D-09-04444R1

S0140-6736(09)61340-4

Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial

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Summary

Background The level to which systolic blood pressure should be controlled in hypertensive patients without diabetes remains unknown. We tested the hypothesis that tight control compared with usual control of systolic blood pressure would be beneficial in such patients.

Methods In this randomised open-label trial undertaken in 44 centres in Italy, 1111 non-diabetic patients with systolic blood pressure 150 mm Hg or greater were randomly assigned to a target systolic blood pressure of less than 140 mm Hg (usual control; n=553) or less than 130 mm Hg (tight control; n=558). After stratification by centre, we used a computerised random function to allocate patients to either group. Observers who were unaware of randomisation read electrocardiograms and adjudicated events. Open-label agents were used to reach the randomised targets. The primary endpoint was the rate of electrocardiographic left ventricular hypertrophy 2 years after randomisation. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00421863.

Results Over a median follow-up of 2.0 years (IQR 1.93–2.03), systolic and diastolic blood pressure were reduced by a mean of 23.5/8.9 mm Hg (SD 10.6/7.0) in the usual-control group and by 27.3/10.4 mm Hg (11.0/7.5) in the tight-control group (between-group difference 3.8 mm Hg systolic [95% CI 2.4–5.2], $p<0.0001$; and 1.5 mm Hg diastolic [0.6–2.4]; $p=0.041$). The primary endpoint occurred in 82 of 483 patients (17.0%) in the usual-control group and in 55 of 484 patients (11.4%) of the tight-control group (odds ratio 0.63; 95% CI 0.43–0.91; $p=0.013$). A composite cardiovascular endpoint occurred in 52 (9.4%) patients in the usual-control group and in 27 (4.8%) in the tight-control group (hazard ratio 0.50, 95% CI 0.31–0.79; $p=0.003$). Side-effects were rare and did not differ significantly between the two groups.

Interpretation Our findings lend support to a lower blood pressure goal than is recommended at present in non-diabetic patients with hypertension.

Funding Boehringer-Ingelheim, Sanofi-Aventis, Pfizer.

Introduction

The relation between the incidence of stroke or coronary heart disease and blood pressure is continuous at all ages.¹ Furthermore, a reduction in systolic blood pressure has explained most of the treatment benefit in outcome trials in patients with hypertension.² Hypertension guidelines recommend that systolic and diastolic blood pressure be reduced to values less than 140/90 mm Hg^{3,4} or 140/85 mm Hg.⁵ Present evidence lends supports to reduced thresholds of diastolic blood pressure in patients with type 2 diabetes,^{6–9} but clinical trials do not support the intensive lowering of mean arterial pressure in patients with renal dysfunction.¹⁰

The 2007 guidelines of the European Society of Hypertension³ and a recent editorial¹¹ have emphasised that the value to which systolic blood pressure should be lowered in patients with hypertension is unknown and that this issue should be regarded as an urgent research priority. In the *Studio Italiano Sugli Effetti CARDIOvascolari del Controllo della Pressione Arteriosa SISTolica* (Cardio-Sis) trial,¹² we tested the hypothesis that tight control

(<130 mm Hg) compared with usual control (<140 mm Hg) of systolic blood pressure would be beneficial in non-diabetic patients with hypertension.^{13,14}

Methods

Patients

We have previously described the design of Cardio-Sis in detail.¹² Briefly, we enrolled patients aged 55 years or older with a systolic blood pressure of 150 mm Hg or higher, who had been receiving antihypertensive treatment for at least 12 weeks. Patients were enrolled from 44 centres in Italy between Feb 22, 2005, and Feb 28, 2007. Eligible patient had to have at least one additional risk factor, as described in the guidelines of the European Society of Hypertension³ (cigarette smoking, total cholesterol ≥ 5.2 mmol/L, HDL cholesterol <1.0 mmol/L, LDL cholesterol ≥ 3.4 mmol/L, family history of premature cardiovascular disease in first degree relative [<65 years in women and <55 years in men], previous transient ischaemic attack or stroke, or established coronary or peripheral arterial disease). We

