Invited review

Diabetes and hypertension

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Abstract

Hypertension in diabetes is a prevalent risk factor with serious consequences, not only for the development of macrovascular endpoints in patients with both type 1 and type 2 diabetes, but also for microvascular endpoints. Based on modern therapies, often used in synergistic combinations, it is possible to reverse this development of increased risk. Recent randomised controlled trials have shown that tight blood pressure control is associated with improved prognosis, for example in patients with type 2 diabetes recruited for the blood pressure arm of the ADVANCE trial. It is still, however, not determined where the goal for blood pressure control should be based on evidence in these patients. In the still ongoing blood pressure arm of the ACCORD trial the hypothesis is currently being tested whether lowering the systolic blood pressure below 120 mm Hg might confer extra benefits as compared to the usual control (less than 140 mm Hg). Data are awaited in 2010.

Key words: diabetes, hypertension, insulin resistance, obesity, treatment, trials.

In patients with diabetes elevated blood pressure is very common and increases with age, duration of diabetes and the co-existence of target organ damage, most notably albuminuria and arterial stiffness [1]. Hypertension is more than twice as common in these patients as in the general population, affecting 10-30% of type 1 diabetic patients and 60-80% of those with type 2. Hypertension is also present in 20-40% of people with impaired glucose tolerance (IGT). The risk of both macro- and microvascular complications is increased in direct proportionality to the degree of blood pressure elevation during 24 h [2].

The association between hypertension and impaired glucose metabolism/diabetes mellitus has long been recognised. In 1923, the Swedish physician Eskil Kylin described a syndrome of diabetes, hypertension and hyperuricaemia [3], which are now regarded as aspects of the broader metabolic syndrome that has been linked to insulin resistance [4]. The relationship between diabetes and hypertension is however complex. Both conditions are common and so they are sometimes likely to be associated only by chance. However, in some instances they may have a common cause. Hypertension can develop as a consequence of diabetic nephropathy, while some drugs used to treat hypertension can induce hyperglycaemia and new-onset diabetes (NOD), e.g. high-dose thiazide diuretics and β-receptor blockers [5].

Hypertension is also a risk factor for microvascular complications, such as nephropathy and retinopathy. The management of hypertension in

diabetes has been widely debated, and treatment strategies and appropriate drug therapy have still to be agreed. During the last two decades, several large-scale trials have added considerably to the evidence, demonstrating convincingly the benefits of lowering blood pressure but also how difficult it can be to achieve this in clinical practice. One recommendation should therefore be to follow mean blood pressure levels over time in cohorts of treated patients as shown in the National Diabetes Register (NDR) of Sweden [6].

Definitions of blood pressure levels

Hypertension is generally defined if above a mean level after several recordings of 140/90 mm Hg. People with diabetes are still at risk of macrovascular and microvascular complications at blood pressure levels well below these thresholds, and the optimal treatment target range is therefore lower (130/80 mm Hg) for all patients that can tolerate such blood pressure reduction. In the ongoing blood pressure arm of the ACCORD trial an even lower systolic blood pressure goal is aimed for, less than 120 mm Hg [7]. Results are awaited with interest in 2010.

Causes and consequences of hypertension in diabetes

Essential hypertension and isolated systolic hypertension are both common in the non-diabetic population, especially in the elderly. It is estimated that essential hypertension accounts for about 10% of cases in diabetic people. Other important causes are the hypertension that coexists with insulin resistance, obesity and glucose intolerance in the metabolic syndrome [8], or is secondary to diabetic nephropathy.

Hypertension worsens both macrovascular and microvascular complications in diabetes. The effects of blood pressure on the risk of fatal coronary heart disease (CHD) are 2-5-fold greater than in non-diabetic people, and hypertension accentuates the deleterious influence of diabetes on left ventricular mass and function. The risks of nephropathy and end-stage renal failure are also increased 2-3-fold by hypertension.

