Renin-angiotensin system inhibition prevents type 2 diabetes mellitus
Part 1. A meta-analysis of randomised clinical trials

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SUMMARY

Most individuals with arterial hypertension or congestive heart failure are insulin-resistant and at a higher risk of developing type 2 diabetes (T2DM). The inhibition of the renin-angiotensin system (RAS), using an angiotensin converting enzyme inhibitor (ACEI) or a selective angiotensin receptor AT1 blocker (ARB), may exert favourable metabolic effects capable of preventing T2DM in high risk individuals. We performed a meta-analysis of randomised clinical trials (RCTs) assessing the effects of RAS inhibition on the incidence of new cases of T2DM in patients with arterial hypertension or congestive heart failure. Ten RCTs with cardiovascular prognosis as primary endpoints analysed the incidence of T2DM as secondary endpoints or as post-hoc analysis after a mean follow-up of 1 to 6 years: five with an ACEI and five with an ARB, compared with a placebo (n = 4) or a reference drug (beta-blocker or diuretic: n = 5; amlodipine: n = 2). Eight RCTs concerned hypertensive patients: STOP Hypertension-2 (lisinopril or enalapril *vs* beta-blocker or diuretic), CAPPP (captopril *vs* thiazide or beta-blocker), HOPE (ramipril *vs* placebo), ALLHAT (lisinopril *vs* chlorthalidone and lisinopril *vs* amlodipine), LIFE (losartan *vs* atenolol), SCOPE (candesartan *vs* placebo), ALPINE (candesartan *vs* placebo) and VALUE (valsartan *vs* amlodipine). Two RCTs concerned patients with congestive heart failure: SOLVD (enalapril *vs* placebo) and CHARM-overall programme (candesartan *vs* placebo). Overall, 2 675 new cases of T2DM (7.40%) were observed in the group of 36167 patients receiving a treatment with ACEI or ARA as compared with 3 842 events (9.63%) in the group of 39 902 control patients. A mean weighed relative risk reduction of new T2DM of 22% (95% CI: 18, 26; p < 0.00001) was observed after RAS inhibition. The beneficial effect was similar with ACEIs and with ARBs as well as in patients with hypertension and in those with heart failure, and was also present whatever the comparator (placebo or beta-blockers/diuretics or amlodipine). The number needed-to-treat to avoid one new case of T2DM averaged 45 patients over 4-5 years. In conclusion, RAS inhibition consistently and significantly reduces the incidence of T2DM in individuals with arterial hypertension or with congestive heart failure. Considering the pandemic of T2DM, such pharmacological approach deserves further attention among the strategies aiming at preventing T2DM.

Key-words: ACE inhibitors – Angiotensin – AT1 receptor blockers – Hypertension – Congestive heart failure – Meta-analysis – Type 2 diabetes mellitus.

L'inhibition du système rénine-angiotensine prévient le diabète de type 2.
Partie 1. Méta-analyse des essais cliniques randomisés

RESUME

La plupart des personnes avec hypertension essentielle ou décompensation cardiaque congestive sont insulinorésistantes et davantage sujets à développer un diabète de type 2 (DT2). Le blocage du système rénine-angiotensine (RAS), en utilisant un inhibiteur de l'enzyme de conversion de l'angiotensine (IEC) ou un antagoniste sélectif des récepteurs AT1 de l'angiotensine II (ARA), peut exercer des effets métaboliques favorables capables de prévenir la survenue d'un DT2 chez des sujets à risque. Nous avons réalisé une méta-analyse des essais cliniques randomisés ayant analysé les effets d'une inhibition du RAS sur l'incidence de nouveaux cas de DT2 chez des sujets hypertendus ou décompensés cardiaques. Dix études, ayant comme objectif principal le pronostic cardio-vasculaire, ont analysé l'incidence de DT2, soit comme critère d'évaluation secondaire, soit lors d'une analyse post-hoc, après un suivi moyen de 1 à 6 années : cinq avec un IEC et cinq avec un ARA, par comparaison à un placebo (n = 4) ou un médicament de référence (bêta-bioquant ou diurétique: n = 5 ; amlodipine: n = 2). Huit essais ont concerné des sujets hypertendus: STOP Hypertension-2 (lisinopril ou énalapril *vs* bêta-bloquant ou diurétique), CAPPP (captopril vs thiazide ou bêta-bloquant), HOPE (ramipril *vs* placebo), ALLHAT (lisinopril vs chlorthalidone et lisinopril *vs* amlodipine), LIFE (losartan *vs* aténolol), SCOPE (candésartan *vs* placebo), ALPINE (candésartan *vs* placebo) et VALUE (valsartan *vs* amlodipine). Deux essais ont concerné des patients avec insuffisance cardiaque: SOLVD (énalapril *vs* placebo) et CHARM (candesartan *vs* placebo). Au total, 2 675 nouveaux cas de diabète (7,40 %) ont été observés dans le

