Effect of candesartan cilexetil on carotid intima-media thickness in hypertensive type 2 diabetic patients. MITEC study: design and baseline characteristics

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Abstract

Media Intima Thickness Evaluation of Candesartan (MITEC), a multicentre, randomised, double-blind, parallel-group study assessed the effect of candesartan cilexetil (CC) versus amlodipine (AML) administered during three years, on carotid intima-media thickness (IMT) in hypertensive type 2 diabetic patients. The study design, the baseline characteristics, and the determinants of carotid IMT are presented.

After a placebo run-in period of four weeks, patients were randomised to CC (n=100) or AML (n=109). The mean blood pressure values were 155.9±11.0 mmHg, 91.3±8.0 mmHg and 64.6±11.8 mmHg for systolic, diastolic and pulse pressure respectively, and the mean HbA_{1C} was 7.1±1.3%. The mean common carotid IMT was 0.74±0.16 mm. The univariate regression analyses showed a significant correlation between IMT and age (p<0.0001), gender (p=0.013) and creatinine clearance (p=0.03). Only age was significantly correlated with carotid IMT (p<0.0001) in the multivariate analysis.

In conclusion, the MITEC population has good metabolic control at baseline where carotid IMT is mainly related with age.

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Key words: candesartan cilexetil, amlodipine, carotid intima-media thickness, diabetes, hypertension.

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Introduction

Hypertension and type 2 diabetes mellitus are two cardiovascular risk factors with increasing prevalence among people over 40 years old in industrialised countries. Around half of diabetic people also have hypertension, but this is well controlled in < 30% of these patients.[1] To decrease the risk of developing cardiovascular complications, BP should be maintained at < 130/80 mmHg in those patients.[2,3]

Vascular damage caused by hypertension contributes to arterial stiffness through structural and functional mechanisms. With ageing, vessel elastin fibres undergo structural changes. Proliferation of collagen and deposition of calcium occur which conspire to reduce vascular compliance. High BP accelerates arterial damage by increasing load and fracturing elastin fibres.[4,5]

In diabetes different biochemical mechanisms consecutive to hyperglycaemia provide an environment which favours premature arterial stiffening.[6]

Hypertension and diabetes together with environmental factors and genetic predisposition contribute to the progression of atherosclerotic lesions.[7,8]

Several clinical studies have shown a correlation between carotid atherosclerosis and coronary disease and, in hypertensive patients, alterations in large artery structure seem to be determined by variability of BP.[9,10]

Ultrasonography allows accurate and reproducible measurement of IMT and lumen diameter and detection of structural (thickening, plaque) and/or functional (stiffness, reactivity) alterations associated with preclinical atherosclerosis.[11] Changes in IMT can predict cardiovascular risk[12-14]

AML is a calcium channel blocker, which has been shown to slow or stabilise IMT and retard early atherosclerotic progression.[9,15-18] The mechanisms responsible for these effects are unclear.

CC is an ARB suitable to treat hypertension effectively which, at the dosage of 8 to 16 mg once daily, has shown good tolerance even in elderly patients and offers nephroprotection in diabetic patients.[19] The CACHET study provides us with precious data since it compares the effects of CC and atenolol on IMT progression in hypertensive patients.[20] In the CACHET study, both candesartan and the beta-blocker atenolol reduced

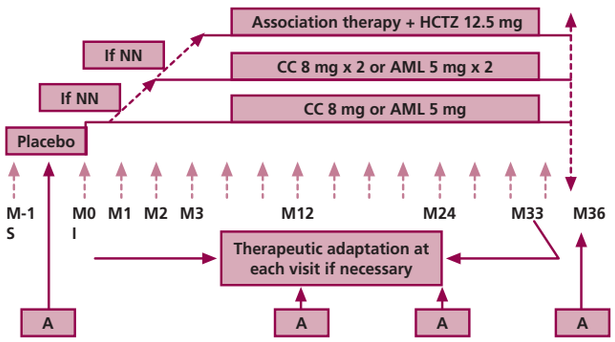
Abbreviations

ABPM	ambulatory BP monitoring
AML	amlodipine
ARB	angiotensin II receptor antagonist
BP	blood pressure
CC	candesartan cilexetil
ECG	electrocardiogram
HbA_{1C}	haemoglobin A_{1C}
HCTZ	hydrochlorothiazide
HDL-C	high density lipoprotein-cholesterol
IMT	intima-media thickness
LDL-C	low density lipoprotein-cholesterol
MI	myocardial infarction
PP	pulsed pressure