Hypertension and diabetic nephropathy

This association is most obvious in young type 1 diabetic patients, in whom the presence of hypertension is strikingly related to renal damage and even minor degrees of proteinuria. Blood pressure begins to rise when the albumin excretion rate (AER) enters the microalbuminuric range (>30 mg/day) and is usually over the WHO threshold (140/90 mm Hg) when AER reaches the macroalbuminuric stage (>300 mg/day) [9]. The association may be partly genetically determined. Diabetic subjects with microalbuminuria commonly have parents with hypertension and may also inherit over-activity of the cell-membrane Na^+-H^+ pump (indicated by increased Na^+-Li^+ counter-transport in red blood cells) which would tend to raise intracellular Na^+ concentrations and thus increase vascular smooth muscle tone [10].

The basic mechanisms of hypertension include decreased Na^+ excretion with Na^+ and water retention. Peripheral resistance is increased, to which raised intracellular Na+ will contribute. The role of the renin-angiotensin-aldosterone system (RAS) is uncertain, as both increased and decreased activity have been reported [11, 12]. These discrepancies may be explained by differences in diet, treatment, metabolic control and the type and duration of diabetes. Na^+ retention and hypertension would be predicted to suppress the RAS, while renin levels may be influenced by other complications of diabetes. Neuropathy can also lower plasma renin, while renin may be raised in retinopathy and advanced nephropathy. Patients with microalbuminuria who are insulin resistant appear to be particularly susceptible to hypertension [13].

Impact of hypertension in diabetes on target organs

A large proportion of hypertensive diabetic patients show signs of target-organ damage, particularly affecting the cardiovascular system [14]. Hypertension, as an independent risk factor for atherogenesis, synergises with the effects of diabetes and significantly increases the development and progression of CHD, cerebrovascular disease and peripheral vascular disease.

The deleterious effects of hypertension on left ventricular function are also accentuated by the presence of diabetes. These include impaired left ventricular relaxation [15] and increased left ventricular mass, LVH [16] – the latter being an independent predictor of premature death from CHD. Also diastolic dysfunction seems to be present in patients with long-standing diabetes complicated by hypertension. In addition the influence of arterial stiffness and early vascular ageing (EVA) will add to the elevated blood pressure and LVH in patients with diabetes [17].

Hypertension predisposes to the development of certain microvascular complications, particularly nephropathy and end-stage renal failure, for which the risk is increased by 2- to 3-fold. It is also a risk factor for retinopathy, as has been confirmed by the beneficial effects of improved blood pressure control in type 2 diabetic patients, reported by the United Kingdom Prospective Diabetes Study [18].

Diagnosis of hypertension in diabetes

The criteria issued by the European Society of Hypertension (ESH) define hypertension as an office blood pressure exceeding 140/90, and borderline hypertension as being below these limits but above 130 systolic and/or 85 mm Hg diastolic [19].

It is clear from numerous epidemiological studies that this threshold is too high in diabetic subjects because of their additional risk of both macro- and microvascular disease, and that there are definite benefits from treating microalbuminuric subjects whose diastolic pressure is <90 mm Hg [19]. A consensus would be to aim for a blood pressure of less than 130 mm Hg systolic and below 80 mm Hg diastolic, if tolerated.

All diabetic patients should have their blood pressure checked at diagnosis and at least annually thereafter. This is especially important in those with other cardiovascular risk factors, such as nephropathy, abdominal obesity, dyslipidaemia, smoking or poor glycaemic control in general.

Management of hypertension in diabetes

Data from randomised trials have increasingly shown the benefits of tight blood pressure control in patients with type 2 diabetes [20]. Current guidelines have therefore emphasised the screening, evaluation, and vigorous treatment of elevated blood pressure if combined with diabetes [21], especially systolic blood pressure.

Strict blood pressure control is the primary goal of treatment, less than 130/80 mm Hg, for all patients who can tolerate this without suffering side-effects such as orthostatic reactions or compromising arterial circulation in critical vascular beds. Management begins with lifestyle modification, but few patients respond to this alone, and most will require more than one antihypertensive drug to control blood pressure adequately [22].

Lifestyle intervention

This should include weight reduction or weight stabilisation in the obese, sodium restriction, diet modification and regular physical exercise of moderate intensity (40-60 min, 2-3 times a week). Dietary intake of saturated fat has been associated with impairment in insulin sensitivity [23] and should therefore be reduced. Alcohol should be restricted to 3 and 2 units/day in men and women respectively, but omitted altogether if hypertension proves difficult to control. In some cases of therapy resistance the true contributing factor is poor compliance caused by alcohol over-consumption.