Lancet 2009; 374: 525–33

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Figure 1: Trial profile

SBP=systolic blood pressure. ECG=electrocardiogram. LVH=left ventricular hypertrophy. BBB=left or right bundle branch block. PM=pacemaker.

excluded patients with a fasting glucose of 7.0 mmol/L or higher and those with a history of diabetes, because existing evidence⁶⁻⁹ lends supports to intensive lowering of diastolic blood pressure in such patients and because present guidelines recommend tight blood-pressure control in patients with diabetes.³⁻⁵ Other exclusion criteria were any disease reducing life expectancy, renal dysfunction (serum creatinine >176.8 µmol/L), clinically relevant hepatic or haematological disorders, valvular heart disease, disorders confusing the electrocardiographic diagnosis of left ventricular hypertrophy (complete right or left bundle block, Wolff-Parkinson-White syndrome, previous Q-wave myocardial infarction, and paced heart rhythm), atrial fibrillation, and substance misuse. The ethics review committee of each participating centre approved the protocol, and all patients provided written informed consent.

Randomisation and masking

Eligible patients entered a run-in period to ascertain that at two visits 7–14 days apart their systolic blood pressure on their present antihypertensive drug treatment was 150 mm Hg or higher.¹² After stratification by centre, we used a computerised random function to allocate patients in a 1:1 ratio to tight (<130 mm Hg) or usual control (<140 mm Hg) of systolic blood pressure. Randomisation was done with a fully computerised system, with the group assignment concealed and blocks of four patients per site. Field investigators entered patient's data into the system, which verified the appropriateness of each patient for randomisation on the basis of inclusion and exclusion criteria. After all steps were completed successfully, a randomisation code was provided by the system and patients were assigned in an open manner to one of the two groups.

	Usual control (n=553)	Tight control (n=558)
Age (years)	67 (7)	67 (7)
Body-mass index (kg/m ²)	27·8 (4·0)	27·8 (4·3)
Waist circumference (cm)	98·5 (11·6)	98·6 (12·2)
Systolic pressure (mm Hg)	163·3 (11·1)	163·3 (11·3)
Diastolic pressure (mm Hg)	89·7 (8·8)	89·6 (8·8)
Heart rate (beats per min)	70·4 (10·7)	71·2 (10·2)
Serum creatinine (μmol/L)	83·8 (18·6)	83·2 (19·4)
Glucose (mmol/L)	5·43 (0·63)	5·46 (0·71)
Total cholesterol (mmol/L)	5·63 (1·14)	5·57 (1·0)
HDL cholesterol (mmol/L)	1·50 (0·51)	1·50 (0·50)
LDL cholesterol (mmol/L)	3·40 (0·98)	3·38 (0·94)
Women	324 (59%)	329 (59%)
Current cigarette smoking	115 (21%)	120 (22%)
Dyslipidaemia*	425 (77%)	418 (75%)
Coronary artery disease	69 (13%)	59 (11%)
Stroke or transient ischaemic attack	49 (9%)	42 (8%)
Occlusive arterial disease	11 (2%)	19 (3%)
Drugs		
Diuretics	259 (47%)	226 (41%)
β blockers	212 (38%)	180 (32%)
ACE inhibitors	243 (44%)	245 (44%)
Angiotensin-receptor blockers	159 (29%)	193 (35%)
Calcium-channel blockers	196 (35%)	184 (33%)
α1 blockers	52 (9%)	50 (9%)
Centrally acting drugs	13 (2%)	13 (2%)
Statins	128 (23%)	125 (22%)
Aspirin	104 (19%)	107 (19%)

Data are mean (SD) or number (%). ACE=angiotensin-converting enzyme.
 *Dyslipidaemia is a total cholesterol of 5·2 mmol/L or more, an HDL cholesterol of less than 1·0 mmol/L, or an LDL cholesterol of 3·4 mmol/L or more at randomisation.

Table 1: Baseline characteristics

The steering committee was responsible for the scientific integrity, conduct, and publication of the trial. An endpoint committee, unaware of the randomisation code, adjudicated all incident clinical events according to published diagnostic criteria¹² on the basis of the records provided by the clinical investigators. The coordinating office was located at the research centre of the Italian Association of Hospital Cardiologists (ANMCO) in Florence, Italy. Blinded experts, unaware of the randomisation group, read all electrocardiograms at a central facility.

