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The association of hypertension and diabetes: prevalence, cardiovascular risk and protection by blood pressure reduction

Abstract Diabetes and hypertension frequently coexist, and their combination provides additive increases in the risk of life-threatening cardiovascular events. Recent guidelines agree on the need for early, aggressive reduction of blood pressure, with a goal of <130/80 mmHg, in patients with diabetes. The mechanism that underpins the increased sensitivity of diabetic subjects to hypertension is not known, but may involve impaired autoregulation or attenuated nocturnal decrease of blood pressure. All classes of antihypertensive agents are effective in reducing blood pressure in diabetic subjects, and all show evidence of a concomitant reduction in cardiovascular risk. Although there is some evidence that agents that interrupt the renin–angiotensin system (RAS) provide greater protective effects, the data are not conclusive. However, most diabetic subjects will require combination therapy to reach goal blood pressure. Antihypertensive drugs can also significantly influence the probability that otherwise healthy individuals will develop metabolic syndrome or type 2 diabetes. While diuretics and beta-blockers have a prodiabetic effect, angiotensin–converting enzyme inhibitors and angiotensin II receptor blockers may prevent diabetes more effectively than the metabolically neutral calcium channel blockers. Given that diabetes is an important cardiovascular risk factor, there is the potential for reductions in risk due to reduced blood pressure to be offset by an increased risk due to the development of diabetes. Such concerns should be considered in the selection of antihypertensive therapy.

Key words Antihypertensives · Diabetes · Diuretics · Angiotensin II receptor blockers · Calcium channel blockers · Cardiovascular risk

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Introduction

Hypertension is a common co-morbidity in diabetes, although the natural history differs in type 1 and type 2. Type 1 patients typically develop hypertension some years after the diagnosis of diabetes, especially those with nephropathy, whereas type 2 diabetic patients frequently present with hypertension at the time of diagnosis [1]. And while diabetes is a recognised risk factor for hypertension, it is also becoming increasingly clear that hypertension is a risk factor for diabetes, independently of another important risk factor – body fat. In the 12 500 patients recruited to the Atherosclerosis Risk in Communities Study, even after adjusting for adiposity, the risk of developing diabetes was found to be 2.4-fold greater in hypertensive individuals than in those who were normotensive [2]. A likely explanation for these results is that hypertension and insulin resistance have a common

causal mechanism, typically as part of the suite of metabolic disturbances that characterise the metabolic syndrome and probably related to hormonal derangement in these individuals.

Prevalence of hypertension and type 2 diabetes

Estimates of the prevalence of hypertension in diabetics depend upon the definition of hypertension used and the population studied. For example, of 3648 type 2 diabetics in the United Kingdom Prospective Diabetes Study (UKPDS), 39% were either hypertensive, with a systolic blood pressure/diastolic blood pressure (SBP/DBP) ≥160/90 mmHg, or receiving antihypertensive therapy, with a significant relationship between hypertension and body mass index [3]. However, a nationwide survey of diabetic adults in England, conducted from 1991 to 1994, found a prevalence of hypertension (SBP/DBP ≥160/90 mmHg) of 51% [4]. Tarnow et al. estimated a prevalence of 61% using the criterion of ≥160/95 mmHg, but this increased to 80% using the criterion of ≥140/90 mmHg [5]. More recently, guidelines have recommended even more stringent reductions in blood pressure for diabetics compared with non-diabetics, with convergence towards a consensus goal SBP/DBP of ≤130/80 mmHg appearing in recent guidelines [1, 6, 7]. Using this more exacting target, the prevalence of hypertension in type 2 diabetes is likely to be even higher.

Cardiovascular risk associated with hypertension in type 2 diabetics

Hypertension clearly increases cardiovascular risk in type 2 diabetes, as shown most strikingly by data from the Multiple Risk Factors Intervention Trial [8]. Of the 350 000 men aged between 35 and 57 years who were recruited to this study, the absolute risk of cardiovascular death was three-fold higher in those who were diabetic, even after adjusting for other common risk factors such as age, race, income, serum cholesterol and smoking. Importantly, the risk at any given level of SBP was 2.5–3 times higher in those with type 2 diabetes than in their non-diabetic counterparts at every level of SBP assessed.