groupe des 36167 patients bénéficiant d'un IEC ou d'un ARA par comparaison à 3 842 événements (9,63 %) dans le groupe des 39 902 patients témoins. La méta-analyse montre une réduction relative du risque, avec une moyenne pondérée de 22 % (95 % IC : 18,26 ; p < 0,00001), pource qui concerne la survenue d'un DT2 après inhibition du RAS. L'effet bénéfique est comparable avec un IEC ou un ARA, se retrouve chez les patients avec hypertension artérielle ou insuffisance cardiaque et est observé quel que soit le comparateur (placebo ou bêta-bloquant/diurétique ou amlodipine). Le nombre de sujets à traiter pour éviter un nouveau cas de DT2 est de 45 patients sur une période de 4-5 années. En conclusion, l'inhibition du système rénine-angiotensine réduit, de façon consistante et significative, l'incidence de DT2 chez les personnes avec hypertension artérielle ou décompensation cardiaque congestive. Compte tenu de la pandémie de DT2, cette intervention pharmacologique mérite une attention particulière parmi les différentes stratégies visant à prévenir cette maladie.

Mots-clés : Angiotensine – Diabète de type 2 – Hypertension – Inhibiteur de l'enzyme de conversion – Insuffisance cardiaque – Méta-analyse – Sartan.

INTRODUCTION

Arterial hypertension is intimately associated with type 2 diabetes mellitus (T2DM) [1]. Both elevated arterial pressure and impaired glucose tolerance (IGT) are key-components of the metabolic syndrome ("syndrome X" or insulin resistance syndrome), a leading cause of cardiovascular morbidity and mortality [2, 3]. Patients with essential hypertension have been shown to have a higher risk of developing T2DM than non-hypertensive individuals in several large prospective studies on various populations [4, 5]. Antihypertensive agents may exert negative, neutral or even positive metabolic effects that may diversely affect the risk of developing T2DM [6].

The renin-angiotensin system (RAS) is a coordinated hormonal cascade in the control of cardiovascular, renal, and adrenal function. It governs fluid and electrolyte balance and blood pressure regulation, but may also exert various, although still poorly understood, cellular effects [7]. RAS inhibition plays a key-role in cardiovascular pharmacology. Pharmacological agents include angiotensin-converting enzyme inhibitors (ACEIs), that block the conversion of pro-hormone angiotensin I to active hormone angiotensin II, and selective angiotensin II receptor-1 blockers (ARBs). Both compounds are now widely used as first-line antihypertensive agents in patients with diabetes mellitus, essentially because of their renal protection effect [8].

Recent data showed that RAS inhibition may result in a significant reduction in the incidence of T2DM in patients with arterial hypertension [6, 9] or with congestive heart failure (CHE) [9]. We performed a meta-analysis of randomised clinical trials (RCTs) that assessed the incidence of new cases of T2DM as secondary endpoints or as post-hoc analysis in addition to the effects of RAS inhibition on cardiovascular prognosis, used as primary endpoint, in patients with essential hypertension or CHF [10].

MATERIAL AND METHODS

To identify relevant studies, we searched MEDLINE, EMBASE, Science citation index (Web of Science and ISI Proceedings) from January 1990 to June 2004. We also searched the reference lists of identified studies assessing the effects of RAS inhibition on the cardiovascular prognosis. Searching was limited to English-language papers. Studies were considered eligible for inclusion in the metaanalysis only if they compared either an ACEI or an ARB with a reference drug (either placebo or active drug) within a RCT Studies should also concerned non-diabetic individuals with arterial hypertension or CHF. Furthermore, accurate data should be provided in the selected papers regarding the total number of patients included in the trial, the mean duration of follow up, the number of non-diabetic individuals at baseline, the criteria used to define diabetes, the number of new cases of T2DM during follow up.

Details of participant characteristics (age, gender, body mass index, comorbidity, lost of follow up) and study design (primary and secondary objectives, dose titration, coexisting drugs, statistical analysis) were carefully recorded.

Meta-analysis was conducted for new diabetes throughout the follow-up period in patients receiving either an ACEI or an ARB and in patients receiving the reference drug. Data in the form of odds ratios (OR) and 95% confidence intervals (95% CI) were analysed using the Mantel-Haenszel method, fixed-effect model provided by the RevMan Analyses 1.0 application contained in RevMan 4.2 [11]. Heterogeneity was tested by the chi-square test in RevMan Analyses 1.0.

RESULTS

A total of ten cardiovascular RCTs assessed as secondary objective or in a post-hoc analysis the potential prevention of diabetes by ACEIs (five RCTS) *(Tab I)* or ARBs (five RCTs) *(Tab II)*. Eight trials were performed in patients with essential hypertension and two trials concerned patients with CHF. Five trials compared ACEIs or ARBs *vs* placebo while four RCTs included a diuretic and/or a beta-blocker as comparator and two trials used amlodipine as reference drug (among these RCTS, one study compared an ACEI with either a diuretic or amlodipine).