Smoking causes an acute increase in blood pressure and greater variability overall [24]. Smoking cessation is especially important, as smoking not only accelerates the progression of atherosclerosis, but also impairs insulin sensitivity [25] and worsens albuminuria [26]. Treatment with nicotine supplementation for 4-6 weeks (chewing gum or patches) or drugs such as bupropion or varenicline may be useful. When adopted by the patient, lifestyle modification can be very effective and facilitate the effectiveness of concomitant drug therapy [27].

Anti-hypertensive drug therapy

Several drugs are available to lower blood pressure, but some are better suited than others to the particular needs of diabetic people because of their favourable or neutral effects on glucose metabolism. Most patients (at least two-thirds) will require combinations of antihypertensive drugs to control blood pressure. Accordingly, the clinician must be able to use a wide variety of antihypertensive drugs and to choose combinations for pharmacological synergy. Combination therapy usually means that lower dosages of individual drugs can be used, thus reducing the risk of their adverse effects.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme (ACE) inhibitors may be used in most cases of diabetic hypertension, even in cases where the RAS in general is not activated; instead, the drugs may interfere with local angiotensin action in specific target tissues.

Angiotensin-converting enzyme inhibitors have no adverse metabolic effects, and may also improve insulin sensitivity [28]. Even hypoglycaemia has been reported [29]. These drugs are particularly beneficial in diabetic nephropathy, by reducing albuminuria and possibly delaying progression of renal damage [30]. Their anti-proteinuric effect may be due specifically to relaxation of the efferent arterioles in the glomerulus (which is highly sensitive to vasoconstriction by angiotensin II), thus reducing the intraglomerular hypertension that is postulated to favour albumin filtration; however, the importance of this mechanism remains controversial [31]. Angiotensin-converting enzyme inhibitors are also indicated in cardiac failure, in combination with relatively low dosages of thiazide diuretics. A dry cough is reported by 10-15% of patients treated with ACE inhibitors, because these drugs also interfere with the breakdown of kinins in the bronchial epithelium. Changing to another ACE inhibitor or an angiotensin II receptor blocker may avoid this problem. Side-effects (rashes, neutropenia, taste disturbance, angioedema) are unusual with the low dosages currently recommended but become more prominent in renal failure. Because ACE inhibitors cause potassium retention, they should not generally be taken together with potassium-sparing diuretics (spironolactone and amiloride) or potassium

supplements. Serum creatinine and potassium levels should be monitored regularly, especially in patients with renal failure or renal tubular acidosis, in whom hyperkalaemia can rapidly reach dangerous levels.

The first dose of an ACE inhibitor should be low and taken just before bedtime to minimise postural hypotension, which may be marked in subjects receiving diuretics or on a strict sodium-restricted diet. The same problem may arise in patients with autonomic neuropathy. Angiotensin-converting enzyme inhibitors are recommended in patients with left ventricular dysfunction following myocardial infarction. Ramipril has been shown to prevent cardiovascular morbidity and mortality in high-risk diabetic patients, with or without pre-existing ischaemic heart disease [32].

Angiotensin II receptor antagonists

This promising new class includes drugs which act on the angiotensin II (AT_1) receptor to decrease blood pressure. They are metabolically neutral [33], and unlike the ACE inhibitors, do not cause cough. They are effective antihypertensive drugs in diabetic patients [34] and have been shown to slow the progression of nephropathy in diabetes patients with varying degrees of albuminuria [35-37]. Data from the ONTARGET trial comparing an angiotensin II (AT_1) receptor antagonist (telmisartan) with an ACE-inhibitor (ramipril) showed similar results for both these drugs as well as with the combination for cardiovascular events reduction [38].