Reducing cardiovascular risk with antihypertensive treatment

There is unequivocal evidence for a beneficial effect of blood pressure reduction on cardiovascular risk in type 2 diabetes, and these benefits have been demonstrated with all classes of antihypertensive drugs.

The Systolic Hypertension in the Elderly Program (SHEP) showed that blood pressure reduction was effective in reducing cardiovascular risk in both diabetics and non-diabetics [9]. SHEP compared blood pressure reduction using chlorthalidone 12.5–25 mg/day with placebo. Patients in the chlorthalidone group were allowed step-up to atenolol 25–50 mg/day or reserpine 0.05–0.1 mg/day as needed, and those in the placebo group were allowed any active antihypertensive drugs required. Diabetics had a higher 5-year cardiovascular event rate than did non-diabetics, but a similar reduction in the relative risk (RR) with chlorthalidone (0.66 in both groups). The risk reduction was associated with, and probably explained by, a greater reduction in SBP in chlorthalidone group (amounting to 9.8 mmHg in the diabetic patients).

Trial data on the effects of beta-blockers in diabetes are limited, and the presence of diabetes is often considered to be a contraindication to the use of beta-blockers. However, because in SHEP 19% of diabetic patients received concomitant atenolol, the benefit was suggestive of a beneficial effect of this class of drugs. Furthermore, patients in UKPDS assigned to tight blood pressure control with either atenolol or captopril benefited similarly when compared with those assigned to less tight blood pressure control (see below) [10]. Finally, the studies in which beta-blockers were used for secondary prevention of myocardial infarction show that administration of these drugs is protective both in non-diabetic and in diabetic patients [11]. In the diabetic subgroup of two large trials of metoprolol in post-myocardial infarction, the Göteborg Metoprolol Trial (GMT) and the Metoprolol In Acute Myocardial Infarction (MIAMI) study, the reduction in mortality and late infarction was even greater than in the non-diabetic groups, with a 58% reduction of diabetic mortality in GMT and a 50% reduction in MIAMI [12]. The first International Studies of Infarct Survival trial showed a significant reduction in post-myocardial infarction mortality with atenolol that was comparable in the diabetic and non-diabetic groups [13], and similar results were obtained in the Norwegian Timolol Multicenter Study [14].

These benefits are also apparent in the general patient population. The Cooperative Cardiovascular Project followed over 200 000 post-myocardial infarction patients, including 58 000 diabetics, over 2 years. Although the reduction in mortality in diabetics was 36%, which was somewhat lower than for the general population, the absolute survival benefit was greater, owing to the higher mortality in this high-risk population [15].

The benefit provided by angiotensin-converting enzyme (ACE) inhibitors is clear. Probably the strongest evidence for the cardiovascular benefit of ACE inhibitors in diabetic patients comes from the diabetic subgroup of

the Heart Outcomes Prevention Evaluation trial [16]. Ramipril gave a 22% reduction in the relative risk (RR) of myocardial infarction, a 33% reduction in the RR of stroke, a 37% reduction in the RR of cardiovascular death and a 24% reduction in the RR of overall mortality. There was also a 16% reduction in the RR of microvascular disease (overt nephropathy, laser therapy or dialysis).

The use of calcium channel blockers in diabetes is often limited due to a perceived increase in the risk of cardiac events. Such an effect was found in the Appropriate Blood pressure Control in Diabetes (ABCD) trial, in which, of the 870 patients with diabetes, 24 in receipt of nisoldipine experienced a myocardial infarction over the 5-year follow-up, compared with only four patients treated with enalapril [17]. However, this was not confirmed by the results obtained in the normotensive arm of the same study [18]. Furthermore, data from the diabetic subgroup in the Systolic Hypertension in Europe trial show that calcium channel blockers do provide a protective effect compared with placebo [19]. In the 492 diabetic patients, SBP was reduced by an additional 8.6 mmHg and DBP by an additional 3.9 mmHg in the nitrendipine group compared with the placebo group. This was accompanied by a 69% reduction in stroke, a 57% reduction in cardiac events, a 70% reduction in cardiovascular mortality and a 41% reduction in overall mortality in comparison with placebo.