Brief description of RTCs

Stop-hypertension-2

The STOP-Hypertension-2 study was a prospective, randomised trial in 6614 patients aged 70-84 years with hypertension (blood pressure > 180 mmHg systolic, > 105 mmHg diastolic, or both) [12]. Patients were randomly assigned conventional antihypertensive drugs (beta-blockers as atenolol 50 mg, metoprolol 100 mg, pindolol 5 mg daily, or a diuretic combination hydrochlorothiazide 25 mg plus amiloride 2.5 mg daily) or newer drugs (ACEIs as enalapril 10 mg or lisinopril 10 mg daily, or calcium channel antagonists as felodipine 2.5 mg or isradipine 2-5 mg daily). After 6 years of follow-up, a total of 97 patients (10%) developed T2DM on conventional drugs group *vs* 93 patients (9.6%) in the ACE inhibitors *vs* 95 patients (9.9%) in the calcium antagonists group. The relative risk of developing T2DM on ACEIs averaged 0.96 (95% CI 0.72-1.27), p = 0.77) as compared to that observed with conventional drugs. Thus, this trial failed to show any protective effect of ACEIs against the development of T2DM. However, the studied population was rather old (mean age: 76 years) and the criteria of definition of T2DM were not clearly specified. Moreover, in this trial, drugs from opposing study arm were used as second-line agents, raising the possibility of treatment contamination that could somewhat dampen the potential protective effect of RAS inhibition.

CAPPP

The Captopril Prevention Project (CAPPP) was a prospective, randomised, open trial with blinded evaluation [13]. Patients (n = 10985) aged 25-66 years with a measured diastolic blood pressure of 100 mmHg or more on two occasions were randomly assigned captopril (50 to 200 mg/day) or conventional antihypertensive treatment (diuretics, essentially hydrochlorothiazide and bendrofluazide, and/or beta-blockers, essentially atenolol and metoprolol). Follow-up lasted for a mean of 6.1 years. Secondary endpoints included new onset of T2DM. Diagnosis of T2DM required at least two abnormal fasting glucose values (> 140 mg/dl or 7.8 mmol/l) or, if not unequivocal, confirmation by an oral glucose tolerance test according to the 1985 WHO criteria [14]. The incidence of T2DM was lower in the captopril group than in the conventional group (odds ratio or OR: 0.86 (95% CI, 0.74-0.99); p = 0.039). Similar results were observed in previously untreated patients (n = 5245) after adjustment for age, sex, and systolic blood pressure OR: 0.78 (95% CI, 0.62-0.99), p = 0.041. On-treatment analysis, rather than intention-to-treat analysis, was also available in the CAPPP trial and the difference was even more significant: OR: 0.79 (95% CI, 0.67-0.94); p = 0.007. However, because of the design of the study, it is not clear whether the differences in development of T2DM in the CAPPP trial were due to a protective effect of ACEI or an adverse effect of beta-blockers or diuretics. Furthermore, the scientific value of this study is somewhat dampened by the fact that the randomisation procedure resulted in an imbalance between groups at baseline in terms of blood pressure measurements and prevalence of T2DM [15]. Whether this initial imbalance might have influenced the results of incidence of new cases of T2DM during the trial is not known. Finally, as in the STOP Hypertension-2 trial, drugs from opposing study arm (essentially diuretics) were used as second-line agents, again raising the possibility of treatment contamination.

Table I: *Reduction in the incidence of type 2 diabetes in five large clinical trials investigating the effect of RAS inhibition with ACEIs. TZ: thiazide diuretic; BB: beta-1 blocker. NA: not available. AAR: absolute risk reduction. RRR: relative risk reduction. NNT: number needed-to-treat.*

Clinical trials	ST0P-Hypertension2 (12)		CAPPP (13)		HOPE (16,17)			ALLHAT (18)			SOLVD (31)	
	Enalapril/ lisinopril	TZ/BB	captopril	TZ/BB	ramipril	placebo	lisinopril	chlorthadilone	amlodipine	enalapril	placebo
Patients												
n total	2205	2213	5492	5493	4645	4652	9054	15255	9048	2111	2117
age (years)	76.1	76.0	52.4	52.7	66.0	66.0	66.9	66.9	66.9	59.1	59.1
body mass index (kg/m^2)	26.7	26.7	28	28	28.0	28.0	29.8	29.7	29.8	NA	NA
diabetes (%)	10.7	11.4	5.6	4.8*	38.9	38.0	35.5	36.2	36.7	7.3	7.1
Mean follow-up (years)	6.0	6.0	6.1	6.1	4.5	4.5	4.9	4.9	4.9	3.2	3.2
Primary cardiovascular outcome n %	226 / 10.2	221 / 10.0	363 / 6.6	335 / 6.1	651 / 14.0	826 / 17.8**	796 / 8.8	1362 / 8.9	798 / 8.8	313 / 14.8	334 / 15.8
Non-diabetic patients n (at randomisation)	1969	1961	5184	5229	2837	2883	5840	9733	5727	153	138
New cases of diabetes n	93	97	337	380	102	155	473	1129	561	9	31
%	9.6	10.0	6.5	7.3*	3.6	5.4**	8.1	11.6**	9.8*	5.9	22.4*
ARR %	-0.4		-0.8		-1.8			-2.5	-1.7	-16.5	
RRR%	-4		-14		-34			-30	-17	-78	
NNT	250		125		56			40	59	6	

*p< 0.05. **p<0.001.