Diuretics

Diuretics are often effective antihypertensive agents in diabetes, in which the total body sodium load is increased and the extracellular fluid volume expanded [39]. However, diuretics that increase urinary potassium and magnesium losses can worsen hyperglycaemia, as insulin secretion is impaired by potassium depletion and insulin sensitivity in peripheral tissues may also be decreased. The use of high-dose thiazide diuretics is reported to increase the risk of non-diabetic hypertensive patients developing diabetes by up to 3-fold [22]. This does not seem to occur to the same degree with use of low dosages. Potassium depletion is particularly severe with high-dose chlorthalidone, less with furosemide and bendrofluazide and apparently negligible with indapamide. Thiazides may also aggravate dyslipidaemia, although low dosages probably carry a low risk. These drugs have also been associated with gout and impotence and are generally avoided in middle-aged diabetic men with hyperuricaemia or erectile dysfunction. Diuretics may precipitate hyperosmolar, non-ketotic coma and should be avoided or used at the lowest effective dose in patients with a history of this complication.

Diuretics have been shown to successfully prevent cardiovascular disease in elderly subjects with type 2 diabetes and systolic hypertension [40]. Overall, these drugs are effective and safe when used appropriately at low dosage in diabetic patients, often for combination therapy, sometimes in combination with potassium supplements or potassium-sparing drugs like amiloride. If ineffective, diuretics should be combined with another first-line drug, e.g. an ACE inhibitor or an angiotensin II receptor antagonist, rather than given at increased dosage. Spironolactone is normally not combined with an ACE inhibitor, as this increases the risk of hyperkalaemia. Furosemide is useful in patients with renal impairment (serum creatinine >150 µmol/l) or oedema. Serum urea, creatinine and potassium should be checked when starting diuretic therapy and every 6-12 months thereafter, as hyperkalaemia can develop, especially in patients with renal impairment.

β-adrenergic receptor blocking agents

β-Receptor blockers may significantly lower blood pressure levels in diabetic patients with hyper-tension, even though renin release (a major target for these drugs) is commonly reduced in diabetes because of sodium and fluid retention. Another mechanism of action is to reduce blood pressure, heart rate and cardiac output via interference with β_1 and β_2 receptors in the myocardium and in the vessel wall.

Like diuretics, β-receptor blockers may aggravate both hyperglycaemia and dyslipidaemia. These effects depend on both dosage and the degree of selectivity of the individual drug. The hyperglycaemic effect is attributed to inhibition of β_2-adrenergic- mediated insulin release and decreased insulin action in peripheral tissues. The long-term risks of a non-diabetic person developing the disease may be increased by 6-fold and even more if given together with thiazides, so this combination is not recommended [22]. The metabolic side-effects of β-blockers can be reduced by using low dosages combined with other agents, particularly dihydropyridine calcium antagonists, or by intensifying efforts to decrease weight and improve physical activity.

β-Blockers have other side-effects relevant to diabetes. They may interfere with the counter-regulatory effects of catecholamines released during hypoglycaemia, thereby blunting manifestations such as tachycardia and tremor and delaying recovery from hypoglycaemia [41]. In clinical practice, however, this rarely presents a serious problem, especially when cardioselective β_1-blockers are used. β-Blockers may also aggravate erectile dysfunction, and are generally contraindicated in second- or third-degree atrioventricular (AV) heart block, severe peripheral vascular disease, asthma and chronic airway obstruction.

In the UKPDS, clinical effects of atenolol were comparable to those of the ACE inhibitor captopril [42]. Both non-selective and selective β-blockers are effective in the secondary prevention of myocardial infarction after an initial event in diabetic patients [43]. β-Blockers in general are useful in patients who also have angina or tachyarrhythmias.

Calcium channel antagonists

These vasodilator agents do not generally worsen metabolic control when used at conventional dosages, although sporadic cases of hyperglycaemia have been reported [44]. This may be due to inhibition of insulin secretion (a calcium-dependent process) in susceptible patients, or to a compensatory sympathetic nervous activation (which antagonises both insulin secretion and action) following vasodilatation.

Calcium antagonists exhibit a slight negative inotropic effect and are contraindicated in significant cardiac failure; they often cause mild to moderate ankle oedema. This is due to relaxation of the peripheral precapillary sphincters and raised capillary pressure rather than to right ventricular failure. Because of their potent vasodilator properties, these drugs can cause postural hypotension and can aggravate haemodynamic effects of autonomic neuropathy.