Rationale for aggressive blood pressure reduction

Regardless of the antihypertensive class employed, it seems clear that a reduction of blood pressure will suppress the incidence of cardiovascular events in patients with diabetes. However, it seems that equivalent blood pressure reductions do not abolish the excess risk of hypertension in diabetics compared with non-diabetics. For example, in the Hypertension Optimal Treatment (HOT) study, diabetic and non-diabetic patients both showed a similarly effective blood pressure reduction during treatment (about 140 mmHg SBP and 83 mmHg DBP), the cardiovascular risk of the former remaining clearly higher than that of the latter [20]. Another example is represented by the International Verapamil-Trandolapril (INVEST) study in which both verapamil and atenolol provided equivalent reductions in stroke and myocardial infarction, regardless of whether the patients were diabetic or not [21]. Nevertheless, throughout the study, diabetics continued to show a higher rate of the combined endpoint (hazard ratio 1.77 compared with non-diabetics).

The continued high level of cardiovascular risk, even in treated diabetics, highlights the need for the aggressive reduction in blood pressure in these patients. The benefit of such aggressive blood pressure reduction was shown in the HOT study, in which patients were assigned to antihypertensive therapy, employing felodipine as the initial treatment, with differing DBP targets of ≤90, ≤85 or ≤80 mmHg [22]. There was a progressive reduction in the risk of major cardiovascular events from the first to the third target group, the incidence per 1000 patient-years decreasing from 24.4 in the ≤90-mmHg group to 18.6 in the ≤85-mmHg group and to 11.9 in the ≤80-mmHg group. This represents a halving of the RR in the group with the lowest target, a result that is all the more remarkable because only 4 mmHg separated the actual DBP achieved in these groups (DBP in the ≤90-mmHg target group was 85.2 mmHg, compared with 81.1 mmHg in the ≤80-mmHg group).

Additional evidence showing the effects of long-term (approximately 10 years) levels of SBP is provided by retrospective analysis of 4800 patients in the UKPDS [23]. A clear, continuous relationship was found between SBP ranging from 113 to 169 mmHg and the incidence of myocardial infarction or microvascular endpoints, with no evidence of a lower threshold. The hazard ratio of any diabetes-related endpoint in the group with mean SBP of 135 mmHg was around 1.5 times higher than that of the group with mean SBP of 113 mmHg, and the risk of death was doubled.

It is because of these and similar results that modern guidelines recommend more stringent blood pressure reduction in diabetics (target <130/80 mmHg) than in non-diabetics (target <140/90 mmHg) [1, 6, 7].

Mechanism for the protective effect of aggressive blood pressure reduction

Although clinical intervention trials have convincingly demonstrated that aggressive blood pressure reduction is protective in diabetics, they do not offer an insight into the pathophysiology that links raised blood pressure with increased cardiovascular risk in these patients. Two plausible mechanisms can be postulated: impaired autoregulation and attenuation of the nocturnal decrease of blood pressure.

Impaired autoregulation, i.e. the inability of arterioles to contract when blood pressure is increased, leads to increased pressure in the microcirculation, damage to the microvascular endothelium and microvascular sclerosis [24, 25]. This loss of the autoregulatory response can amplify the damaging effects of systemic blood pressure on small blood vessels. Attenuated nocturnal decrease of blood pressure, or non-dipping, is more common in diabetics than in the general population. Non-dipping is frequently associated with other cardiovascular risk factors; however, it seems likely that it is not simply a marker for