Table II: *Reduction in the incidence of type 2 diabetes in five clinical trials investigating the effect of RAS inhibition with ARBs. HCT: hydrochlorothiazide. NA: not available. AAR: absolute risk reduction. RRR: relative risk reduction. NNT: number needed-to-treat.*

Clinical trials	LIFE (20, 21)		SCOPE (22)		ALPINE (23)		VALUE (24)		CHARM (26)	
	Losartan	Atenolol	Candesartan	Placebo	Candesartan	HCT	Valsartan	Amlodipine	Candesartan	Placebo
Patients										
n total	4605	4588	2468	2455	196	196	7649	7596	3796	3793
age (years)	54.0	54.0	76.4	76.4	54.5	55.4	67.2	67.3	65.9	66.0
body mass index (kg/m2)	28.0	28.0	27.0	26.9	27.8	28.1	28.6	28.7	28.3	28.2
diabetes (%)	13.0	13.0	12.5	11.6	0	0	31.1	32.2	28.6	28.3
Mean follow-up (years)	4.8	4.8	3.7	3.7	1.0	1.0	4.2	4.2	3.2	3.2
Primary cardiovascular outcome n	508	588	242	268	NA	NA	810	789	886	945
%	11.0	12.8*	9.8	10.9	NA		10.6	10.4	23.3	24.9*
Non-diabetic patients n (at randomisation)	4006	3992	2160	2170	196	196	5267	5152	2715	2721
New cases of diabetes										
n	241	319	93	115	1	8	690	845	163	202
%	6.0	8.0**	4.3	5.3	0.5	4.1*	13.1	16.4**	6.0	7.4*
ARR%	-2.0		-1.0		-3.6		-3.3		-1.4	
RRR%	-25		-25		-75		-23		-36	
NNT	50		100		28		30		71	

*p< 0.05. **p<0.001.

HOPE

In the "Heart Outcomes Prevention Evaluation" (HOPE) study, a total of 9297 high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor were randomly assigned to receive ramipril (10 mg once per day orally) or matching placebo for a mean of 5 years [16]. The HOPE study included 5720 patients without known diabetes (2837 on ramipril and 2883 on placebo) [17]. The diagnosis of T2DM determined from self-report at follow-up visits every 6 months during a mean period of 4.5 years was compared between the 2 groups. One hundred and two individuals (3.6%) in the ramipril group developed T2DM compared with 155 (5.4%) in the placebo group (OR: 0.66 (95% CI 0.51-0.85); $p < 0.001$). Similar results were noted when different diagnostic criteria were used. The proportion of patients diagnosed to have T2DM and a documented glycated haemoglobin of 110% or more above the upper limit of normal (1.8% *vs* 3.0%; OR: 0.60 (95% CI 0.43-0.85); $p = 0.003$), the proportion of those receiving an oral glucose-lowering agent or insulin (2.1% *vs* 3.6%; OR: 0.56 (95% CI, 0.41-0.77); $p < 0.001$), and the proportion of those with all criteria (1.3% *vs* 2.5%; OR: 0.51 (95% CI, 0.34-0.76); $p < 0.001$) were significantly lower in the ramipril group compared with the placebo group. These protective effects of ramipril were also consistently seen in several subgroups examined. For instance, the relative risk for T2DM in the subgroup individuals who never took beta-blockers or diuretics during the study was consistent with the overall results (OR, 0.62; 95% CI, 0.43-0.90) [17]. Although the data on new diagnoses of T2DM were collected prospectively in the HOPE study, the development of T2DM was not a primary or secondary outcome of the trial and this specific outcome was only considered in a post-hoc analysis [16, 17]. Therefore, the results, despite their clear statistical significance and consistency across subgroups, should be interpreted with caution.

ALLHAT

The "Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial" (ALLHAT) was a randomised, double-blind, trial designed to determine whether treatment with a calcium channel blocker or an ACEI lowers the incidence of coronary heart disease or other cardiovascular disease events *vs* treatment with a diuretic [18]. A total of 33357 participants aged 55 years or older with hypertension and at least one other coronary risk factor (36% had type 2 diabetes) were randomly assigned to receive chlorthalidone (12.5 to 25 mg/day; n = 15255), amlodipine (2.5 to 10 mg/day; n = 9048) or lisinopril (10 to 40 mg; n = 9054). Among individuals classified as non diabetic at baseline according to new criteria (initial fasting serum glucose < 126 mg/dl or 7 mmol/l) [19], the incidence of T2DM was 9.6% in the chlorthalidone group, 7.4% in the amlodipine group and 5.8% in the lisinopril group at 2 years ($p < 0.001$ lisinopril vs chlorthalidone) and 11.6%, 9.8% and 8.1%, respectively, at 4 years ($p < 0.001$ lisinopril vs chlorthalidone). Thus, the relative risk reduction (RRR) of developing T2DM averaged 30% (95% CI: 23-37%; $p < 0.001$) among hypertensive patients treated with lisinopril as compared to patients treated with the diuretic chlorthalidone and 17% (95% CI: 7-26%; $p < 0.01$) as compared to patients treated with the calcium channel antagonist amlodipine, a molecule that is considered as metabolically neutral.