Because of their other cardiac actions, these drugs are particularly indicated in hypertensive patients who also have angina, or supraventricular tachycardia (e.g. verapamil). Their vasodilator properties may also be beneficial in peripheral vascular disease. Calcium antagonists are ideally combined with selective β_1-blockers, but the specific combination of verapamil and β-blockers (especially together with digoxin) must be avoided because of the risk of conduction block and asystole. Overall, calcium channel antagonists appear to be less cardioprotective, but better at preventing stroke than either β-blockers or thiazide diuretics [45].

α_1-Adrenoreceptor antagonists

α_1-Blockers can lower blood pressure effectively and also improve dyslipidaemia and insulin sensitivity [46]. Doxazosin is normally well tolerated, especially in combination therapy, and side effects include nasal congestion and postural hypotension.

Overview of clinical trials for hypertension in diabetes

The assumption that improved blood pressure control would improve cardiovascular and other prognoses in type 2 diabetes has been confirmed by the United Kingdom Prospective Diabetes Study (UKPDS) [18]. In this landmark study, tighter blood pressure control (averaging 144/82 mm Hg) for over 8 years led to significant improvements in several outcomes, as compared with less strict control that averaged 154/87 mm Hg. The most powerful effects were related to microvascular complications (retinopathy and nephropathy), although significant reductions were seen in the risk of stroke (44%) and heart failure (56%). Myocardial infarction and peripheral vascular disease showed non-significant reductions. Overall, therefore, tight blood pressure control has been proven to provide substantial benefits for hypertensive diabetic patients. This treatment strategy also seems to be cost-effective [47]. In the recent 10-year follow-up study of the UKPDS it was however shown that the benefits of tight blood pressure control did not last as also patients in the control group achieved a similar degree of blood pressure control soon after termination of the randomised study period [48]. This means that blood pressure lowering medications should not be terminated or reduced as otherwise the clinical benefits will soon diminish.

In the Systolic Hypertension in the Elderly Program (SHEP) low-dose, diuretic-based treatment was found to be effective compared with placebo in preventing CV complications in elderly patients with type 2 diabetes mellitus (n=583) and isolated systolic hypertension [40]. Similarly, the Systolic Hypertension in Europe (Syst-Eur) Trial compared calcium-antagonist based treatment with placebo in elderly patients with isolated systolic hypertension and in a rather large subgroup with type 2 diabetes (n=492). In Syst-Eur, treatment for 5 years prevented 178 major CV events in every 1000 diabetic patients treated [49], i.e. approximately 6 patients had to be treated for five years to prevent one major CV event.

The Hypertension Optimal Treatment Study (HOT) [50] investigated the intensity of antihypertensive treatment using a calcium-antagonist as baseline therapy in hypertensive patients averaging 61.5 years of age and 170/105 mm Hg in baseline BP of whom 1.501 also had type 2 diabetes. In HOT the incidence of major CVD events was lowered from 24.4 to 18.6 and 11.9 events/1000 patient-years, respectively, in the randomised tertiles of diabetes patients who had achieved 84, 82 and 81 mm Hg, respectively, in diastolic BP.

Also nearly normotensive subjects with diabetes may sometimes benefit from the use of drugs with blood pressure lowering properties. The results of the Heart Outcomes Prevention Evaluation (HOPE) Study and the Microalbuminuria, Cardiovascular, and Renal Outcomes (MICRO) HOPE substudy [32] showed that treatment with the ACE-inhibitor ramipril compared with placebo significantly lowered the risk of CVD events (by 25%) and overt nephropathy in people with type 2 diabetes with a previous CVD event or at least one other risk

factor, including 56% with a history of hypertension. Uncontrolled diabetic hypertensives (BP >160/90 mm Hg) were however not randomised. HOPE was not a hypertension trial, but gives an argument in favour of blockade of the RAS in cardiovascular risk patients with diabetes.