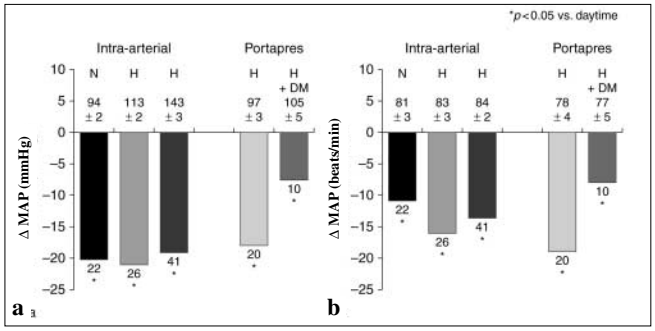

Fig. 1 Reductions in (**a**) mean arterial pressure (MAP) and (**b**) heart rate (HR) during night-time in normotensive subjects (N), essential hypertensives (H) and patients with hypertension and diabetes (H+DM). Blood pressure was measured either intra-arterially or by a beat-to-beat non invasive device (*Portapres*). Note the attenuation in blood pressure fall in patients with diabetes [26, 27]

cardiovascular risk, but also a risk factor in itself as a result of the increased 24-h blood pressure load. The attenuation of nocturnal decrease of blood pressure is an early feature of diabetes, occurring even before the onset of diabetic complications (Fig. 1) [26, 27].

Achieving blood pressure reduction targets

Although the aggressive blood pressure reduction targets have been shown to be beneficial in diabetics, achieving them is an extremely difficult task and one that often mandates the use of a combination of antihypertensive therapies with complementary modes of action that lower blood pressure more than the combination components [28]. For example, the combination of telmisartan and hydrochlorothiazide in patients with diabetes has been shown to reduce SBP by 26.1 mmHg and DBP by 12.6 mmHg [29], i.e., much more than what was obtained by using the two drugs as monotherapy [30].

In only half of the published studies was the mean DBP reduced to the target value in diabetes (<80 mmHg) [24]. Goals for SBP (<130 mmHg) have not been achieved in any published study, and only a minority reached the less stringent target of <140 mmHg. It seems that even expert physicians working on motivated patients in clinical trial situations are not able to reach is goal blood pressure.

Part of the problem is that, although blood pressure targets are more stringent in diabetic patients, reduction is more difficult to achieve. The mean reduction of SBP in diabetic patients was consistently lower (by 2–3 mmHg) than in non-diabetic patients in HOT [22], Losartan Intervention For Endpoint reduction in hypertension (LIFE) [31, 32] and International Nifedipine GITS Study of Intervention as a Goal in Hypertension Treatment (INSIGHT) [33]. SBP remained higher in diabetic than in non-diabetic patients, despite the greater use of combination therapy (use of combination therapy was greater by around 4 percentage points in diabetic patients than non-diabetic in HOT and LIFE, and 14 percentage points more in INSIGHT). Because achieving adequate blood pressure reduction is such a difficult task in diabetes, the choice of antihypertensive drugs is likely to be greatly influenced by their effects on cardiovascular and other outcomes beyond simple blood pressure control.

Differential effects of antihypertensive drug classes on cardiovascular outcomes

Several comparative studies have focused on the ability of some antihypertensive drugs to suppress or prevent adverse outcomes more effectively than others for the same degree of blood pressure reduction. As long ago as 1983, it was shown that early, aggressive treatment of blood pressure using a combination of atenolol, hydralazine and either frusemide or thiazide can dramatically reduce albuminuria and slow the decline in glomerular filtration rate [34]. However, when the Irbesartan Diabetic Nephropathy Trial (IDNT) investigators compared amlodipine, irbesartan and placebo in 1715 diabetic patients with macroalbuminuria over a mean 2.6-year follow-up, they found significant differences in renal outcomes [35]. Although both irbesartan and amlodipine reduced blood pressure to a similar degree compared with placebo, irbesartan significantly reduced progression to the combined endpoint of a doubling of serum creatinine, end-stage renal disease or death.