Acronyms

MITEC	Media Intima Thickness Evaluation of Candesartan
CACHET	candesartan cilexetil on carotid intima-media thickness

Figure 1. Design of MITEC study



Key: A = annual check-up (including: carotid ultrasound, ambulatory blood pressure measurement, electrocardiogram, and laboratory check); S = selection; I = inclusion; M = month; NN = not normalised
Normalised BP: SBP < 130 mmHg and DBP < 85 mmHg

carotid IMT to similar extents after 52 weeks of treatment. However, despite similar reductions in brachial and carotid BP, candesartan was associated with outward remodelling of the carotid artery compared with atenolol.[21] The main objective of the MITEC study is to compare the effects of the calcium antagonist AML and the ARB CC, on carotid IMT in hypertensive type 2 diabetic patients. In the present paper, the study design, the determinants of carotid IMT at baseline are shown and the baseline characteristics of the study population are described.

Materials and methods

Study design

This was a multicentre, randomised, double-blind study on two parallel groups performed in France.

A first assessment, which included physical examination, office and ABPM, carotid ultrasonography, laboratory tests and ECG, was carried out just before randomisation. The same check-up was undertaken yearly (figure 1). When a patient was enrolled in the study, the antihypertensive treatment (if any) was discontinued and a wash-out period of four weeks (placebo run-in period) was started. At randomisation, the study drug consisted of either CC 8 mg or AML 5 mg given once daily in the morning. The study treatment was reassessed after four weeks by office BP measurement and doubled (16 mg for CC or 10 mg for AML) if systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg. Subsequently, if the BP target was not reached on the next month, HCTZ 12.5 mg was added. For blinding purposes, both CC and AML were encapsulated.

The study was carried out according to the French regulation, the declaration of Helsinki and the Good Clinical Practice guidelines. The study was approved by the ethical committee of Grenoble, France.

Patients

Inclusion criteria

Male and female type 2 diabetic patients, aged 40–74 years, with stable glycaemic control ($HbA_{1C} \leq 10\%$) treated by diet and/or oral antidiabetic agents, with mild-to-moderate hypertension (sitting systolic BP [140–180 mmHg] and diastolic BP [90–109 mmHg]) either treated or not, and fasting serum total cholesterol < 6.40 mmol/L (250 mg/dL), LDL < 4.10 mmol/L (160 mg/dL), triglycerides < 4.50 mmol/L (400 mg/dL), and common carotid artery IMT of 0.6–1.2 mm measured by ultrasound (five measures by the calipers of the echograph) were eligible for inclusion in the study.

Exclusion criteria

Patients with type 1 or secondary diabetes, malignant, severe or secondary hypertension, uncontrolled heart failure, stroke or myocardial infarction within the last six months, cardiac arrhythmia, severe renal failure (S-creatinine > 200 µmol/L), abnormal liver tests, past history of carotid endarterectomy, chronic alcoholism, childbearing potential or pregnant or lactating women, terminal phase of serious illness, were not included in the study. All patients gave their written informed consent before entering the study.

Efficacy and safety assessment

The primary end point was to evaluate the effects of the two randomly allocated treatments on carotid IMT changes at after one year (M12), two years (M24) and three years (M36) as compared to baseline. The secondary end points were analyses of other carotid ultrasonography parameters (lumen diameter and cross-sectional area), office and ambulatory changes in BP. Occurrences of adverse events were notified for all the patients who received at least one dose of study medication.

Demographic, clinical and biological data

Data of each patient were gathered at selection visit (M-1) including gender, age, weight, height, duration of hypertension and diabetes, smoking and alcohol habits, relevant past medical history and concomitant medications.