In the Losartan Intervention For Endpoint reduction (LIFE) trial [51], a subgroup of 1195 patients with diabetes, hypertension, and signs of LVH on electrocardiograms were randomised to either a losartan-based or atenolol-based treatment. Mortality from all causes was 63 and 104 in losartan and atenolol groups, respectively; RR 0.61 (0.45-0.84), P=0.002. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [52] a subgroup of 12 063 patients (36%) with diabetes were randomised to treatment with chlorthalidone, amlodipine, or lisinopril. There were no differences in the primary composite CV outcome between these three drugs, used in a very heterogeneous study population according to ethnicity.

In the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial, 15 245 patients, aged 50 years or older with treated or untreated hypertension and high risk of cardiac events, participated in a randomised trial based on valsartan or amlodipine. The primary endpoint was defined as a composite of cardiac mortality and morbidity. Patients were followed up for a mean of 4.2 years. Blood pressure was reduced by both treatments, but the effects of the amlodipine-based regimen were more pronounced, especially in the early period. The primary composite endpoint occurred in 810 patients in the valsartan group (10.6%, 25.5/1000 patient-years) and 789 in the amlodipine group (10.4%, 24.7/1000 patient-years; HR 1.04, P=0.49). Valsartan treatment reduced new onset diabetes by 23%. The main outcome of cardiac disease did not differ between the treatment groups and not for patients with diabetes [53].

The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) trial was a prospective, randomised controlled trial in 19 257 patients with hypertension who were aged 40-79 years and had at least three other cardiovascular risk factors [54]. Patients were assigned either amlodipine adding perindopril as required (amlodipine-based regimen) or atenolol adding bendroflumethiazide and potassium as required (atenolol-based regimen). The primary endpoint was non-fatal myocardial infarction (including silent myocardial infarction) and fatal CHD. The study was stopped prematurely after 5.5 years' median follow-up and accumulated in total 106 153 patient-years of observation. Though not significant, compared with the atenolol-based regimen, fewer individuals on the amlodipine-based regimen had a primary endpoint (HR 0.90, 95% CI 0.79-1.02, P=0.1052), fatal and non-fatal stroke (HR 0.77, 0.66-0.89, P=0.0003), and all-cause mortality (HR 0.89, 0.81-0.99, P=0.025). The incidence of developing diabetes was lower on the amlodipine-based regimen. The amlodipine-based regimen prevented more major cardiovascular events than the atenolol-based regimen, and this was the same also for patients with established diabetes [54].

In the Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE) trial 11 140 patients with type 2 diabetes were randomised to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy (Figure 1) [55]. The primary endpoints were composites of major macrovascular and microvascular events, defined as death from cardiovascular disease, non-fatal stroke or non-fatal myocardial infarction, and new or worsening renal or diabetic eye disease. After a mean of 4.3 years of follow-up, 73% of those assigned active treatment and 74% of those assigned control remained on randomised treatment. Compared with patients assigned placebo, those assigned active therapy had a mean reduction in systolic blood pressure of 5.6 mm Hg and diastolic blood pressure of 2.2 mm Hg. The relative risk of a major macrovascular or microvascular event was reduced by 9%, HR 0.91 (95% CI 0.83-1.00, P=0.04). The separate reductions in macrovascular and microvascular events were similar but were not independently significant. The relative risk of death from cardiovascular disease was reduced by 18%, HR 0.82 (0.68–0.98, P=0.03) and death from any cause was reduced by 14%, HR 0.86 (0.75-0.98, P=0.03). The authors of the ADVANCE trial conclude that routine administration of a fixed combination of perindopril and indapamide to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death. The results suggested that over 5 years, one death due to any cause would be averted among every 79 patients assigned active therapy.

Treatment strategies

In general, lifestyle modification should be tried initially for a few months or so, but if severe hypertension (diastolic >110 mm Hg) or signs of hypertensive tissue damage are present drug therapy should be started immediately. Initially, mono-therapy with one of the first-line drugs suggested below should be used, the choice being influenced by other factors such as coexistence of angina, LVH, heart failure, or nephropathy.

