulfonylurea–insulin group and the conventional therapy group [24]. The thiazolidinediones (TZDs) rosiglitazone and pioglitazone improve glycemic control, metabolic profile, and have been suggested as having potential cardiovascular benefits [25]. However, TZDs are associated with weight gain, edema [26] and increased risk of congestive heart failure [25]. The frequency of edema is approximately 5% when TZDs are used in mono or combination oral therapy, and approximately 15% when used with insulin [27]. Although there is concern of increasing risk of myocardial infarction and death with TZD treatment, the majority of TZD trials were limited to individuals younger than 65 years of age [25,28–30]. A recent study explored the association between TZD therapy and cardiac end points in older diabetics who are 66 years of age or more. In this study, after a median follow-up of 3.8 years, treatment with TZD monotherapy was associated with a significantly increased risk of congestive heart failure (RR: 1.60; 95% CI: 1.21–2.10; p < .001), acute myocardial infarction (RR: 1.40; 95% CI: 1.05–1.86; p = 0.02) and death (RR: 1.29; 95% CI: 1.02–1.62; p = 0.03). This increased risk with TZD use appeared to be limited to rosiglitazone [31]. In a recent meta-analysis of pioglitazone trials, death, myocardial infarction or stroke occurred in only 4.4% of patients receiving pioglitazone and 5.7% of patients receiving control therapy (HR: 0.82; 95% CI: 0.72–0.94; p = 0.005). However, serious heart failure was reported in 2.3% of the pioglitazone-treated patients and 1.8% of the control patients (HR: 1.41; 95% CI: 1.14–1.76; p = 0.002) [25]. It is not clear why these two TZDs have different effects on cardiovascular outcomes. It may be related to the favorable effect of pioglitazone on the lipid profile with greater reductions in serum triglycerides and increases in high-density lipoprotein cholesterol levels [32]. Although the cardiovascular outcome data for pioglitazone are reassuring, there is a need for randomized clinical trials in older people with diabetes for further clarification of the role of TZDs in cardiovascular risk reduction.

Dyslipidemia

Although the evidence for cholesterol lowering with statins is established for individuals up to the age of 80 years, there is some evidence of benefit from observational studies for those older than 80 years [33–35]. However, no mortality benefit was found for those aged above 80 years who received a statin, whereas those aged 65–79 years had a significant (11%) reduction in mortality. There was a trend towards mortality benefit in those aged 80–85 years versus those aged above 85 years [35]. The magnitude of risk reduction is similar in older and younger patients. In the Cholesterol Treatment Trialists Collaborators (CTTC) systematic prospective meta-analysis, those aged over 65 years had a 19% reduction in the risk of major cardiovascular events, a benefit similar to the 22% reduction in risk experienced by those aged under 65 years [36]. Although statins reduce the proportional risk as effectively in older as in younger people, limited data are available for elderly patients with Type 2 diabetes. In the CTTC meta-analysis, which included 18,686 patients with diabetes out of a total of 90,056 participants, there was a 21% reduction (95% CI: 19–23) in major vascular events per 1 mmol/l reduction in low-density lipoprotein