LIFE

The LIFE study ("Losartan Intervention For Endpoint reduction in hypertension study") was a double-masked, randomised, parallel-group trial in 9193 participants aged 55-80 years with essential hypertension (sitting blood pressure 160-200/95-115 mmHg) and left ventricular hypertrophy [20]. Participants were assigned to once daily losartan-based (50-100 mg/day) or atenolol-based (50-100 mg/day) antihypertensive treatment for at least 4 years (mean follow-up of 4.8 years). Among other prespecified endpoints, new onset diabetes, defined according to 1985 WHO criteria [14], was assessed by a subcommittee of the steering committee [21]. There was a 25% lower incidence of new-onset T2DM in the losartan group than in the atenolol group: 241 cases (6% or 13.0 per 1000 patient-years of follow-up) *vs* 319 cases (8% or 17.5 per 1000 patient-years of follow-up); OR: 0.75 (95% CI 0.63 to 0.88); $p < 0.001$). A univariate proportional hazard regression model indicated that random allocation to the losartan group resulted in lower incidence of development of T2DM after adjustment for four major risk factors, i.e. baseline serum glucose, body mass index, HDL cholesterol and systolic blood pressure levels. After correction for these confounding risk factors, the estimated relative risk reduction of T2DM attributable to losartan was approximately 29% ($p < 0.001$) [21].

SCOPE

The Study on Cognition and Prognosis in the Elderly (SCOPE) included 4964 patients aged 70-89 years, with systolic blood pressure 160-179 mmHg, and/or diastolic blood pressure 90-99 mmHg [22]. Patients were assigned randomly to receive the ARB candesartan (8-16 mg/day) or placebo, with open-label active

antihypertensive therapy added as needed, with a mean follow-up of 3.7 years. New-onset T2DM was reported in 4.3% and 5.3% of the patients in the candesartan and control groups, respectively, a difference that corresponds to a RRR of 25% (p = 0.09). The absence of statistical difference in this study may be explained by the shorter follow-up (3.7 years instead of 4.8 to 6.1 years in the other trials). This study was also the only one which specifically recruited elderly people (mean age: 76.4 years). Finally, the criteria used to define diabetes were not clearly described in the original paper and the development of new diabetes was only considered in a post-hoc analysis.

ALPINE

The Antihypertensive treatment and Lipid Profile In a North of Sweden Efficacy Evaluation (ALPINE) study was a much smaller clinical trial with a lower number of subjects followed during a shorter period of time. Furthermore, this RCT was the only one which was not designed to assess cardiovascular prognosis. Rather, it compared the metabolic effects of one year treatment with candesartan 16 mg (n = 197, with addition of felodipine if needed) and with hydrochlorothiazide 25 mg (n = 196, with addition of atenolol if needed) in patients with mild to moderate hypertension (mean age 55 years, 48% of men) [23]. After 12 months, fasting plasma glucose increased from 5.29 to 5.42 mmol/l and fasting serum insulin increased from 9.65 to 11.00mIU/L in the diuretic group, while slight reductions (respectively, from 5.17 to 5.10 mmol/L and from 9.25 to 8.96 mlU/L) were observed in the candesartan group (between-group differences: p < 0.001). New T2DM was diagnosed in 8 patients in the hydrochlorothiazide group and only one patient in the candesartan group. This difference was statistically significant (p = 0.03) despite the rather low number of participants in the study.

VALUE

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was an investigator-designed, prospective, multinational, double-blind, randomised, active controlled, parallel-group trial [24]. A total of 15245 patients, aged 50 years or older with treated or untreated hypertension and high risk of cardiac events were randomised to receive either valsartan 80-160 mg or amlodipine 5-10 mg, possibly combined with hydrochlorothiazide. Patients were followed up for a mean of 4.2 years. To detect new-onset diabetes (defined according to 1999 WHO criteria) [25] the protocol first excluded all patients who at entry were diagnosed with diabetes, received anti-diabetic agents, or had abnormal glucose levels. In the remaining group, individual patient study forms and adverse events databases were monitored for new use of antidiabetic drugs and for newly reported diabetes. A blood chemistry report was mandatory at the end of the trial, and the diagnosis of new T2DM diabetes was made if the serum glucose concentration exceeded 7.8 mmol/l. New-onset diabetes arose in significantly fewer hypertensive patients on valsartan than on amlodipine: 690 (13.1%) *vs* 845 (16.4%), hazard ratio: 0.77 (95% CI: 0.69-0.86); p < 0.0001. Absolute relative risk of new T2DM was rather high in this RCT, averaging 13.1% in the valsartan group and 16.4% in the amlodipine group. The reduction of new diabetes with valsartan seen in VALUE is especially interesting because the comparison group was a calcium antagonist, considered to be metabolically neutral.