At visits immediately prior to M0 and one month after commencing treatment M1, and then annually or when the patient prematurely left the trial, laboratory tests were undertaken, including haemogram, natremia, kaliemia, glycaemia, hepatic enzymes, S-creatinine, lipid profile (total cholesterol, HDL-C, triglycerides and LDL-C calculated according to Friedwald formula), HbA_{1C}, urinary strip test and albumin excretion rate on a urine sample. Venous blood samples were obtained in the morning after an overnight fast.

BP measurement

Office BP was measured at each visit using a mercury sphygmomanometer or other validated equipment.[2] After five minutes rest the patient remained in the sitting position and BP was measured three times at one minute intervals, the average being used to define office values. BP was measured once more after one minute in the standing position.

At the first visit, BP was measured on both arms and the arm with the highest values was determined and used for all future BP measurements. Heart rate was noted at the same time. Investigators were advised to use the same equipment throughout the study. On each visit day, the patient had to take the study drug after BP measurement in order for the haemodynamic investigation to be performed at trough.

ABPM over 24 hours was performed at M0 visit and then once a year. The equipment was connected between 8-10 am, and on that day patients had to take their study drug just after the first BP measurement. The equipment was a monitor oscillometric method or other validated monitor (BHS agreement). Several conditions were necessary to validate the ABPM: at least 24 hours, at least 64 valid measurements over 24 hours, at least one measurement between the 23rd and the 24th hour and less than two consecutive hour's between any recorded measurement.

Intima-media thickness evaluation

For echograph reading an expert committee of independent investigators was created. This committee was in charge of echographic examination training, selecting centres, checking echographic inclusion criteria and verifying the quality of criteria of echographic recording.

The B-mode ultrasonography was performed with echo machine using a probe with frequency transmission of $\geq$ 7.5 MHz. Both common carotid arteries were studied consecutively in the long axis with a probe incidence allowing good quality images. A zoom was used to define a zone of interest of 20 mm in length (stretching from 10 to 30 mm above the carotid bifurcation). A good image was defined by the presence of two hyper-echogenic lines, separated by a hypo-echogenic zone from the posterior artery wall. The IMT was defined as the distance separating the most internal parts of these lines and the luminal diameter by the distance between the blood-intima interfaces on the anterior and posterior walls.[22] The images were recorded in end-diastole and stored on an optical or floppy disk for subsequent analysis by a specific programme (TIMC laboratory, CHU Grenoble, France).

Methodology to determine the mean common carotid IMT has been previously described.[23] The value of IMT for each subject was the mean value for the two common carotid arteries.

An independent investigator, who was blinded to treatment group and trained in the interpretation of IMT images, performed off-line analysis of B-mode ultrasound images (Cardiology & Arterial Hypertension Dept, Grenoble University Hospital, France).

Sample size

To calculate the sample size, the following assumptions were considered: a significant difference of carotid IMT progression of 0.05 mm between the two treatment groups after 3-year follow-up (σ = 0.10 mm) with a risk α = 5% and power β = 90%. The size of the population had to be 84 patients randomised and completing the study in each group. To achieve this goal and anticipating premature study discontinuation of about 30%, 220 patients had to be included.

Statistical analysis

All data shown here have been calculated in the intention-to-treat population (i.e. all the patients who received any dose of study treatment during the active period of the trial).

Patient characteristics are expressed as mean $\pm$ SD values. A Chi^2 test or signification degree analysis with Fisher exact method was used to compare nominal qualitative variables in the two treatment groups, and either Students *t*-test if there was a normal distribution in both groups and Wilcoxon, was used for continuous variables. Pearson's coefficient was used to analyse the correlation between the IMT values (or the PP values) and other variables as follows: demographic and clinical characteristics, BP measurements (office and ambulatory), and biological laboratory values classically considered as cardiovascular risk factors; $p<0.05$ was significant.

A blind interim analysis on the first 100 randomised patients who had taken the study treatment for one year was initially planned but, this blind analysis was carried out on all the patients who had taken the treatment for a year and also had valid M12 carotid ultrasonography.

Results

Data at baseline

A total of 254 patients were recruited by physicians (n=131) from June 2000 to March 2002. Patients were randomised either into the CC arm (n=100) or into the AML arm (n=109) and, 45 patients did not enter the randomisation period for various reasons such as protocol violation (n=23) or baseline carotid ultrasonography not validated (n=19).