(LDL) cholesterol, and no difference in treatment effect between patients with and without diabetes [36]. In the updated CTTC meta-analysis of 18,686 diabetic patients with mean (standard deviation [SD]) age of 63.1 (8.9) years, there was a 9% reduction in all-cause mortality per mmol/l reduction in LDL cholesterol (rate ratio: 0.91; 99% CI: 0.82–1.01; p = 0.02), which was similar to the 13% reduction in those without diabetes (rate ratio: 0.87; 99% CI: 0.82–0.92; p < 0.0001). This finding reflected a significant reduction in vascular mortality (rate ratio: 0.87; 99% CI: 0.76–1.00; p = 0.008) and no effect on nonvascular mortality (rate ratio: 0.97; 99% CI: 0.82–1.16; p = 0.7) in participants with diabetes. In diabetic participants, there were reductions in myocardial infarction or coronary death (rate ratio: 0.78; 99% CI: 0.69–0.87; p < 0.0001), coronary revascularization (rate ratio: 0.75; 99% CI: 0.64–0.88; p < 0.0001) and stroke (rate ratio: 0.79; 0.67–0.93; p = 0.0002). Among people with diabetes, the proportional effects of statin therapy were similar, irrespective of whether there was a prior history of vascular disease and irrespective of other baseline characteristics including age. The incidence of major vascular events was reduced by approximately a fifth per mmol/l LDL cholesterol reduction in all age groups (RR: 0.77; 95% CI: 0.68–0.87 for patients ≤65 years and RR: 0.81; 95% CI: 0.71–0.92 for patients >65 years) [37]. In the Heart Protection Study, there were 5806 (28%) older patients above the age of 70 years and 5963 (29%) diabetics. The reduction in cardiovascular events was 25% after 5 years of follow-up in all subgroups. Although the RR reduction was similar in all subgroups, the absolute benefit depends on the individual's baseline risk, which is higher in diabetics [38]. In the *post hoc* analysis of the Collaborative Atorvastatin Diabetes Study (CARDS), treatment with 10 mg/day atorvastatin resulted in a 38% reduction in the RR (95% CI: -58 to -8; p = 0.017) of first major cardiovascular event in older patients (n = 1129; aged 65–75 years) and a 37% reduction (95% CI: -57 to -7; p = 0.019) in younger patients (n = 1709). Corresponding absolute risk reductions were 3.9 and 2.7%, respectively (difference: 1.2%, 95% CI: -2.8–5.3; p = 0.546), and numbers needed to treat (NNT) for 4 years to avoid one event were 21 and 33, respectively. All-cause mortality was reduced nonsignificantly by 22% (95% CI: -49–18; p = 0.245) and 37% (95% CI: -64–9; p = 0.98), respectively. The reduction in total cholesterol, LDL cholesterol and triglycerides, and the overall safety profile of atorvastatin, was similar between age groups [39]. It appears, from the evidence stated previously, that statins should be prescribed for older people with diabetes. Given the larger reduction in event rates, treatment would be expected to be more cost-effective in older than in younger patients [40].

Hypertension

Elderly persons with Type 2 diabetes derive more benefit from aggressive blood pressure lowering in reducing cardiovascular risk than those without diabetes. This risk reduction was even more impressive than the tight blood-glucose control in the UKPDS. The benefits of diastolic blood pressure reduction to 82 mmHg in the tight-control group versus 87 mmHg in the usual-care group dramatically outweighed those of intensive glucose control [41]. In the Hypertension Optimal Treatment (HOT) study, there was a 51% reduction of cardiovascular events by reducing diastolic blood pressure to less than 80 mmHg in comparison to diastolic blood pressure of 90 mmHg in the diabetic subgroup of patients. In contrast, participants without diabetes received no benefit from this further diastolic blood pressure reduction [42]. On the other hand, reduction of the systolic pressures from 175 to 153 mmHg reduced cardiovascular mortality by 16% in nondiabetic patients versus 70% for the diabetic patients in the Systolic Hypertension in Europe (Syst–Eur) trial, although the magnitude of blood pressure lowering was similar (22.0 ± 16 mmHg in non-diabetics vs 22.1 ± 14 mmHg in diabetics) [43]. This has also been demonstrated in the Systolic Hypertension in the Elderly Program (SHEP) study, with 34% (95% CI: 6–54) RR reduction in cardiovascular events . The absolute risk reduction was twice for diabetic as compared with nondiabetic patients, 10.1 versus 5.1%, respectively [44]. From these data, it appears that most older people with diabetes will benefit from tight blood pressure control, and to achieve that most patients will need a combination of at least two or three antihypertensive medications [45]. Data from five large clinical trials demonstrated that the average number of antihypertensive medications required to achieve a target blood pressure of 130/85 mmHg in diabetic subjects was 2.6–4.3 [46]. However, tight blood pressure control should avoid inducing symptomatic hypotension, especially in those frail older patients on multiple medications who are at risk of fall and fracturing the neck of the femur. Angiotensin-converting enzyme (ACE)