CHARM

The Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity (CHARM) study [26] was a parallel, double-blind RCT comparing candesartan with placebo in patients with CHF. Overall, 7599 patients were randomly assigned candesartan (n = 3803; titrated up to 32 mg once daily) or matching placebo (n = 3796) and had a mean follow up of 37.7 months. In patients without a prestudy diagnosis of T2DM, the number of patients in the candesartan group who during the programme were newly diagnosed as having T2DM was significantly lower than that in the placebo group: candesartan 163 (6%) of 2715 and placebo 202 (7%) of 2721 (OR = 0.78; 95% CI, 0.64-0.96; p = 0.020).

The CHARM programme was specifically designed as three parallel, independent, integrated, randomised, double-blind, clinical trials comparing candesartan with placebo in three distinct but complementary populations of patients with symptomatic CHF: patients with reduced left-ventricular systolic function taking ACEIs (CHARM-Added trial) [27], patients with left-ventricular dysfunction intolerant to ACEIs (CHARM-Alternative trial) [28] and patients with preserved left-ventricular ejection fraction (CHARM-Preserved trial) [29]. The results regarding the effect of candesartan on the incidence of new cases of T2DM was particularly impressive in the latter trial, while the differences did not reach statistical significance in the two other sub-trials. Indeed, in the CHARM-Preserved trial [28], 40% fewer individuals were diagnosed as having new diabetes in the candesartan group than in the placebo group (47 *vs* 77; OR: 0.60; 95% CI 0.41-0.86; p = 0.005). In the CHARM-Alternative trial [27], among patients without a pre-study diagnosis of diabetes, 44 in the candesartan group and 53 in the

placebo group developed diabetes (OR: 0.79; 95% CI 0.53-1.18; p = 0.254). In contrast, in the CHARM-Added trial [27], no difference was observed between the two populations: 72 (6%) patients in the candesartan group and 72 (6%) in the placebo group developed new diabetes (unadjusted OR: 0.98; 95% CI 0.70-1.35; p = 0.88). These latter observations suggest that adding an ARB to an ACEI does not provide any further protection against T2DM in patients with CHF.

SOLVD

In "Studies Of Left Ventricular Dysfunction" (SOLVD), patients with asymptomatic left ventricular dysfunction were randomly assigned to receive either placebo (n = 2117) or enalapril (n = 2111) at doses of 2.5 to 20 mg per day in a double-blind trial, with a mean follow-up of 37.4 months [30]. There was a trend toward fewer deaths due to cardiovascular causes among the patients who received enalapril. A recent retrospective study assessing the effect of the ACEI enalapril on the incidence of T2DM in a subgroup of SOLVD reported a dramatic reduction of new cases of diabetes in patients with CHF treated with enalapril as compared to those receiving placebo [31]. Indeed, 9 among 153 patients (5.9%) developed T2DM after 2.9 years of follow up in the enalapril group compared to 31 among 138 (22.4%) in the placebo group (p < 0.0001). By multivariate analysis, enalapril remained the most powerful predictor for risk reduction of developing T2DM (hazard ratio = 0.22; 95% CI, 0.10 to 0.46; p < 0.0001). The effect of enalapril was striking in the subgroup of CHF patients with impaired fasting plasma glucose at baseline (1 on enalapril *vs* 12 patients on placebo developed T2DM; p < 0.0001).

Meta-analysis of RTCs

Overall, 2675 new cases of T2DM (7.40%) were observed in the group of 36167 patients receiving a treatment with ACEI or ARA as compared with 3842 events (9.63%) in the group of 39902 control patients *(Tab I* and *II)*. All comparisons demonstrated a trend (n = 3) or a significant (n = 8) reduction in the incidence of T2DM after RAS inhibition. Results are summarized in *figure 1*. The overall effect was a mean weighed relative risk reduction of T2DM of 22% (95% CI: 18, 26), p < 0.00001. A significant heterogeneity (p =0.004) was observed between RCTs with the greatest effect being observed in the two RCTs including lowers numbers of participants (ALPINE and SOLVD). The relative risk was similar with ACEIs (OR = 0.77; 95% CI 0.72, 0.82; p = 0.0006) and with ARBs (OR = 0.79; 95% CI 0.73, 0.85; p < 0.00001). Furthermore, it was similar in patients with arterial hypertension (OR = 0.78; 95% CI 0.75, 0.82; p < 0.0001) and in those with CHF (OR = 0.73; 95% CI 0.61, 0.89; p = 0.001). Finally, it was present in RCTs comparing RAS inhibition with placebo (OR = 0.73; 95% CI 0.64, 0.83; p < 0.00001), with beta-blockers/diuretics (OR = 0.77; 95% CI 0.71, 0.82; p < 0.00001) or with the metabolically neutral calcium channel antagonist amlodipine (OR = 0.81; 95% CI 0.75, 0.87; p < 0.00001). This excludes the possibility that most of the difference between RAS inhibition and comparator was due to a deleterious effect of the comparator (beta-blocker or diuretic), but rather favours the conclusion of a beneficial direct effect exerted by ACEI or ARBs. The absolute risk of developing T2DM over a mean follow-up period of 4 years averaged 7.40% in the group treated with ACEI or ARB and 9.63% in the group receiving placebo or a reference drug, corresponding to a mean absolute risk reduction of 2.23% (p < 0.00001). Thus, the number-needed-to-treat to avoid one new case of T2DM averaged 45 patients over a period of 4-5 years.