General characteristics of the 209 randomised patients are

Table 1. Patients baseline characteristics

	CC n=100	AML n=109	Total n=209
Sex, Male, n (%)	60 (60.0%)	73 (67.0%)	133 (63.6%)
Age, years	59.7±8.6	59.7±8.4	59.7±8.5
BMI, kg/m²	31.0±5.6	30.3±4.8	30.7±5.2
Smokers, n (%)			
current	15 (15.0%)	18 (16.5%)	33 (15.8%)
never	53 (53.0%)	52 (47.7%)	105 (50.2%)
ex	32(32.0%)	39 (35.8%)	71(34%)
Duration of hypertension			
years	7.5±7.5	7.9±7.8	7.7±7.6
median	5.1	6.5	5.9
Antihypertensive therapy, n (%)	75 (75.0%)	83 (76.1%)	158 (75.6%)
Duration of diabetes			
years	7.2±7.5	6.7±6.7	7.0±7.1
median	4.4	4.9	4.7
Glucose-lowering medications, n (%)	85 (85.0%)	91(83.5%)	176 (84.2%)

Key: Values are numbers (%), or mean (± SD);
CC = candesartan cilexetil; AML = amlodipine; BMI = body mass index

Table 2. Body mass index repartition

Category	BMI kg/m²	CC n=100	AML n=109	Total n=209
Normal	18.5–24.9	13%	9%	11%
Overweight	25–29.9	35%	43%	39%
Common obesity (class I)	30–34.9	39%	37%	35%
Severe obesity (class II)	35–39.9	8%	15%	11%
Massive obesity (class III)	≥ 40	4%	2%	3%

Key: CC = candesartan cilexetil; AML = amlodipine; BMI = body mass index

Table 3. Treatment at selection

	CC n=100	AML n=109	Total n=209
Antihypertensive medications*			
ACE-Inhibitors	24 (24.0)	37 (33.9)	61 (29.2)
Diuretics	26 (26.0)	30 (27.5)	56 (26.8)
Calcium channel blockers	14 (14.0)	25 (22.9)	39 (18.7)
Angiotensin II receptor antagonists	23 (23.0)	15 (13.8)	38 (18.2)
Beta-blockers	13 (13.0)	23 (21.1)	36 (17.2)
Vasodilatators	4 (4.0)	3 (2.8)	7 (3.3)
Drugs with central action	2 (2.0)	2 (1.8)	4 (1.9)
Glucose-lowering medications*			
Sulfonylureas	57 (57.0)	50 (45.9)	107 (51.2)
Metformin	50 (50.0)	55 (50.5)	105 (50.2)
Alpha-glucosidase inhibitors	13 (13.0)	17 (15.6)	30 (14.4)
Repaglinide	6 (6.0)	6 (5.5)	12 (5.7)
Others: benfluorex	5 (5.0)	5 (4.6)	10 (4.8)
Lipid-lowering medications			
Statins	29 (29.0)	37 (33.9)	66 (31.6)
Fibrates	8 (8.0)	20 (18.3)	28 (13.4)
Others: benfluorex	3 (3.0)	0 (0.0)	3 (1.4)

Key: Results are given as Numbers (percentage). * Several medications were taken by some patients; CC = candesartan cilexetil; AML = amlodipine

Table 4. Ultrasound measurements on the common carotid artery at baseline

	CC n=100	AML n=109	Total n=209
IMT, mm	0.76±0.16 (n=100)	0.73±0.15 n=108)	0.74±0.16 (n=108)
Lumen diameter, mm	6.47±0.77 (n=100)	6.51±0.70 (n=102)	6.49±0.73 (n=102)
Cross-sectional area, mm²	17.58±4.87 (n=100)	16.65±4.50 (n=102)	17.1±4.70 (n=102)

Key: Results are given as mean ± SD; the number of evaluated patients is given between parentheses; CC = candesartan cilexetil; AML = amlodipine

presented in table 1. Most of the patients were overweight (39%) or obese (50%) with no significant difference between both treatment groups (table 2).