inhibitors may have a role in reducing cardiovascular risk in older diabetics. The elderly Heart Outcomes Prevention Evaluation (HOPE) trial, which included 2755 older patients aged 70 years or more with vascular disease or diabetes, demonstrated that those assigned to ramipril, when compared with those assigned to placebo, had fewer major vascular events (18.6 vs 24.0%; HR: 0.75; p = 0.0006), cardiovascular deaths (9.3 vs 13.0%; HR: 0.71, p = 0.003), myocardial infarctions (12.0 vs 15.6%; HR: 0.75; p = 0.006) and strokes (5.4 vs 7.7%; HR: 0.69; p = 0.013). Ramipril was generally safe and equally well tolerated in patients aged 70 years or more and those under 70 years. Due to the high baseline risk in elderly patients, the absolute risk reductions were higher. For example, the absolute risk reduction for the primary end point was 5.4% in patients aged 70 years or more and 3% for those under 70 years, so that for elderly patients the NNT to prevent one major cardiovascular event over 4.5 years was 18, compared with 33 for younger patients [47]. The cardiovascular benefits of ramipril were independent of blood pressure reduction. In the original HOPE study [48], ramipril reduced risk of the primary outcome (myocardial infarction, stroke and cardiovascular death) by 25% (12–36; p = 0.0004) in a group of 3577 diabetic patients compared with placebo after adjustment for the changes in systolic and diastolic blood pressures (Table 2). The cardiovascular benefits were greater than that attributable to the decrease in blood pressure. Also, the previous Captopril Prevention Project (CAPPP) study [49] demonstrated nonsignificant lower cardiovascular mortality on captopril treatment compared with conventional diuretic/β-blocker treatment. Although the fatal and nonfatal stroke was more common with captopril (RR: 1.25; 95% CI: 1.01–1.55; p = 0.044), this was probably due to the lower levels of blood pressure obtained initially in previously treated patients randomized to conventional therapy. β-blockers appear to be associated with an increased risk for new-onset diabetes mellitus, no benefit for reducing end points of death or myocaridal infarction, and with a 15% increased risk for stroke compared with other agents. In a meta-analysis of 12 studies including 94,492 patients, β-blocker therapy resulted in a 22% increased risk for new-onset diabetes (RR: 1.22; 95% CI: 1.12–1.33) compared with nondiuretic antihypertensive agents. The risk for diabetes was greater with atenolol, in the elderly, and increased exponentially with increased duration on β-blockers. On the other hand, calcium channel blockers (CCBs) and ACE inhibitors or angiotensin II receptor blockers (ARBs) resulted in 21 and 23% reductions, respectively, in the risk for new-onset diabetes, and their antihypertensive efficacy was superior compared with β-blockers [50]. Diuretics resulted in an increased risk for new-onset diabetes, but their blood-pressure-lowering efficacy was superior compared with β-blockers. This diabetogenic effect of β-blockers could contribute to uncontrolled glycemia in diabetic patients. In the UKPDS, patients taking atenolol required more frequent addition of new glucose-lowering agents than those taking captopril [41]. A recent meta-analysis demonstrated that the association of an antihypertensive class of drug on new-onset diabetes was lowest for ARBs and ACE inhibitors, followed by CCBs, β-blockers and diuretics in rank order [51]. The CCB (amlodipine), the diuretic (chlorthalidone) and the ACE inhibitor (lisinopril) had similar effects on cardiovascular outcome in a subgroup of 12,063 (36%) diabetic patients in the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [52]. A similar effect of equity of these classes of antihypertensive medications on the cardiovascular outcomes has also been demonstrated in the Swedish Trial in Old Patients with Hypertension-2 (STOP-2) and in the Intervention as a Goal in Hypertension Treatment (INSIGHT) study (Table 2) [53,54]. The ARBs reduce renal end points and also cardiovascular events [55–57]. In a subgroup analysis of 1195 patients with diabetes in the Losartan Intervention for Endpoint Reduction (LIFE) study, the losartan group had a substantially lower risk for cardiovascular end points and total mortality than the atenolol group. All-cause mortality was 63 in the losartan group and 104 in the atenolol group (risk reduction: 0.61, 95% CI: 0.45–0.84; p = 0.002) [58]. ARB and ACE inhibitors have similar antihypertensive efficacy, although ACE inhibitors cause higher rates of cough than ARBs [59]. Although antihypertensive therapy was evidence-based only in individuals up to the age of 80 years, the recently published Hypertension in the Very Elderly Trial (HYVET) provides evidence that antihypertensive treatment with the diuretic indapamide (sustained release), with or without the ACE inhibitor perindopril, in individuals aged 80 years or older, is associated with reduced risks of heart failure, death from stroke and death from any cause, although only around 7% of subjects were diabetics [60]. Optimal blood pressure control must be maintained if the cardiovascular protective benefits are to be sustained [61].

