Editorial

Effect of Antihypertensive Drug-Associated Diabetes on Cardiovascular Risk

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Type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular disease (CVD).[1,2] Patients with T2DM have a 2- to 4-fold increased CVD risk compared with non-diabetic subjects and approximately 2/3 of patients with T2DM die from coronary heart disease (CHD) or stroke.[1,2] In this context, it is of interest that T2DM is almost 2.5 times more frequent in hypertensive patients than in normotensive subjects and that insulin resistance is also highly prevalent in hypertensives.[3] Insulin resistance is more prevalent in obese hypertensive patients, but a 40% lower insulin sensitivity was also reported in lean hypertensive patients.[4,5] Data from the Framingham study also show that approximately 15-18% of hypertensive patients are "glucose intolerant" and that this may contribute to their increased CV risk.[6] Furthermore, the metabolic syndrome, i.e. the coexistence of hypertension, insulin resistance, central obesity, and dyslipidaemia, represents a common condition associated with increased risk of both T2DM and CVD.[7]

Given the association between T2DM and hypertension, it is not surprising that many hypertensive patients will develop T2DM even without receiving antihypertensive treatment.[3,8-11] However, both epidemiological studies and randomised controlled trials have also linked antihypertensive treatment with new-onset T2DM.[3,12-14] A recent network meta-analysis of 22 trials with more than 140,000 hypertensive patients has shown that, compared with placebo, β-blockers and diuretics increase the risk for T2DM, calcium channel blockers (CCBs) have a neutral effect, whereas both angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduce the risk of T2DM.[12] However, in most randomised controlled studies of antihypertensive agents the development of new-onset T2DM was evaluated as a secondary endpoint (Table 1).[15-33] In addition, it is difficult to separate the effects of a single antihypertensive medication, since placebo, as well as the active agent, was given in most trials on top of other antihypertensive drugs. Besides, discontinuation or administration of non-trial antihypertensive drugs varied during follow up.

The only double-blind randomised study that assessed the impact of antihypertensive treatment on the incidence of T2DM was the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study.[34] Among 5,269 individuals without CVD, but with impaired fasting plasma glucose or impaired glucose tolerance, treatment with

Table 1. Summary of new-onset diabetes interventional trials.

Study	Patients	Duration (yrs)	Treatment	Relative risk	p
Active treatment vs. placebo					
EWPHE[15]	840	4.7	Diuretic vs. placebo	1.50	NS
SHEP[16]	4,736	3.0	Diuretic vs. placebo	1.20	NS
HOPE[17]	9,297	4.5	ACEI vs. placebo	0.66	<0.001
SCOPE[18]	4,964	3.7	ARB vs. placebo	0.81	NS
CHARM[19]	3,023	3.1	ARB vs. placebo	0.78	0.02
SOLVD[20]	291	2.9	ACEI vs. placebo	0.26	<0.0001
PEACE[21]	6,904	4.8	ACEI vs. placebo	0.83	0.01
FEVER[22]	9,800	3.3	CCB vs. placebo	1.20	NS
ACEIs or ARBs vs. conventional therapy					
ALLHAT[23]	24,309	4.0	ACEI vs. diuretic	0.70	<0.001
ALPINE[24]	392	1.0	ARB vs. diuretic	0.13	0.03
CAPPP[25]	10,985	6.1	ACEI vs. BB/diuretic	0.86	0.039
STOP-2[26]	4,418	4.0	ACEI vs. BB/diuretic	0.96	NS
LIFE[27]	9,194	4.8	ARB vs. BB	0.75	<0.001
AASK[28]	815	3.8	ACEI vs. BB	0.53	0.001
ACEIs or ARBs vs. CCBs					
STOP-2[26]	4,401	4.0	ACEI vs. CCB	0.98	NS
VALUE[29]	15,245	4.2	ARB vs. CCB	0.77	<0.0001
AASK[28]	612	3.8	ACEI vs. CCB	0.49	0.003
CCBs vs. conventional therapy					
STOP-2[26]	4,409	4.0	CCB vs. BB/diuretic	0.97	NS
INSIGHT[30]	5,019	3.5	CCB vs. diuretic	0.77	0.023
NORDIL[31]	10,881	4.5	CCB vs. BB/diuretic	0.87	NS
ALLHAT[23]	24,303	4.0	CCB vs. diuretic	0.84	0.04
INVEST[32]	22,576	2.7	CCB vs. BB	0.85	0.004
ASCOT[33]	19,257	5.5	CCB vs. BB/diuretic	0.70	0.001

ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; CCB – calcium channel blocker; BB – β-blocker.

ramipril for 3 years did not reduce the incidence of T2DM compared with placebo. However, there was increased regression to normoglycaemia in the ramipril arm.[34] It is notable that participants in the DREAM study were relatively younger (mean age 55 years vs. 65 years in other trials) and were not hypertensive (the mean blood pressure at baseline was 136/83 mmHg, i.e. substantially lower than in hypertension trials). The degree of activation of the renin-angiotensin system is greater in older or hypertensive individuals and therefore ACE inhibition may have a greater effect in the former compared with younger or normotensive subjects. In addition, the 3-year study duration may have been too short to demonstrate a positive effect of ramipril on the risk of T2DM.[34]