As for hypertension, 24.4% of the patients were not treated and 57.9% were on ≥ 3 antihypertensive drugs. In 64.7% of the patients, hypertension was treated but not controlled. More than 80% of patients (84.2%) were on oral antidiabetic drugs, mainly sulphonylureas and metformin, some of them taking both. About two thirds of them (46.4%) were on lipid lowering drugs. Both groups were very similar as to associate treatments (table 3).

Haemodynamic data

Office BP and heart rate were similar in the two treatment groups, showing a mean systolic BP of 156±11 mmHg, a mean diastolic BP of 91±8 mmHg, a mean PP of 67±12 mmHg and a mean heart rate of 74±9 bpm. Ambulatory BP measurements over 24 hours were lower than office measurements with a mean systolic BP of 138±13 mmHg, a mean diastolic BP of 81±9 mmHg, and a mean PP of 57±10 mmHg. To the contrary, the heart rate was higher in the ambulatory measurements with a mean of 77±9 mmHg. The mean BP and heart rate values were similar between groups.

Laboratory measurement

Mean HbA_{1C} was < 7% for 56.4% patients, and 7–9% for 35.4% patients, with no significant differences between the two treatment groups.

Table 5. Univariate correlation of common carotid IMT and pulse pressure with clinical parameters (part A), blood pressure and heart rate (part B) and biological parameters (part C)

Part A

	Age	BMI	Duration of hypertension	Duration of diabetes	Number of cigarettes/day	Cornell index	Sokolow index
IMT	0.409*** (n=182)	-0.098 (n=182)	-0.037 (n=181)	0.144 (n=177)	-0.009 (n=182)	0.093 (n=116)	0.032 (n=116)
PP	0.203** (n=182)	0.024 (n=182)	0.147* (n=181)		-0.037 (n=182)	0.099 (n=116)	-0.058 (n=116)

Part B

	Office				Ambulatory			
	SBP	**DBP**	**PP**	**HR**	**SBP**	**DBP**	**PP**	**HR**
IMT	0.066 (n=182)	0.001 (n=182)	0.063 (n=182)	0.001 (n=182)	-0.04 (n=108)	-0.083 (n=108)	0.029 (n=108)	-0.000 (n=108)

Part C

	Glycaemia	Total C	LDL-C	HDL-C	Triglycerides	HbA_{1C}	Creatinaemia	Creatinine clearance
IMT	-0.005 (n=176)	0.096 (n=178)	0.136 (n=176)	-0.044 (n=178)	-0.013 (n=178)	0.138 (n=173)	0.171 (n=177)	-0.220** (n=177)
PP	-0.094 (n=176)	-0.019 (n=178)	-0.066 (n=176)	0.071 (n=178)	0.066 (n=178)	-0.036 (n=173)	0.045 (n=177)	- 0.089** (n=177)

Key: Results are given as R (regression) values; the numbers of patients included in the correlation analysis are shown in parentheses
BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; PP = pulsed pressure; HR = heart rate; C = cholesterol; HbA_{1C} = glycated haemoglobin; *p<0.05; **p<0.01; ***p<0.001

A total of 83.2% of patients had lipid abnormalities. Serum LDL-C was < 3.33 mmol/L (130 mg/dL) for 57.9% patients and 3.3–4.1 mmol/L (130–160 mg/dL) for 29.4% patients. Serum triglyceride was < 2.25 mmol/L (200 mg/dL) in 77% of the patients. These biochemical parameters were similar in the two treatment groups.

Ultrasonography measurement

Ultrasonography values of IMT, lumen diameter and cross-sectional area of the common carotid artery did not significantly differ between the two treatment groups at baseline (table 4).

Prediction of common carotid IMT and peripheral pulse pressure from baseline parameters

Correlations were calculated at baseline between carotid IMT and various parameters on the overall series of 209 randomised patients. Usual risk factors as age, gender, BMI, duration of hypertension, smoking habit, BP parameters, glycaemia, HbA_{1C} and lipid parameters, were tested in univariate correlation analyses. Significant correlations were found with age, male gender (p=0.013), S-creatinine and creatinine clearance (table 5). There was no significant correlation between IMT and ambulatory or office BP.

A multivariate analysis was performed where IMT of the common carotid artery was considered the dependent variable, and age, duration of diabetes, HbA_{1C} value and creatinine clearance were considered as the independent variables. Only age was significantly correlated with common carotid IMT in the global model (R^2= 0.22, p<0.0001).