Table 2. Summary of trials of hypertension in patients with diabetes.

Study (year)	Population with diabetes	Intervention	Outcome	Ref.
UKPDS (1998)	1148, mean age 56 years	Tight BP control with captopril or atenolol (<150/85 mmHg) vs less tight control (<180/105 mmHg)	RRR (95%CI): DM-related end points: 24% (8–38), p = 0.0046 DM-related death: 32% (6–51), p = 0.019 Stroke: 44% (11–65), p = 0.013 Microvascular end points: 37% (11–56), p = 0.0092	[41]
HOT (1998)	1501, mean (SD) age 61.5 (7.5) years, range 50–80 years	Felodepine ± other agents to reduce DBP to three targets: ≤80 mmHg ≤85 mmHg ≤90 mmHg	51% reduction in major CV events and 30% in stroke in group with diastolic BP ≤ 80 mmHg compared with diastolic BP ≤90 mmHg, p = 0.005	[42]
Syst–Eur (1999)	492, age ≥60 years	CCB nitrendipine vs placebo to reduce SBP by ≥20 mmHg	RRR (95%CI) in: CV mortality: 70% (19–89), p = 0.01 All CV events: 62% (19–80), p = 0.002 Stroke: 69% (14–89), p = 0.02	[43]
SHEP (1996)	583, age ≥60 years	Diuretic chlorthalidone ± atenolol or reserpine vs placebo	RRR (95% CI) in: CV events: 34% (6–54)	[44]
HOPE/MicroHOPE (2000)	3577	Ramipril vs placebo	RRR (95%CI): Combined MI, stroke, CV death: 25% (12–36), p = 0.004 MI: 22% (6–36) Stroke: 33% (10–50) CV death: 37% (21–51) Total mortality: 24% (8–37) Revascularization: 17% (2–30) Nephropathy: 24% (3–40)	[48]
CAPPP (1999)	572, age 25–66 years	Randomized to captopril or diuretic/β-blocker	No difference in fatal/nonfatal MI, stroke, CV death: RR: 1.05 (0.9–1.220), p = 0.52 Lower mortality with captopril: RR: 0.77 (0.57–1.04), p = 0.09 More stroke with captopril: RR: 1.25 (1.01–1.55), p = 0.04	[49]
ALLHAT (2004)	12,063, mean age 66 years	Randomized to one of three treatments with chlorthalidone, amlodipine or lisinopril	No difference between three drugs on outcome (fatal and nonfatal MI or all-cause mortality	[52]

ACE: Angiotensin-converting enzyme; ALLHAT: Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; BP: Blood pressure; CAPPP: Captopril Prevention Project; CCB: Calcium channel blocker; CV: Cardiovascular; DBP: Diastolic blood pressure; DM: Diabetes mellitus; HF: Heart failure; HOPE: Heart Outcomes Prevention Evaluation; HOT: Hypertension Optimal Treatment; HYVET: Hypertension in the Very Elderly Trial; INSIGHT: Intervention as a Goal in Hypertension Treatment; LIFE: Losartan Intervention for Endpoint Reduction; MI: Myocardial infarction; RR: Relative risk; RRR: Relative risk reduction; SBP: Systolic blood pressure; SD: Standard deviation; SHEP: Systolic Hypertension in the Elderly Program; SR: Sustained release; STOP-2: Swedish Trial in Old Patients with Hypertension-2; Syst–Eur: Systolic Hypertension in Europe; UKPDS: United Kingdom Prospective Diabetes Study.

Table 2. Summary of trials of hypertension in patients with diabetes.