Hypertension in type 1 diabetes

Angiotensin-converting enzyme inhibitors are especially suitable if the patient has albuminuria or

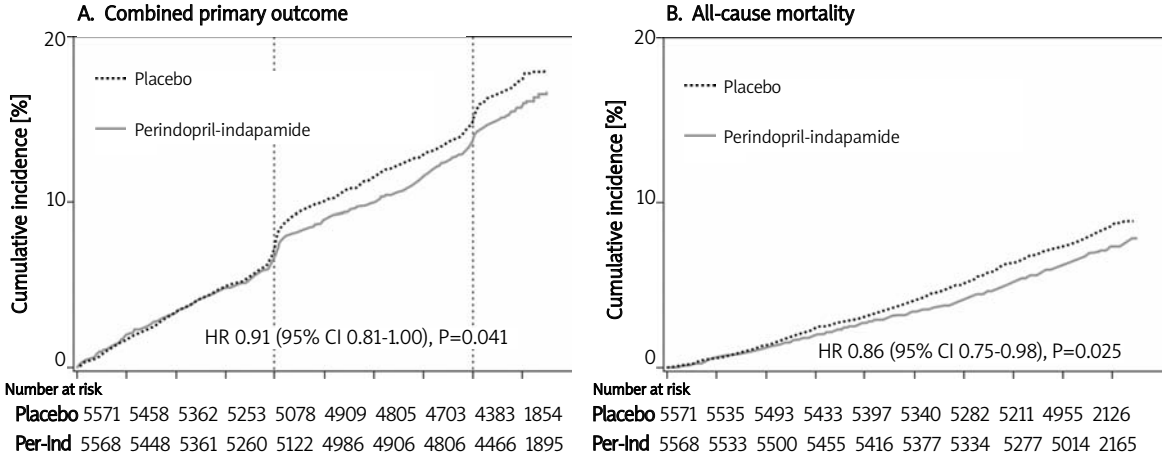

Figure 1. Kaplan-Meier curves for the primary outcome and all-cause mortality in the two study groups in the ADVANCE Trial [55]. The combined primary outcome was a composite of major macrovascular and microvascular events. Major macrovascular events were cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Major microvascular events were new or worsening nephropathy or retinopathy

more advanced stages of diabetic nephropathy. Diuretics, calcium antagonists and β_1-selective blockers (as second line) are equally useful alternatives with regard to blood pressure reduction.

If renal function is moderately impaired (serum creatinine values >150 µmol/l), thiazide diuretics become less effective and loop diuretics should be used instead. However, in established renal failure (serum creatinine >500 µmol/l), furosemide may be toxic and dialysis must be started. In some patients, hypoglycaemia attacks may be masked by use of β-blockers.

Hypertension in type 2 diabetes

Blood pressure control is generally more important than the choice of individual drugs. First-line antihypertensive drugs suitable for use in diabetic patients are ACE inhibitors and angiotensin-II (AT_1) receptor antagonist (ARB) to block RAS, but also low-dose diuretics (e.g. in combination with agents that block the RAS), cardioselective β-blockers (UKPDS), and calcium-channel antagonists. Drugs can be selected for their beneficial effects on coexistent problems, e.g. angina or arrhythmia (β-blockers, calcium antagonists), heart failure (ACE inhibitors, ARB, certain β-blockers), previous myocardial infarction (ACE inhibitors, β-blockers), or nephropathy (ACE inhibitors, ARB).

Ramipril has strong evidence-based support for its use in type 2 diabetic patients because of their high cardiovascular risk. β-Receptor blockers (in combination with low-dose aspirin) are indicated as secondary prevention for patients who have suffered a myocardial infarct, as long as no serious contraindications are present. Low doses of thiazide diuretics are useful in elderly diabetic patients, as this class of drugs has proven efficacy in preventing stroke and all-cause mortality in elderly hypertensives, also with diabetes [56]. Indapamide is well tolerated and with no metabolic side effects. Spironolactone may also be of value, especially for elderly, obese female patients with hypertension and hypervolaemia with a low-renin profile. α_1-receptor blockers may be used as part of combination therapy, especially in patients with dyslipidaemia (high triglycerides, and low HDL cholesterol levels) and prostatic hyperplasia.