Cardiovascular disease is the major cause of death in diabetics, even in those with end-stage renal disease, and is therefore the foremost indicator of the health impact of antihypertensive intervention. Currently, the strongest evidence of a differential effect of different classes of antihypertensives on cardiovascular outcomes has been provided by LIFE, which compared atenolol with losartan in hypertensive patients, including 1193 diabetics, with left ventricular hypertrophy [32, 36]. Mean blood pressure reductions over the 4.7-year follow-up period were not substantially different in the diabetic patients treated with one or the other drug (although mean SBP remained at 147 mmHg), but losartan significantly reduced both total mortality and the composite endpoint of cardiovascular death, stroke or myocardial infarction compared with atenolol. The largest effect was the reduction in cardiovascular death with losartan.

The results from LIFE should be considered within the context of other, smaller comparative studies in diabetes with a cardiovascular endpoint [36]. Aside from LIFE, only the Captopril Prevention Project (CAPPP) [37] and the ABCD trial [17] showed a relative reduction in major cardiovascular events, mostly coronary events, with one

antihypertensive class compared with another: an ACE inhibitor *vs*. a diuretic/beta-blocker in the case of CAPPP, and an ACE inhibitor *vs*. a calcium channel blocker in the case of ABCD. However, CAPPP has been the subject of methodological criticisms [38], and there was no effect observed in normotensive patients in ABCD [17], leaving open the question of whether these observations genuinely reflect an effect beyond blood pressure control.

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) is the largest comparative cardiovascular outcomes trial yet undertaken [39]. ALLHAT compared chlorthalidone, amlodipine and lisinopril in 33 357 patients, including 12 063 type 2 diabetics, over a 4–8-year follow-up period. In the diabetic subgroup, no significant differences were found between the treatment arms in the incidences of the primary outcome (non-fatal myocardial infarction plus coronary heart disease), all-cause mortality, stroke, coronary heart disease or overall cardiovascular disease. There was a significant benefit in favour of chlorthalidone in the incidence of heart failure, but this result is controversial, as the diagnosis of heart failure was largely based on signs and symptoms and not extensively confirmed by external, independent validation. In addition, compared to the other drugs, diuretics might have had a masking effect on the major clinical signs of heart failure [40].

Differential effects of antihypertensive drug classes on target-organ damage

Any attempts to compare the non-blood pressure-related effects of antihypertensive drug classes on cardiovascular events encounters the fundamental problem that the magnitude of any such effect is likely to be smaller than the major benefits intrinsically associated with blood pressure lowering. Furthermore, the mechanism of action proposed for blockade of the renin–angiotensin system (RAS) includes beneficial effects across the cardiovascular continuum, including at the earliest stages. It may take many years before beneficial effects early in the continuum manifest as a reduction in life-threatening clinical events.

The alternative is to examine intermediate endpoints along the cardiovascular continuum. In diabetes, such endpoints have particular importance because of the evidence that organ damage can commence extremely early in the course of the disease. Giannattasio et al. [41] compared arterial distensibility in the radial artery, the carotid artery and the aorta of control patients and in those with type 1 diabetes. Even in diabetic patients with no hypertension and no evidence of macrovascular or microvascular complications there was a significant decrease in radial, carotid and aortic distensibility. The loss of distensibility became more pronounced in patients with diabetes-related microvascular or macrovascular complications, and even more so in those with hypertension. As less distensible arteries are likely to experience greater trauma due to intravascular pressure, this study is a clear example of the early onset of target-organ damage in these patients.

The evidence for class effects on intermediate endpoints is stronger than for cardiovascular outcomes. In particular, there are convincing data to suggest that angiotensin II receptor blockers are more effective than other antihypertensive classes in reducing proteinuria and other markers of renal damage in type 2 diabetes [42]. There is also evidence in non-diabetic patients that angiotensin II receptor blockers, ACE inhibitors and calcium channel blockers are more effective than the traditional ones (e.g., beta-blockers) in causing regression of left ventricular hypertrophy and arteriolar structural alterations [43, 44].