Outcomes

The primary study outcome was the prevalence of electrocardiographic left ventricular hypertrophy at the final 2-year visit.¹² This endpoint is an intermediate outcome that is a strong predictor of cardiovascular outcomes.^{15,16} According to the validated Perugia score,^{17,18} the diagnosis of left ventricular hypertrophy required at least one of three criteria: (1) modified Cornell voltage

Figure 2: Rate of left ventricular hypertrophy by randomisation groups at baseline and follow-up

The odds ratio (OR) was estimated by the PROC GENMOD procedure, taking into account the randomised groups, the time of observation, the group-by-time interaction, and the rate of left ventricular hypertrophy at entry. Error bars denote 95% CIs.

(SV3+RaVL >2·0 mV in women and >2·4 mV in men); (2) left ventricular strain (inverted asymmetric T wave with flat or downsloping ST-segment and at least 0·05 mV depression 80 ms after the J point); or (3) a Romhilt-Estes score of 5 or more.¹⁹ The main prespecified¹² secondary outcome was a composite of all-cause mortality, fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, transient ischaemic attack, congestive heart failure of New York Heart Association stages III or IV requiring admission to hospital, angina pectoris with objective evidence of myocardial ischaemia, new-onset atrial fibrillation, coronary revascularisation, aortic dissection, occlusive peripheral arterial disease, and renal failure requiring dialysis. Other predefined¹² secondary outcomes were the single components of the main secondary outcome and the baseline-adjusted difference between groups in the achieved systolic blood pressure.

Procedures

After randomisation, patients were followed up every 4 months for 2 years.¹² At every visit, physicians measured blood pressure by auscultation (diastolic phase 5), with standard mercury sphygmomanometers, after patients had been seated for at least 10 min. Blood pressure was the average of three consecutive readings at every visit. At the second run-in visit and at 1 and 2 years, patients had a 12-lead electrocardiogram and biochemical blood tests (total cholesterol and HDL and LDL cholesterol, glucose, creatinine, and potassium). Patients not attending one or more visits remained in follow-up by telephone.

Treatment to lower blood-pressure was open label and tailored to every patient's needs. Antihypertensive drug treatment included various combinations of

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For the **Cardio-Sis website** see <http://www.cardio-sis.it>

previous drugs (background therapy) plus drugs made available for the purpose of the study. We dispensed furosemide (25 mg per day), ramipril (5 mg or 10 mg per day), telmisartan (80 mg per day), amlodipine (5 mg or 10 mg per day), bisoprolol (5 mg per day), and transdermal clonidine (2.5 mg or 5.0 mg per day). Ramipril and telmisartan were also available in fixed combinations with hydrochlorothiazide (12.5 mg or 25.0 mg per day for ramipril, and 12.5 mg per day for telmisartan). At every visit, the choice of drugs in individual patients was left to the discretion of the investigators. In the tight-control group, one systolic blood-pressure reading higher than 130 mm Hg at any visit led to intensification of treatment. Conversely, in the usual-control group, achievement of a systolic blood pressure below 130 mm Hg entailed downtitration of treatment.

We tested the inter-reader degree of agreement for the categorical diagnosis of left ventricular hypertrophy (absent or present) in a random sample of 200 patients. There was agreement between the two readers in 193 of 200 tracings (κ statistic 0.89, 95% CI 0.81–0.97;

$p < 0.0001$). Under supervision of the steering committee, Clinical Research Technology S.r.l., Salerno, Italy developed the clinical-report forms, which ran entirely on the Cardio-Sis website. The quality of the electronic data was checked against the source documents by on-site audits undertaken every 6 months and at the end of the study. Drug supply to the clinical centres was automated on the basis of the information in the submitted electronic case-report forms.

Statistical analysis

For database management and statistical analysis, we used the SAS package (version 9.1.3). We computed sample size, assuming that the prevalence of left ventricular hypertrophy would be 25% at enrolment, and 19% in the usual-control group and 12% in the tight-control group at the final 2-year visit. To show a 7% absolute difference between the groups in the prevalence of left ventricular hypertrophy on two-sided tests with an α -level of 0.05 and 0.85 power, assuming a drop-out rate of 12% over 2 years, 1100 patients (550 per group) needed to be randomly assigned.

