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PREVENTION OF TYPE 2 DIABETES MELLITUS WITH ANTIHYPERTENSIVE DRUGS

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Introduction

Type 2 diabetes is a prevalent and important cardiovascular risk factor [1], and it is well known that patients with established diabetes run a cardiovascular risk between two and four times greater than that run by non-diabetics. It is therefore of importance to prevent the development of type 2 diabetes if possible by an appropriate lifestyle and by a careful selection of antihypertensive drugs in patients at risk, such as those with the metabolic syndrome and hypertension. Observational studies have shown that the risk of drug-induced hyperglycaemia is in fact equal to already existing hyperglycaemia and overt type 2 diabetes during follow-up [2]. Data from the Framingham cohort have also shown that approximately 15–18% of hypertensive patients were "glucose intolerant" and that this may contribute to the increased cardiovascular risk in hypertensive patients [3]. It is therefore of interest to investigate the issue of whether different antihypertensive treatment regimens have different effects on glucose metabolism and the development of diabetes mellitus.

Systematic review of drug effects

Padwal et al. [4] reported that the incidence of diabetes is unchanged or increased during treatment with "old/conventional" antihypertensive drugs such as thiazide diuretics and beta-adrenergic blockers, whereas it is unchanged or decreased with "new" drugs including angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs). New-onset diabetes mellitus during treatment has not influenced the outcome of cardiovascular mortality and morbidity in large clinical trials like ALLHAT [5], INSIGHT [6] and VALUE [7]. However, drug-induced diabetes in hypertensive patients carries the same cardiovascular risk as that seen in patients previously known to have diabetes [2], but it may take 10–15 years for the increased risk to manifest itself and this is not seen in relatively short-term clinical trials. In view of the predicted increase in the number of diabetic patients during the coming decades [8], the choice of treatment strategy of hypertensive subjects may become of increasing importance. As the duration of adverse drug effects on metabolism is important, it is very likely that it is more important to take these effects into consideration for the middle-aged patient with newly discovered hypertension than for the elderly patient for whom the short-term benefits of blood pressure control clearly outweigh the adverse effects on metabolism.

New-onset diabetes in large hypertension trials

The effects of different antihypertensive regimens on new-onset diabetes as demonstrated by some major hypertension trials are shown in the Table 1. The difference in risk reduction between conventional and newer therapies ranges from 0% to 34% (87% when including the small ALPINE study [9]). However, different criteria have been used for diagnosing diabetes. Thus the 1985 WHO criteria [10] were used in the CAPPP study [11], the 1999 WHO criteria [12] in the VALUE study [7] and both WHO criteria in the LIFE study [13, 14], whereas new antidiabetic medication, increased glycated haemoglobin (HbA_{1c}) and self-reported diabetes were the criteria in the HOPE study [15]. The study design varies between the trials, and not all the studies were double-blind. The CAPPP [11], NORDIL [16] and STOP-2 [17] studies used an open-label design with blinded end-point assessment (PROBE), and this can lead to detection bias; for example, diabetes is more actively sought in thiazide or beta-blocker arms.

There are some randomised placebo-controlled trials, not all of them antihypertensive (CHARM [18], EWPHE [19], HOPE [15], SCOPE [20], SHEP [21], and SOLVD [22]) reporting new-onset diabetes, but it is unclear whether this is due to the antihypertensive effect *per se* or to specific drug effects. It is also difficult to draw conclusions from the results of other trials comparing two or more antihypertensive agents because the observed effects may represent a detrimental effect of one agent in contrast to a beneficial effect of the other. For example, the results from INSIGHT [6] and LIFE [13, 14] might reflect adverse metabolic effects of thiazide diuretics or beta-blockers rather than the beneficial effects of calcium channel blocker or ARB therapy.