DISCUSSION

T2DM prevention is considered as a main objective according to the WHO [29] and the American Diabetes Association [30]. Lifestyle changes play a major role and have proven a remarkable efficacy, although various pharmacological interventions also showed a significant prevention effect [32-34]. Insulin resistance plays a major role in the pathophysiology of T2DM [35-37]. Such metabolic abnormality is also present in most patients with arterial hypertension [38, 39] or CHF [40, 41]. Interestingly, as essential hypertension [4], CHF has been shown to be associated with a higher risk of developing T2DM [42], in a proportional manner to the functional class of the patients [43]. Considering the high prevalence of hypertension in the general population, especially in presence of overweight (abdominal adiposity) or obesity, it would be of major importance from a public health point of view to evaluate the potential influence of RAS inhibition on the incidence of T2DM in individuals with essential hypertension. The present meta-analysis demonstrates that RAS inhibition results in a consistent and significant 22% RRR of T2DM incidence. Such protective effect is only slightly lower than that observed with antidiabetic agents such as metformin (RRR = -31% without drug withdrawal and RRR = -25% after 1-2 weeks of washout in the Diabetes Prevention Program) [44, 45] or acarbose (RRR = -25% without drug withdrawal and RRR = -14% after a 3-month wash-out period in the STOP-NIDDM trial) [46]. As previously questioned, it is not clear whether the protective effects of oral antidiabetic agents are preventing, delaying or simply masking effects [47]. The amplitude of the protection effect resulting from RAS inhibition was similar with ACEI (RRR = -23%) and ARB (RRR = -21%), despite previous observations from glucose clamp studies

suggesting that ACEIs might exert a greater effect on insulin-mediated glucose disposal than ARBs [48]. The number needed-to-treat (around 45 subjects over a 4-5 year period) to avoid one new case of T2DM may appear rather high as compared to other trials. However, it should be kept in mind that the main purpose of RAS inhibition was not to prevent T2DM, but rather to provide a cardiovascular protection [9]. Therefore, the prevention of T2DM should be considered as an additional beneficial effect and the number needed-to-treat should be considered in view of the high number of individuals with hypertension (or CHF) in the general population, a proportion that may further increase in the next decades in a population with increasing prevalence of obese and elderly subjects. Finally, as discussed recently [6], nearly all randomised controlled trials reported intention-to-treat rather than on-treatment analyses when calculating diabetes risk. On-treatment analysis may be the more accurate method if large differences in treatment adherence between study arms were observed. For instance, in the HOPE trial, 90% of patients randomised to ramipril remained on the study drug and 27% of placebo-treated patients were taking open-label ACEIs [17]. Therefore, the difference in risk of T2DM between the two treatments is underestimated using the intention-to-treat analysis as published rather than the on-treatment analysis (data not provided). The CAPPP trial reported both types of analysis and indeed found a greater difference between drug classes with the on-treatment analysis rather than with the intention-to-treat analysis [13]. However, as already mentioned, treatment contamination limits the conclusion that can be drawn from this trial. Ideally, RCTs should report both types of analyses, particularly when large discrepancies in treatment adherence between study arms are observed [6].

The positive effect after RAS inhibition could not be simply interpreted as a worse effect in the comparative group as it was observed not only *vs* beta-blocker or diuretic [RRR = -23%), but also *vs* placebo [RRR = -27%) or *vs* amlodipine, a calcium channel antagonist that is generally considered as metabolically neutral [RRR = -19%). However, one may argue that most patients in the placebo groups also received other antihypertensive agents that might negatively influence the metabolic profile of the patients. If this was probably true, this was the case in the two parallel groups as all trials were conducted in a double-bind manner, and thus RAS inhibition provided a significant protection against the development of T2DM in all such circumstances. The criteria used to define T2DM were not always clearly specified and varied from trial to trial. However, in the HOPE trial, the reduction of the incidence of new cases of T2DM was significant whatever the criteria used to define diabetes [17] and there was a between-trial consistent favourable effect whatever the definition of T2DM. Finally, the major criticism against published studies assessing the effect of RAS inhibition on the incidence of T2DM was that the results were the product of a post hoc analysis or the secondary results of trials projected for a different scope as the primary endpoint was indeed cardiovascular protection. Thus, the positive findings of the present meta-analysis should receive further and definite confirmation from RCTs in which the incidence of new T2DM will be considered as primary or pre-specified secondary endpoints and the criteria used to define diabetes will be widely accepted. Three large-scale trials specifically designed to answer this important question are ongoing in both hypertensive and non-hypertensive individuals: DREAM ("Diabetes REduction Approaches with ramipril and rosiglitazone Medications"), NAVIGATOR ("Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research") and ONTARGET ("Telmisar-tan Alone and in combination with Ramipril Global Endpoint trial")—TRANSCEND ("Telmisartan Randomized Assessment Study in Angiotensin Inhibitor-Intolerant Patients with Cardiovascular Disease"). A concise description of these three ongoing RCTs has been provided in a recent extensive review [9].