Study (year)	Population with diabetes	Intervention	Outcome	Ref.
STOP-2 (2000)	719, age range 70–84 years, mean 75.8 years	Randomized to one of three treatments with conventional therapy (diuretic or β-blocker), CCB or ACE inhibitor	Reduction of blood pressure was similar CV mortality was similar Fewer MI with ACE inhibitor compared with CCB: RR: 0.51 (0.28–0.92), p = 0.025 Nonsignificant more stroke with ACE inhibitor compared with CCB: RR: 1.16 (0.71–1.91)	[53]
INSIGHT (2003)	1302, age 55–80 years	Randomized to nifedipine or conventional therapy (β-blocker or diuretic)	No difference in CV death, MI, HF, stroke: RR: 0.9 (0.69–1.42), p = 1.0 All-cause mortality better for nifedipine: RR: 0.76 (0.59–0.97), p = 0.03	[54]
LIFE (2002)	1195, mean (SD) age 67 (7) years, range 55–80 years	Losartan vs atenolol	Risk reduction better for losartan compared with atenolol: CV death: 76% (58–98) All-cause mortality: 61% (45–84)	[58]
HYVET (2008)	263, mean age 83.6 years	Randomized to indapamide SR or placebo ± perindopril or placebo	Indapamide/perindopril better than placebo in reducing fatal or nonfatal stroke: RR: 30% (-1–51), p = 0.06 Stroke mortality: RR: 39% (1–62), p = 0.05 All-cause mortality: RR: 21% (24–78), p = 0.001	[60]

ACE: Angiotensin-converting enzyme; ALLHAT: Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; BP: Blood pressure; CAPPP: Captopril Prevention Project; CCB: Calcium channel blocker; CV: Cardiovascular; DBP: Diastolic blood pressure; DM: Diabetes mellitus; HF: Heart failure; HOPE: Heart Outcomes Prevention Evaluation; HOT: Hypertension Optimal Treatment; HYVET: Hypertension in the Very Elderly Trial; INSIGHT: Intervention as a Goal in Hypertension Treatment; LIFE: Losartan Intervention for Endpoint Reduction; MI: Myocardial infarction; RR: Relative risk; RRR: Relative risk reduction; SBP: Systolic blood pressure; SD: Standard deviation; SHEP: Systolic Hypertension in the Elderly Program; SR: Sustained release; STOP-2: Swedish Trial in Old Patients with Hypertension-2; Syst–Eur: Systolic Hypertension in Europe; UKPDS: United Kingdom Prospective Diabetes Study.