Table 1. Summary of drug effects on the risk of diabetes mellitus. **A**. ACEIs or ARBs *vs.* placebo; **B**. ACEIs or ARBs *vs.* conventional therapy; **C**. CCBs *vs.* conventional therapy; **D**. ACEIs or ARBs *vs.* CCB

	Study	Treatment	Duration (years)	Relative risk	*P*
A.	CHARM [16]	ARB *vs.* placebo	3.1	0.78	0.02
	HOPE [15]	ACEI *vs.* placebo	4.5	0.66	< 0.001
	PEACE [23]	ACEI *vs.* placebo	4.8	0.83	0.01
	SCOPE [20]	ARB *vs.* placebo (conventional)	3.7	0.81	0.09
	SOLVD local centre [22]	ACEI *vs.* placebo	2.9	0.26	< 0.0001
B.	ALLHAT [5]	ACEI *vs.* diuretic	4	0.70	< 0.001
	ALPINE [9]	ARB *vs.* diuretic	1	0.13	0.030
	CAPPP [11]	ACEI *vs.* βB/diuretic	6.1	0.86	0.039
	LIFE [13, 14]	ARB *vs.* βB	4.8	0.75	< 0.001
	STOP-2 [17]	ACEI *vs.* βB/diuretic	4	0.96	0.77
C.	ALLHAT [5]	CCB *vs.* diuretic	4	0.84	0.04
	INSIGHT [6]	CCB *vs.* diuretic	3	0.77	0.02
	INVEST [27]	CCB *vs.* βB	2.7	0.85	0.004
	NORDIL [16]	CCB *vs.* βB/diuretic	4.5	0.87	0.14
	STOP-2 [17]	CCB *vs.* βB/diuretic	4	0.97	0.83
	ASCOT [28]	CCB *vs.* βB/diuretic	5.5	0.70	0.001
D.	STOP-2 [17]	ACEI *vs.* CCB	4	0.98	0.91
	VALUE [7]	ARB *vs.* CCB	4.2	0.77	< 0.0001

In the HOPE [15] and PEACE trials [23] the results were *post hoc* analysis. This raises the possibility of publication bias, because positive results are more likely to be reported than negative results. Furthermore, there is a possibility of detection bias, because if an end-point is not pre-planned, the studies are not always adequately powered to prove significance. New-onset diabetes was not always a pre-specified primary end point, but the incidence of type 2 diabetes was a predefined secondary end point in nine of the studies: ALPINE [9], CAPPP [11], CHARM [18], INSIGHT [6], LIFE [13, 14], NORDIL [16], SCOPE [20], STOP-2 [17], and VALUE [7].

The effects of different antihypertensive regimens on glucose metabolism

Antihypertensive drug regimens differ in their effects on glucose metabolism. It is at present unclear whether such differences are due to drug-specific effects or to drug class effects. It is also not known whether such effects are permanent or temporary. A detrimental effect of an antihypertensive agent might simply be due to latent diabetes being unmasked by an increase in blood glucose level. Conversely, a glucose-lowering effect might mask a pre-diabetic state.

Angiotensin-converting enzyme inhibitors (ACEIs)

ACEIs have been shown to improve insulin sensitivity and glycaemic control in diabetic patients and have reduced the incidence of new-onset diabetes in the ALLHAT [5], CAPPP [11], HOPE [15], PEACE [23] and STOP-2 [17] trials. The mechanisms by which ACEIs improve insulin sensitivity may include increased glucose uptake in skeletal muscle via increased GLUT-4 glucose transporter activity [24] and also activation of one of the major enzymes of the glucose pathway, hexokinase [25]. Another possible mechanism is an improvement in blood flow and microcirculation to fat and skeletal muscle tissue via bradykinin activation of cell-surface B2-kinin receptors [24]. ACEI may also im-

prove glucose tolerance in hypertensive individuals by lessening the potassium-lowering effect of insulin and preventing hypokalaemia. This may preserve the insulin secretory response of pancreatic beta cells to glucose, which is decreased during hypokalaemia [26].

Angiotensin receptor blockers (ARBs)

The ARB class has shown a potentially positive effect on insulin action and has a potential role in protecting high-risk hypertensive patients from developing diabetes, as shown in LIFE [13], SCOPE [20] and VALUE [7], but the mechanisms are still not clear. As expected, some of the hypotheses are the same as with the ACEIs, namely improved skeletal muscle blood flow and microcirculation, enhanced transport of glucose across the skeletal muscle cell membranes and prevention of hypokalaemia. Alternatively, the effect of the drugs can be related to actions in the pancreas by the enhancement of insulin release by the beta cells.