Analysis was by intention to treat with all available data. We compared means by the standard normal Z test and proportions by χ^2 analysis. We used logistic regression analysis to compare the primary outcome in the two groups. We used general estimating equations (categorical variables) or linear mixed models (continuous variables), as implemented in the PROC GENMOD and PROC MIXED procedures of the SAS package, with patients set as the random effect. We assessed the incidence of events, with Kaplan-Meier survival function estimates, the log-rank test, and Cox regression. In these analyses, we considered only the first event for each type of outcome.

This trial is registered with ClinicalTrials.gov, number NCT00421863.

Role of the funding source

The sponsors of the study had no role in the design or the conduct of the trial, data collection, database management, statistical analysis, interpretation of the results, or writing of the report. The members of the steering committee and the writing committee had full access to the database and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile and table 1 the baseline characteristics. Of 1193 patients screened, 1111 (93%) were randomly assigned: 553 to usual control and 558 to tight control of systolic blood pressure. Median duration of follow-up was 2.0 years (IQR 1.93–2.03). At the end of the study, the number of patient-years was 1013 in the usual-control group and 1060 in the tight-control group. Only one patient, allocated to usual control, was lost to follow-up.

Figure 3: Sensitivity analyses for the primary outcome

The odds ratios were estimated by the PROC GENMOD procedure, taking into account the randomised groups, the time of observation, the group-by-time interaction, and the rate of left ventricular hypertrophy at entry. The rate in the control group was determined at the final (2-year) visit. TIA=transient ischaemic attack. *Dyslipidaemia is a total cholesterol of 5.2 mmol/L or more, an HDL cholesterol less than 1.0 mmol/L, or an LDL cholesterol of 3.4 mmol/L or more at randomisation.

Blood pressure decreased by 25.8/9.9 mm Hg at 1 year and by 27.7/10.8 mm Hg at 2 years in the usual-control group, and by 30.5/11.4 mm Hg at 1 year and 31.3/12.3 mm Hg at 2 years in the tight-control group ($p<0.0001$). The mean reduction in blood pressure, calculated as the average of all differences in blood pressure between the baseline visit and all subsequent visits, was 23.5/8.9 mm Hg (SD 10.6/7.0) in the usual-control group and 27.3/10.4 mm Hg (SD 11.0/7.5) in the tight-control group. The blood pressure difference between the two groups averaged 3.8 mm Hg systolic (95% CI 2.4–5.2) and 1.5 mm Hg diastolic (0.6–2.4). In the mixed model, the time-by-group interaction was significant for both systolic ($p<0.0001$) and diastolic ($p=0.041$) blood pressure.

The achieved systolic blood pressure was less than 140 mm Hg in 64.4% (331/514) of patients at 1-year follow-up and in 66.9% (334/499) at 2-year follow-up in the usual-control group, compared with 75.5% (385/510) of patients at 1-year follow-up and 78.7% (399/507) at 2-year follow-up in the tight-control group ($p<0.0001$ between groups). The achieved systolic blood pressure was less than 130 mm Hg in 23.3% (120/514) of patients at 1-year follow-up and 27.3% (136/499) at 2-year follow-up in the usual-control group, compared with 45.3% (231/510) of patients at 1-year follow-up and 72.2% (366/507) at 2-year follow-up in the tight-control group ($p<0.0001$ between groups). At the end of the study (2-year visit), blood pressure was 135.6/78.7 mm Hg in the usual-control group and 131.9/77.4 mm Hg in the tight-control group.

Figure 1 shows the number of patients with electrocardiograms that were interpretable for the diagnosis of left ventricular hypertrophy at 1 and 2 years of follow-up. At the 2-year visit (figure 2), the proportion of patients who achieved the primary outcome was 17.0% (82/483) in the usual-control group and 11.4% (55/484) in the tight-control group (odds ratio [OR] 0.63, 95% CI 0.43–0.91; $p=0.013$).