Figure 1: *Meta-analysis of randomised clinical trials evaluating the effect of RAS inhibition using either an ACEI or an ARB ["treatment") on the relative risk of development of new diabetes in hypertensive patients, as compared to either a reference drug or a placebo ["control"), n = cases of new diabetes. N: total number of non-diabetic patients at entry.*
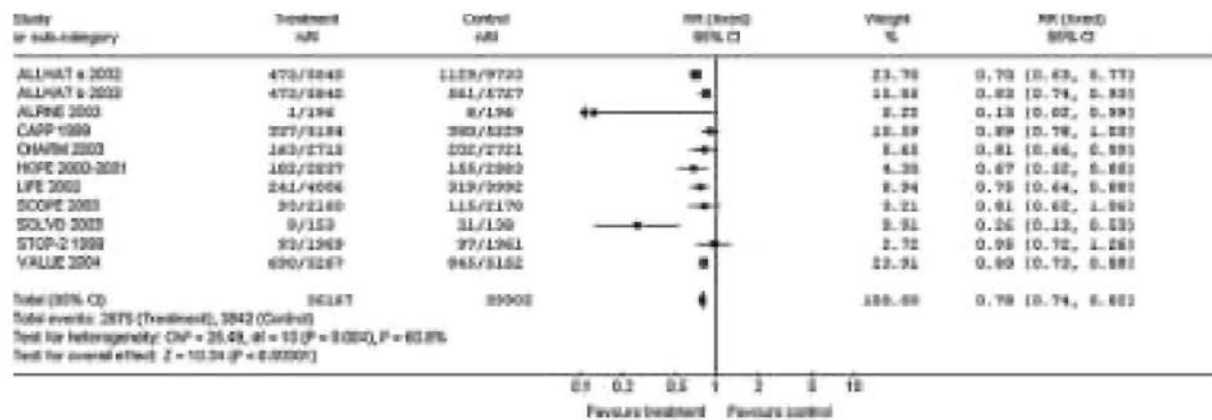
As previously discussed [9], the mechanisms that may explain the preventive effect of RAS inhibition on the development of T2DM are complex. From a theoretical point of view, preventing T2DM by RAS inhibition may result from a preservation of beta-cell function and/or an enhancement of insulin sensitivity, thereby decreasing the need for pancreatic insulin secretion [35-37]. Targeting RAS may lead to alterations in microcirculation and changes in ionic status that indeed could potentially affect both islet insulin secretion and cellular insulin action. However, unexpected mechanisms might also play a role as newly recognised components of the RAS seem to modulate cardiovascular and renal regulation [7] or even adipocyte turnover [49]. Intimate relationships have been described between adipose tissue and RAS [50, 51] and the strong association between obesity and T2DM is well known [52]. Besides a pure haemodynamic effect [53], a direct effect on cellular insulin action by blocking ATII has also been described [54-56]. Finally, a possible agonist effect on PPAR-gamma has been recently described with some ARBs whith high lipophilicity such as telmisartan [57, 58]. The underlying mechanisms possibly involved in the reduction of new onset diabetes with RAS inhibition will be more extensively described in a next paper [59].

CONCLUSION

Besides life-style modifications and classical pharmacological strategies using various antidiabetic or anti-obesity agents, drugs that inhibit RAS activity may be considered as a valuable approach to prevent T2DM. Strategies that interrupt RAS offer effective antihypertensive treatment as well as nephroprotection, especially in diabetic patients. In addition, they have demonstrated their efficacy in reducing cardiovascular disease mortality and morbidity in high-risk individuals such as those with arterial hypertension and/or diabetes mellitus. Finally, they may improve carbohydrate tolerance in some patients, and are essentially neutral (or even slightly positive in certain conditions) on insulin sensitivity. The recent consistent observations in individuals with arterial hypertension or CHF of a protective effect on the development of T2DM with ACEIs or ARBs are enticing and emphasise that there are many aspects of the pathogenesis and treatment of T2DM that still need to be uncovered. Ongoing large RCTs specifically designed to investigate the effect of RAS inhibition on the incidence of T2DM should confirm the present observations and provide more extensive metabolic data that will help to better understand the potential mechanisms underlying the protective effect against T2DM. In case of positive results, patients at very high risk to develop T2DM, such as obese patients with impaired glucose tolerance independently of the presence of arterial hypertension, would be an interesting new target population to be tested in appropriate clinical trials using ACEIs or ARBs.

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