Multiple risks

Cardiovascular risk factors tend to cluster in what is known as the metabolic syndrome. Both age and diabetes increase the prevalence of metabolic syndrome. In a Norwegian study, the prevalence increased from 11.0% in the 20–29 years age group to 47.2% in the 80–89 years age group in men, and from 9.2 to 64.4% for women in the corresponding age groups [62]. In a population-based study of a sample of 5632 individuals of a caucasian cohort (65–84 years old), the prevalence was 64.9 and 87.1% in diabetic men and women, respectively, while in nondiabetics it was 25.9% in men and 55.2% in women [63]. Although metabolic syndrome is recognized as a risk factor for cardiovascular disease, in a prospective study of 1025 elderly subjects aged between 65 and 74 years [64] and a recent analysis of the outcome of two prospective studies in an elderly population above the age of 60 years, metabolic syndrome was demonstrated to be a maker of CVD, but did not enhance risk prediction above and beyond the risk associated with its individual components [65]. Older diabetics are likely to have multiple vascular risk factors at their first presentation with diabetes, and vascular disease is the most common cause of mortality. In the Cardiovascular Health Study, diabetes and increasing age were independent predictors of CHD fatality (odds ratio: 1.66; 95% CI: 1.10–2.31 and 1.21 per 5 years, 95% CI: 1.07–1.37, respectively) among 5888 adults aged over 65 years and followed up for a median of 8.2 years [66]. Identification of these risk factors is of vital importance in the initial evaluation of diabetic patients. Hyperglycemia should not be treated in isolation, but the holistic view of the collective cardiovascular risk should constitute a comprehensive plan of intervention and risk reduction in these patients. The comprehensive plan should start with lifestyle modifications. Lifestyle modifications include changes in diet, weight reduction, exercise and smoking cessation. Overweight elderly people are at increased risk of cardiovascular morbidity and this risk increases with increasing BMI [67]. Weight loss within this group has been demonstrated to reduce cardiovascular events, improve blood pressure control, improve insulin levels and reduce insulin resistance [67]. A diet that is high in fiber and potassium, and lower in saturated fat, refined carbohydrates and salt, improves the lipid profile and significantly lowers blood pressure [68]. Data from the Cardiovascular Health Study [69] revealed that older persons (≥65 years), who consumed a diet rich in fatty fish twice per week, had a 47% lower risk of coronary death compared with those who consumed fatty fish less than once per month, while high cereal fiber intake (approximately two whole-grain bread slices per day) was associated with a 14% lower risk of myocardial infarction or stroke. Compared with little activity, moderate and high leisure-time activity predicted 28% and 44% lower mortality, respectively [69]. Smoking cessation may be the single most effective means of reducing mortality in high-risk populations. 1 year of smoking cessation results in a reduction of the excess risk associated with current smoking of half or more. However, many years of abstinence are needed to reduce the risk of ex-smokers to that of nonsmokers [70]. The achievement of ideal body weight through diet changes and exercise will reduce overall cardiovascular risk, and will have a favorable effect on the metabolic profile of lipids, glycemia and blood pressure. In a small, randomized, controlled trial of patients with Type 2 diabetes comparing structured multifactorial intervention management including behavior modification, aspirin use and tight targets for blood glucose, blood pressure and lipids in a specialist setting with a conventionally managed group receiving usual care in a primary care setting, the risk of CVD was reduced by 0.47 (95% CI: 0.24–0.73) in the multifactorial intervention group after 8 years of follow-up [71]. The beneficial effect of multifactorial intervention was sustained after a total of 13.3 years of follow-up, with reduction in cardiovascular death in the multifactorial intervention group (HR: 0.43; 95% CI: 0.19–0.67; $p < 0.001$) [72]. The effects of aspirin are likely due to the fact that diabetes is associated with increased intrinsic platelet activation and decreased endogenous inhibitors of platelet activity [73]. Aspirin effects may vary in different diabetic populations, with no evidence of cardiovascular risk reduction in diabetic patients with no history of or asymptomatic vascular disease [74,75]. However, the use of aspirin 75 mg daily in the HOT study significantly ($p = 0.03$) reduced major cardiovascular events by 15%. This relative benefit of aspirin on major cardiovascular events and all myocardial infarctions was approximately the same in the groups of patients with and without diabetes mellitus [42]. In addition, it was found in a secondary prevention meta-analysis that aspirin significantly reduced cardiovascular events by 25%, although the analysis included diabetic

and nondiabetic patients [76]. It appeared from the multifactorial interventional trial that the use of statins and antihypertensive drugs might have had the largest effect in reducing cardiovascular events with hypoglycemic agents and aspirin, the next most important interventions [72]. This comprehensive approach is currently suboptimal. In a recent study to assess whether elderly patients with Type 2 diabetes use a comprehensive cardioprotective regimen (CCR) of antihypertensive, lipid-lowering and antiplatelet drugs in the year following oral antidiabetic drug initiation in 48,505 elderly diabetics above the age of 66 years, only 9912 (20.4%) used a CCR during the year following the first antidiabetic medication [77].