Differential effects of antihypertensive classes on new-onset diabetes

Although the hyperglycaemic effects of beta-blockers and diuretics in diabetes have long been known [45], one of the most striking findings from recent clinical trials is the class-differential effects on new-onset diabetes (Fig. 2) [21, 31, 33, 37, 39, 46–50]. Calcium channel blockers,

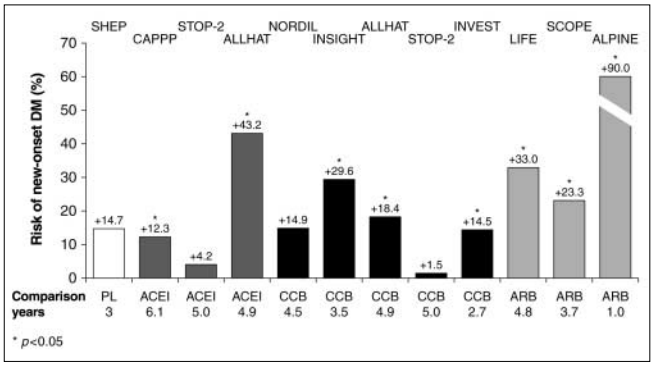

Fig. 2 Incidence of new-onset diabetes mellitus (DM) in large, comparative antihypertensive drug trials comparing newer treatments with conventional one (diuretics and/or beta-blockers): Systolic Hypertension in the Elderly Program (SHEP) [9]; International Verapamil-Trandopril study (INVEST) [21]; Losartan Intervention For Endpoint reduction in hypertension (LIFE) [31]; International Nifedipine GITS Study of Intervention as a Goal in Hypertension Treatment (INSIGHT) [33]; Captopril Prevention Project (CAPPP) [37]; Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) [39]; Study of COgnition and Prognosis in the Elderly (SCOPE) [46]; Antihypertensive treatment and Lipid Profile In North of Sweden Efficacy evaluation (ALPINE) [47]; Nordic Diltiazem study (NORDIL) [48]; Swedish Trial in Old Patients with hypertension-2 (STOP-2) [49] and VAlsartan Long-term Use Evaluation (VALUE) [50]. In SHEP, thiazide diuretic treatment was compared to placebo. *ACEI*, angiotensin-converting enzyme inhibitor; *ARB*, angiotensin II receptor blocker; *BB*, β-blocker; *CCB*, calcium channel blocker; *PL*, placebo

ACE inhibitors and angiotensin II receptor blockers all have a remarkable impact on the risk of new-onset diabetes, which is less frequent when these drugs are administered compared with older drug classes over relatively short trial durations of 3–6 years. There has been some debate over whether such data reflect a prodiabetic effect of older drugs, or an antidiabetic effect of the newer ones. Evidence from trials, however, also shows a reduced incidence of new-onset diabetes in patients treated with ACE inhibitors or angiotensin II receptor blockers as compared with placebo [16, 51, 52], which suggests a true antidiabetic effect of new drugs (Fig. 3). In this regard, some other trials are important. This is the case in particular for the VAlsartan Long-term Use Evaluation (VALUE), which showed a significant benefit for the angiotensin II receptor blocker valsartan over amlodipine, a metabolically neutral calcium channel blocker (Fig. 3) [50].

A possibility which has been advanced is that the apparent diabetogenic effects of diuretics and beta-blockers simply reflect a cosmetic increase in blood glucose, with none of the adverse cardiovascular effects of true type 2 diabetes. Evidence that this is not so was provided by a study of 6886 hypertensive patients enrolled into a treatment programme between 1973 and 1993 for an average of 6.3 years [53]. For most of the treatment period, diuretics or beta-blockers were the first-line drugs. As expected, the incidence of cardiovascular disease during the study was significantly associated with raised blood glucose, whether measured at baseline or during treatment. Furthermore, patients who did not have raised blood glucose at baseline, but did have significantly raised levels (>7.75 mmol/l) at some point in the study, had a 50% increased incidence of cardiovascular disease, a rate very similar to that of patients with raised blood glucose at baseline. Furthermore, in another study, a treatment-induced increase in blood glucose in patients aged 50 years was the major predictive factor for the occurrence of myocardial infarction at the age of 60 years [54]. Based on these data, it seems that increases in blood glucose associated with antihypertensive treatment are just as serious as those that occur as a result of conventional risk factors.