Another important issue is whether T2DM that develops during antihypertensive treatment increases CVD morbidity and mortality. Several observational studies reported an adverse impact of new-onset T2DM. Among 6,886 hypertensive patients followed up for an average of 6.3 years, patients who developed hyperglycaemia had a higher incidence of CVD compared with those who did not.[35] Moreover, among patients who developed hyperglycaemia, those who were treated with diuretics had a greater CVD risk than those who were not on diuretics.[35] In a cohort of 1,860 60-year-old men who were followed up for an average of 17.4 years, those who developed myocardial infarction (MI) experienced greater increases in blood glucose levels between age 50 and 60 years than did those who did not suffer an MI.[36] The increase in blood glucose was an independent risk factor for MI (p=0.0001) in men receiving antihypertensive treatment at 60 years of age, mainly β-blockers and thiazide diuretics, but not in those who were untreated.[36] In the Multiple Risk Factor Intervention Trial (MRFIT), which included 11,645 men followed up for a median of 18.5 years, patients who developed T2DM (more than 70% had received diuretics, often at very high doses) had higher CHD, CVD and all-cause mortality rates than those who did not.[37] In another study of

795 initially untreated hypertensive patients who were followed for up to 16 years (median 6 years), patients who developed T2DM during follow up had a risk for CVD events similar to the risk of patients who had T2DM at baseline.[38] However, these findings were based on only 43 cases of new-onset T2DM and on only 63 CV events.[38] In contrast, another observational study of 686 hypertensive men, followed up for 15 years, showed that new-onset T2DM was not associated with increased CHD morbidity.[39] Nevertheless, in a more recent report from the same cohort that included 754 hypertensive men, followed up for 25-28 years, new-onset T2DM was associated with an increased risk for stroke, MI and all-cause mortality.[40] The average time between the development of new-onset T2DM and first stroke or MI was 9.1 and 9.3 years, respectively, suggesting that long-term follow up is required to detect the adverse effects of new-onset T2DM.[40]

Randomised controlled trials also point to an adverse impact of new-onset T2DM. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the prevalence of new-onset T2DM was higher in the chlorthalidone group compared with the lisinopril and the amlodipine groups.[23] In the whole study population, new-onset T2DM was associated with a greater risk for CHD but not for other CVD events or total mortality.[41] When the 3 treatment arms were analysed separately, new-onset T2DM was not associated with an adverse outcome in the chlorthalidone group, but was associated with a greater risk for all-cause mortality in the amlodipine group, and with a greater risk for CHD events and heart failure in the lisinopril group.[41] However, the test for interaction between treatment and effects of T2DM was not significant, suggesting that new-onset T2DM increases CVD risk regardless of antihypertensive treatment.[41] In the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial (15,245 high-risk patients followed up for an average of 4.2 years), valsartan-based treatment reduced the risk of T2DM compared with amlodipine-based treatment.[29] Patients who developed T2DM during the study had higher CVD morbidity than patients who did not (hazard ratio, HR 1.43, 95% confidence interval, CI 1.16-1.77; $p=0.0008$).[42] However, CVD morbidity was even higher in patients who had T2DM at baseline (HR 2.20 vs. patients who did not develop T2DM; 95% CI 1.95-2.49; $p<0.0001$), suggesting that new-onset T2DM increases CVD risk but is not as detrimental as pre-existing T2DM. This is as expected, given the direct relationship between T2DM duration and the risk for vascular complications.[42] In the Systolic Hypertension in the Elderly Program (SHEP) trial, T2DM that developed during the trial among participants on placebo was associated with a higher CV mortality rate (HR 1.562; 95% CI 1.117-2.184) and total mortality rate (HR 1.348; 95% CI 1.051-1.727) after a mean follow up of 14.3 years.[43] However, T2DM that developed in the diuretic group did not increase CV mortality rate (HR 1.043; 95% CI 0.745-1.459) or total mortality rate (HR 1.151; 95% CI 0.925-1.433).[43] In addition, patients who developed T2DM during chlorthalidone treatment had a better prognosis than patients who had T2DM at baseline.[43] These results have led some investigators to suggest that antihypertensive drug-related new T2DM may not have the same adverse prognostic effect as "spontaneously" occurring T2DM. However, the benefits of blood pressure reduction with chlorthalidone might have outweighed the risks arising from new-onset T2DM.[43]

In conclusion, even though "older" antihypertensive drugs (i.e. diuretics and β-blockers) appear to increase the risk for T2DM, whereas "newer" agents have either a neutral effect (CCBs) or decrease the risk (ACE inhibitors and ARBs), it is not entirely clear whether antihypertensive drug-associated T2DM increases CVD risk. Most data suggest that T2DM that develops during antihypertensive treatment does have an adverse impact, but well-designed trials with large numbers of patients and, most importantly, with long follow up are needed to clarify the prognostic implications of new-onset T2DM associated with antihypertensive treatment. Until more conclusive data are available, diuretics and β-blockers, particularly at high doses and in combination, should be a second-line treatment in patients with a long life expectancy and a high risk for T2DM (e.g. middle-aged hypertensive patients with the metabolic syndrome).

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