Regarding office PP, it was only positively correlated with age and duration of hypertension (table 5).

Discussion

The MITEC study will provide data comparing the effects of candesartan cilexetil and amlodipine on vascular modelling after three years of treatment in hypertensive diabetic patients. Patients enrolled in the study were aged of 59.7±8.5 years and most of them were overweight or obese. Among the patients treated for hypertension, 64.7% were inadequately controlled and 57.9% were taking at least three antihypertensive drugs. Lipid disorders were present in 68% of patients. Glycaemic control was rather good with mean HbA_{1C} 7.1%. These baseline results depict a population of patients with high cardiovascular risk.

The measurement of carotid artery IMT using ultrasonography has emerged as a helpful method to evaluate the anatomical extent of atherosclerosis and its progression. As a major difference with arteriographic methods, ultrasonography of vessels gives an image of the arterial wall where atherosclerosis develops. Moreover, this method is non-invasive, safe and inexpensive and with a good intra-reproducibility for carotid IMT assessment.[24] Several studies have evidenced the important prognostic significance of carotid IMT measured by ultrasonography and IMT is now considered as a candidate marker of cardiovascular risk.[25-28]

At baseline, the mean common carotid IMT was 0.74±0.16 mm. Comparisons between studies is difficult as measures of carotid IMT may vary greatly between studies due to differences

in scanning protocols, instrumentation and methods for data analysis.[29]

Despite the limitations of comparing between studies, Aminbakhsh and Mancini[29] used IMT values from the literature and calculated that the risk of first MI increased with an IMT $\geq$ 0.822 mm and the risk of stroke increased with an IMT $\geq$ 0.75 mm. In many epidemiological studies, patients with an IMT above 1 mm have an increased risk of cerebrovascular or cardiovascular events.[14,27,28] In the ESH-ESC guidelines,[2] a carotid IMT $\geq$ 0.9 mm has been considered indicative of target organ damage due to hypertension.

Population studies have demonstrated that SBP is a major determinant of increased IMT of carotid artery.[21,25,30] In healthy subjects, IMT also increases with age and is higher in males.[31] In patients with cardiovascular risk factors, male gender, ageing, overweight, hypercholesterolemia, diabetes, and smoking are those which are the most strongly associated with IMT increase.[32] In the present study, in univariate regression analyses, IMT values were positively correlated with age and male gender and negatively correlated with creatinine clearance, correlations between BP and IMT were not observed. The negative correlation between IMT and creatinine clearance was not unexpected since it has been demonstrated that atherosclerosis is accelerated in patients with renal insufficiency, particularly in patients with type 2 diabetes.[25] Indeed, in patients with diabetes, microalbuminuria is now considered as an atherosclerotic risk factor.[26] It has been hypothesised that a general endothelial disorder is common to nephropathy, a microangiopathic complication, and atherosclerotic cardiovascular diseases. In the present study, the only factor associated independently with IMT was age. Our study population was relatively homogenous since all the patients had mild-to-moderate hypertension and rather well-controlled type 2 diabetes, and most of them were also overweight and had lipid disorders. Thus, in this high cardiovascular risk population, age appears as the major determinant of IMT as previously shown in a healthy population.[33] Regarding antihypertensive treatments, IMT progression seems to be slowed down or stabilised with amlodipine treatment.[15,16]

In conclusion, the analysis of the baseline data of the MITEC study confirms the importance of age in carotid IMT. Moreover, the negative correlation between creatinine clearance and IMT suggests the potential interest of IMT as a prognostic factor and as an integrative marker for cardiovascular risk in diabetic patients especially those with, frequent hypertension. The MITEC trial will show whether lowering blood pressure is able to prevent IMT progression, and compare the effectiveness of the antihypertensive agents candesartan cilexetil and amlodipine.

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Key messages

- The MITEC study assesses the effect of candesartan cilexetil versus amlodipine administered during three years on carotid intima-media thickness in hypertensive type 2 diabetic patients
- The MITEC population has good metabolic control at baseline
- In this population, carotid intima-media thickness is mainly related with age

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