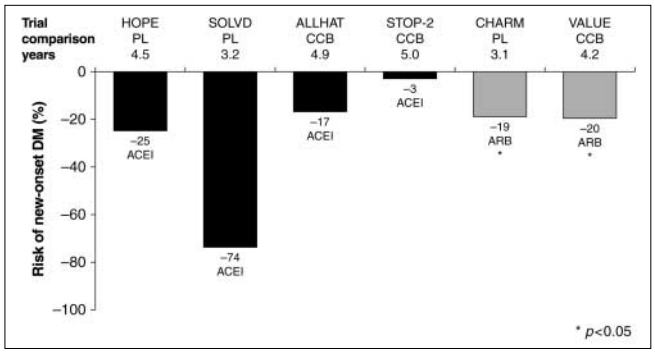

Fig. 3 Reduction in new cases of diabetes mellitus (DM) induced by "new" antihypertensive drugs (angiotensin-converting enzyme inhibitors [ACEI], calcium channel blockers [CCB] and angiotensin II receptor blockers [ARB]). Data from Heart Outcomes Prevention Evaluation (HOPE) [16], Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) [39], Swedish Trial in Old Patients with hypertension-2 (STOP-2) [49], Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) [51], Studies Of Left Ventricular Dysfunction (SOLVD) [52] and VAlsartan Long-term Use Evaluation (VALUE) [50]. *PL*, placebo

There has been much speculation that blockade of the RAS can have a beneficial effect on the development of insulin resistance and the metabolic syndrome [55]. Although the concept remains controversial, data such as those from VALUE [50] and from studies such as the Antihypertensive treatment and Lipid Profile In a North of Sweden Efficacy evaluation (ALPINE) [47] are beginning to provide clinical support for the hypothesis. ALPINE compared candesartan cilexetil with hydrochlorothiazide in treatment-naive, non-diabetic hypertensives over a period of 1 year. Fasting serum glucose was unchanged by the angiotensin II receptor blocker (compared with an increase with the diuretic). However, the incidence of metabolic syndrome was decreased by the angiotensin II receptor blocker (and increased by the diuretic) over the course of the study. As the metabolic syndrome is a paramount risk factor for diabetes, this strongly suggests that RAS blockade provides a real protective effect on the risk of new diabetes.

Conclusions

Hypertension and diabetes are common, additive risk factors for cardiovascular risk. Early, aggressive reduction of blood pressure in diabetics is of fundamental importance – possibly the most important aspect of treatment in these patients. Some evidence exists that the choice of antihypertensive is important, with RAS blockade appearing to offer superior renal protection for a given level of blood pressure reduction. However, given the difficulty of reducing blood pressure to goal levels in diabetics, combination therapy with two, or even three, antihypertensive agents is likely to be required, thus making the choice of which antihypertensive class to give less problematic.

When it comes to non-diabetic hypertensive patients, the debate is more crucial. On the one hand, reduction of cardiovascular risk requires blood pressure control. However, the possibility that some antihypertensive treatments could increase the risk of new-onset diabetes presents the possible paradox of increased cardiovascular risk, or at least a highly attenuated decrease compared with expectations. Even major reductions in SBP, from the range of 160–179 mmHg to 120–139 mmHg, could result in no net decrease in cardiovascular risk if accompanied by a transition to the diabetic state [8].

The choice of antihypertensive class is clearly important in this case. Which antihypertensives to prescribe within a given class may also be important, given the differences in pharmacokinetic properties that exist. As ever, further research is required, and in particular there is a need for carefully designed, high-powered trials with long treatment durations and large patient numbers that compare new effective treatments. A good example of such a trial is the ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) [56], which has 31 546 patients, including 11 412 with diabetes, the results of which are expected in 2007.

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