Since the PROC GENMOD analysis showed a strong evidence of a time-by-group interaction ($p=0.018$), we compared the likelihood of left ventricular hypertrophy in the two groups at all visits. Although the groups did not differ at baseline (OR 1.02, 95% CI 0.86–1.22; $p=0.80$), left ventricular hypertrophy was less likely in the tight-control than in the usual-control group at 1 year (0.48, 0.27–0.84; $p=0.010$) and at 2 years (0.46, 0.26–0.82; $p=0.008$). When we examined the two groups separately, the likelihood of left ventricular hypertrophy, compared with baseline, decreased in tight-control group at 1 year (OR 0.38, 95% CI 0.24–0.59; $p<0.0001$) and at 2 years (0.31, 0.20–0.47; $p<0.0001$). By contrast, the reduction in the likelihood of left ventricular hypertrophy was not significant in the usual-control group both at 1 year (0.82, 0.51–1.30; $p=0.39$) and at 2 years (0.68, 0.41–1.12; $p=0.13$). Sensitivity analyses by prespecified baseline characteristics were confirmatory (figure 3).

Figure 4: Main composite secondary endpoint in the two groups
HR=hazard ratio.

Figure 4 shows the survival function estimates of the composite secondary outcome by treatment group, which occurred in 52 (9.4%) patients in the usual-control group and in 27 (4.8%) in the tight-control group (hazard ratio [HR] 0.50, 95% CI 0.31–0.79; $p=0.003$; table 2). The event rate was 5.14 (95% CI 3.9–6.7) per 100 patient-years in the usual-control group and 2.54 (1.75–3.72) in the tight-control group. With regard to the components of the composite outcome (table 2), new-onset atrial fibrillation and coronary revascularisation occurred less in the tight-control than in the usual-control group (table 2). The incidence of myocardial infarction, admission for heart failure, stroke, transient ischaemic attack, and all-cause death was low and did not differ between the groups (table 2).

Adverse reactions (table 3) were rare, generally mild, and occurred at a similar rate in the two treatment groups. One patient in each group had angioedema. One patient in the tight-control group had a severe skin reaction requiring admission to hospital. During follow-up, serum potassium decreased to less than 3.0 mmol/L in one patient in the usual-control group and in two in the tight-control group ($p=0.56$), and glucose concentrations increased to 7.0 mmol/L or higher in 33 patients in the usual-control group and in 32 in the tight-control group ($p=0.87$).

The number of antihypertensive drug classes used increased from baseline in both study groups ($p<0.0001$); however, neither the difference between the groups ($p=0.79$) or the time-by-group interaction was significant ($p=0.22$). On average, 2.0 (SD 1.00) drug classes were used in both groups at randomisation, 2.8 (1.01) classes

	Usual control (n=553)	Tight control (n=557)	HR (95% CI)	p value
Death from any cause, MI, stroke, TIA, atrial fibrillation, admission for heart failure, angina, or coronary revascularisation*	52 (9.4%)	27 (4.8%)	0.50 (0.31–0.79)	0.003
Death from any cause, MI, stroke, admission for heart failure, angina, or coronary revascularisation†	32 (5.8%)	17 (3.0%)	0.51 (0.29–0.93)	0.027
Single components of composite outcomes				
Coronary revascularisation	15 (2.7%)	5 (0.9%)	0.33 (0.12–0.91)	0.032
New-onset atrial fibrillation	21 (3.8%)	10 (1.8%)	0.46 (0.22–0.98)	0.044
MI	6 (1.1%)	4 (0.7%)	0.66 (0.19–2.34)	0.52
Admission for heart failure	7 (1.3%)	3 (0.5%)	0.42 (0.11–1.63)	0.21
Stroke or TIA	9 (1.6%)	4 (0.7%)	0.44 (0.13–1.42)	0.16
Death from any cause	5 (0.9%)	4 (0.7%)	0.77 (0.21–2.88)	0.70

Data are number of incident events (%). HR=hazard ratio. MI=myocardial infarction. TIA=transient ischaemic attack.
*Pre-defined secondary outcome. †Post-hoc defined composite outcome, which does not include transient ischaemic attack and atrial fibrillation.