Combination therapy

Combination therapy is needed in most diabetic patients (especially those with type 2 diabetes) to achieve satisfactory blood pressure control. It is often better to use low-dose combinations than to increase dosages of single agents, as side effects are commonly dose-dependent. Potassium-sparing agents (spironolactone and amiloride) should not be combined with an ACE inhibitor because of the increased risk for hyperkalaemia.

Certain combinations of antihypertensive drugs have proved very safe and effective in low to moderate doses, e.g. ACE inhibitor/ARB + low-dose thiazide diuretic; calcium antagonist + ACE inhibitor; selective β_1-blocker + calcium antagonist; or β-blocker + α_1-blocker.

The ONTARGET was a very large, randomised, controlled intervention study in patients (n=25 620) at high cardiovascular risk (69% hypertensives), recruited at 733 centres in 40 countries, which means that the results are globally applicable [38]. The primary aim was to show non-inferiority of treatment with the angiotensin-2 receptor blocker telmisartan 80 mg in comparison with the ACE-inhibitor ramipril 10 mg. It also included the aim to show whether a combination of telmisartan and ramipril was more effective than ramipril alone.

The primary composite end-point was cardiovascular mortality, myocardial infarction, stroke, and hospitalisation for congestive heart failure. The main results showed non-inferiority for telmisartan but no added benefits with the combination treatment as compared to ramipril alone. In fact, the combination was associated with more adverse effects and study termination of patients with renal failure, as defined by the participating physicians themselves.

This was the first large clinical trial to compare two different, but related, methods to block the renin-angiotensin system. As no difference was found between the drugs this means that both ramipril and telmisartan can be used, and that other factors such as tolerability, side effects and pricing should guide prescription. There is no need to combine the two drugs, but further analyses in relation to changes in proteinuria will possibly shed more light on this. Not all data have been published in the first publication. As ramipril and telmisartan are equally effective, the choice between them can be determined by other factors (side effects, pricing). If ramipril is not tolerated, telmisartan is a good choice.

Finally, in the ACCOMPLISH trial [57] the use of fixed combinations was tried in a randomised controlled trial in 5721 patients (60% with diabetes) randomised to an ACE inhibitor and a calcium antagonist (benazepril and amlodipine) or in 5741 patients given an ACE inhibitor and a diuretic (benazepril and hydrochlorothiazide) for evaluation of non-fatal myocardial infarction or stroke, as well as hospitalisation for unstable angina or revascularisation). Inclusion criteria were age over 60 years and systolic blood pressure above 160 mm Hg or on antihypertensive therapy, and a history of cardiovascular disease or signs of target organ damage. The results showed that the first combination (benazepril and amlodipine) was clinically better than the comparative combination for the primary end-point, RR 0.80 (95% CI 0.72-0.90, P=0.002). These results underline that the combination of an ACE inhibitor and a dihydropyridine type of calcium antagonist is very effective and should be used more widely in at-risk patients.

In conclusion, the general consensus for treatment of hypertension in type 2 diabetes is now aggressive blood pressure lowering (<130/80 mm Hg), usually based on polypharmacy with synergistic drug combinations, and most available drugs are useful [58]. This should be part of overall ambitious risk factor control, also addressing smoking, dyslipidaemia, and hyperglycaemia, as shown in the Steno-2 trial [59]. Treatment with an ACE inhibitor has been shown to be effective in preventing macro- and microvascular events in high-risk diabetics with controlled hypertension, and should be used in most patients [60]. If not well tolerated, an ARB could be a useful alternative.

Based on evidence, the following conclusions can be made:

1) patients with type 2 diabetes should be aggressively treated for hypertension when blood pressure is above 140 and/or 90 mm Hg, aiming at blood pressure <130/80 mm Hg,

2) these patients usually need two or more drugs/combination therapy to reach the BP target, especially for systolic BP,

3) although ACE inhibitors have been proven to be cardiovascular protective and some angiotensin-II receptor blockers nephroprotective, there is no consensus on the "drug of choice" for all hypertensive type 2 diabetic patients,

4) most studies support the notion that blood pressure reduction *per se* is more important than individual properties of specific drugs in most cases,

5) blockade of the renin-angiotensin system seems to be an appropriate choice for being one of the partner drugs in offering combination therapy to hypertensive patients with diabetes or glucose intolerance.

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