Conclusion

The combination of both diabetes and old age puts older diabetics at the highest baseline risk for cardiovascular disease. Although the RR reduction could be similar in both diabetics and nondiabetics, the absolute risk reduction is likely to be higher in diabetics. This will have favorable implications on the number needed to treat and more cost saving. Therefore, elderly diabetics stand to gain the most benefit of cardiovascular risk reduction. Although most of the clinical trials have excluded or included few older people, there is now enough evidence to suggest that aggressive treatment of risk factors in this age group is beneficial and cost-effective. Because of this, aggressive control of all risk factors is especially important in diabetics and includes both lifestyle modification and pharmacological intervention. This aggressive treatment is appropriate for elderly diabetics with life expectancy of approximately 5–10 years. For those with a limited life expectancy or multiple comorbidities, the objectives should be more conservative [78]. Many older diabetics may not achieve recommended targets for risk factor reduction due to various factors, such as multiple comorbidities, polypharmacy and intolerance of higher doses or multiple medications. However, even a small reduction in these risk factors is beneficial. Quality of life is the primary target in the care of older diabetics and a care plan should involve patients, families and carers, and will need to be considered on an individual basis. Care plans should include discussion with the patient and their carer as to whether the primary goal is tight intervention of risk factors or symptom relieve with avoidance of complications of both hyper- and hypo-glycemia. These goals should take into consideration patient and carer views, life expectancy, functional status of the patients and impact of tight control on patient quality of life.

Future perspective

The current evidence for blood pressure and lipid lowering in older people with diabetes is established. As their baseline risk is generally higher than both younger patients with diabetes and older people without diabetes, intervention to reduce these two risk factors in this group of patients is more cost-effective. There is no legacy effect for blood pressure control, and once control is lost the cardioprotection disappears [61]. However, the benefits of blood glucose control are still not very clear. It appears that there is good evidence for tight blood glucose control for new-onset diabetics who are at low risk of CVD. For older people the situation is more complex because of the diversity of this group of patients in terms of their biological age, functional status, polypharmacy and comorbidities. From the recently published trials (ACCORD, ADVANCE, VADT and UKPDS-follow-up), it appears that tight glycemic control will continue to be the target in the subgroup of older people who have a younger biological age, or who have recently been diagnosed with diabetes, and avoided in the frail group in whom risk of hypoglycemia is expected to be high. There will be a requirement for clinical trials specifically designed for older people with diabetes to explore the benefit of tight blood glucose control in this age group. With this unclear picture of blood glucose lowering, it appears that multifactorial risk reduction will continue to be aimed for, as the benefit seems to be greater for both blood pressure control and statin therapy followed by glucose control and antiplatelet therapy. In other words, cardiovascular risk reduction will be better seen as a package of the multiple risks treated together, rather than tackling each factor in isolation.

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Executive summary

Introduction

- Both aging and diabetes have profound structural and functional effects on the cardiovascular system by increasing cardiovascular risk in older people with diabetes.
- Although most of clinical trials have excluded older people, there is now enough evidence to suggest that aggressive reduction of cardiovascular risk factors is beneficial in this group of patients.

Hyperglycemia

- The benefit of tight glycemic control in older people with diabetes is not very clear in those with an already established cardiovascular disease; however, it appeared to be beneficial in those with new-onset diabetes without evidence of cardiovascular disease, and seems to emerge in the long term.
- In frail older people with diabetes and multiple comorbidities, tight glycemic control is better avoided, especially for those with a high risk of hypoglycemia.

Dyslipidemia

- Cholesterol-lowering with statins has the same benefits for older people as in younger people.
- Relative risk reduction is the same in older people with diabetes as in younger diabetics, but because older people with diabetes have higher baseline risk the absolute risk reduction in this group is higher.

Hypertension

- The impact of blood pressure reduction on cardiovascular risk is greater in older people with diabetes than in those without diabetes.
- The benefit of blood pressure control is even more significant than blood glucose control.
- Optimal blood pressure control must be maintained if the cardiovascular protective benefits are to be sustained.

Multiple risks

- Hyperglycemia should not be treated in isolation but should constitute a part of mutifactorial intervention including lifestyle modification, statins, antiplatelets and blood pressure control.
- As the baseline risk of older people with diabetes is high, absolute risk reduction is more beneficial and cost-effective than in younger people.

Conclusion

- Care plans should be individualized with an aggressive approach considered for older people with diabetes who have reasonable life expectancy, otherwise a conservative approach is appropriate.
- Quality of life is the primary target in the care of older diabetics and the care plan should involve patients, families and carers, and will need to be considered on an individual basis.

Future perspective

- There will be a requirement for clinical trials specifically designed for older people with diabetes to explore the benefit of tight blood glucose control in this age group.

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