Calcium channel blockers (CCBs)

Treatment with CCBs has been associated with a reduced incidence of new-onset diabetes in the ALLHAT [5], INSIGHT [6], INVEST [27] and STOP-2 [17] trials. Vasodilatation and improved peripheral blood flow may explain the improvement in insulin sensitivity seen with calcium channel blockade. However, in the VALUE [7] trial new-onset diabetes was reduced with ARBs compared with CCBs from 16.4% in the amlodipine arm to 13.1% in the valsartan arm ($P < 0.001$), a relative risk reduction of 23%. Finally, in the large ASCOT trial [28] new-onset diabetes was less frequent on the amlodipine-based regimen than in the group treated with conventional drugs (567 *vs.* 799; RR 0.70; 95% confidence interval: 0.63–0.78, $P < 0.0001$).

Diuretics

Thiazide diuretics appear to have an unfavourable dose-dependent effect on glycaemic control and large doses of thiazides are known to have an adverse metabolic effect [5]. Small doses, however, seem mostly to be neutral to metabolism. There are multiple mechanisms through which thiazide diuretics may worsen glycaemic control. For example, diuretics stimulate renin secretion, which stimulates the production of angiotensin II. Furthermore, the hypokalaemic effect of diuretics may blunt the release of insulin from the pancreas. This was originally proposed by Conn to explain the apparent diabetic state found in primary aldosteronism [29]. Preventing hypokalaemia with potassium supplementation attenuates thiazide-induced glucose intolerance and the combination of a diuretic and angiotensin-converting enzyme inhibitor may confer a lesser risk of new-onset diabetes [30].

Beta receptor blockers

In a prospective study of 12,550 adults by Gress et al. [31], beta-blockers increased the risk of subsequent diabetes by 28% among hypertensive patients compared to hypertensive patients not receiving any antihypertensive therapy, with a hazard ratio of 1.28 (95% confidence interval: 1.04–1.57). The mechanism may include weight gain, alterations in insulin clearance and reduced first-phase insulin secretion, and, probably most importantly, reduced peripheral blood flow as a result of increased peripheral vascular resistance [32].

Summary of findings in trials

A majority of hypertensive patients require multiple pharmaceutical preparations for life to prevent cardiovascular risk. Data from cohort and randomised trials suggest that the incidence of type 2 diabetes mellitus is unchanged or increased by thiazides and beta blockers in a dose-dependent way, while it appears to be unchanged or decreased by ACEIs, CCBs or ARBs [4, 28, 31]. A meta-analysis of seven studies in 58,010 individuals by Opie et al. [33], showed that the "new" therapies, namely ACEIs, ARBs and CCBs, provoke less new diabetes than the conventional "old" therapies (diuretics and beta-blockers). ACEIs and ARBs decreased new diabetes by 20% ($P < 0.001$), whereas CCBs decreased new diabetes by 16% ($P < 0.001$).

Conclusions

1) The development of hyperglycaemia in patients with hypertension could either reflect metabolic abnormalities associated with elevated blood pressure *per se* or the influence of antihypertensive drugs. 2) Hyperglycaemia is a proven risk factor for both macrovascular and microvascular disease and should therefore be taken seriously. 3) Some antihypertensive drugs seem to further increase the risk of hyperglycaemia by impairing insulin sensitivity and/or insulin secretion. Examples of such drugs are beta receptor blockers and high-dose thiazide diuretics, especially when used in combination. Calcium antagonists are mostly neutral. 4) ACE inhibitors or angiotensin receptor blockers (ARB), on the other hand, may improve insulin sensitivity and decrease the risk of new-onset diabetes. 5) The risk associated with hyperglycaemia is likely to increase with the duration of treatment. The choice of antihypertensive drug treatment in this perspective should therefore be a matter of greater relevance for the middle-aged than for the elderly patient with a shorter remaining life expectancy. 6) Blockade of the renin-angiotensin system seems to be an appropriate choice as one of the partner drugs in offering combination therapy to hypertensive patients with an increased risk of developing diabetes.

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