Table 2: Incidence of the secondary outcome, its components, and death from any cause by randomisation group

	Usual control (n=553)	Tight control (n=557)	p value
Asthenia	5 (0.9%)	13 (2.3%)	0.06
Cough	7 (1.3%)	14 (2.5%)	0.13
Angioedema	1 (0.2%)	1 (0.2%)	0.99
Skin reactions	8 (1.4%)	15 (2.7%)	0.21
Diarrhoea	5 (0.9%)	7 (1.3%)	0.57
Headache	6 (1.1%)	3 (0.5%)	0.31
Peripheral oedema	27 (4.9%)	18 (3.2%)	0.16
Hypotensive symptoms	2 (0.4%)	5 (0.9%)	0.26
Palpitations	2 (0.4%)	5 (0.9%)	0.26
Dizziness	4 (0.7%)	2 (0.4%)	0.41
Potassium <3 mEq/L	1 (0.2%)	2 (0.4%)	0.56
Glucose ≥7.0 mmol/L	33 (6.7%)	32 (6.4%)	0.87
Any adverse reaction	61 (11.0%)	72 (12.9%)	0.34

Data are number of patients (%).

Table 3: Adverse reactions by randomised group

at 1-year follow-up, and 2.9 (1.01) at 2-year follow-up. When individual drug classes were examined separately (figure 5), after adjustment for imbalances at baseline (table 1), patients in the tight-control group were more likely to receive diuretic drugs than were those in the usual-control group (OR 1.36; 1.08–1.71; $p=0.009$). The use of angiotensin-receptor blockers in the tight-control group was 17% higher than in the usual-control group (OR 1.17, 0.90–1.52; $p=0.066$). The use of β blockers, calcium-channel blockers, and angiotensin-converting enzyme inhibitors did not differ between the two groups (figure 5).

128 (23%) patients were taking statins at baseline and 177 (35%) at 2 years in the usual-control group, and 125 (22%) compared with 178 (35%) in the tight-control group. Aspirin was given to 104 (19%) patients at

baseline and 127 (25%) at 2 years in the usual-control group, and to 107 (19%) and 118 (23%) in the tight-control group. We noted a significant increase in the use of statins and aspirin from baseline to 2-year follow-up (both $p<0.0001$), without any statistical difference between the two groups ($p=0.94$ for aspirin and $p=0.47$ for statins).

Discussion

Findings from our trial have shown that setting a systolic target of less than 130 mm Hg instead of the usual 140 mm Hg in patients with treatment-resistant systolic hypertension was feasible and well tolerated. Over 2 years, tight compared with usual blood-pressure control in non-diabetic patients with uncontrolled hypertension at baseline resulted in a reduction in systolic blood pressure. This reduction decreased the likelihood of left ventricular hypertrophy and the incidence of the prespecified composite cardiovascular outcome.

Seven trials,^{6–11,20,21} of which two are still in progress,^{11,21} aimed to show the potential benefits of tight versus usual blood-pressure control. Only the Japanese trial to assess optimal systolic blood pressure in elderly hypertensive patients (JATOS)²⁰ was specifically designed to compare tight (<140 mm Hg) with moderate (140–160 mm Hg) control of systolic blood pressure irrespective of diastolic blood pressure in hypertensive patients aged 65–85 years with systolic blood pressure greater than 160 mm Hg. During the 2-year follow-up, the incidence of cardiovascular events did not differ between the groups. The enrolment of diabetic patients and those aged 80–89 years with complicated hypertension, and the implementation of a treatment schedule mainly based on efonidipine (51.1%) with underuse of diuretic drugs (12.1%), might explain the difference between results from JATOS²⁰ and our study. Two trials in patients with type 2 diabetes^{7,9} had either only diastolic blood pressure goals^{8,9} or both systolic and diastolic blood pressure goals.⁷ The United Kingdom Prospective Diabetes Study (UKPDS)⁷ was undertaken exclusively in hypertensive patients with diabetes. In the Hypertension Optimal Treatment Trial (HOT),⁶ better control of diastolic blood pressure resulted in a reduction of the composite cardiovascular endpoint only in the subset of 1501 patients with diabetes (incidence 9.0% with the blood pressure goal <90 mm Hg, 6.8% with goal <85 mm Hg, and 4.4% with goal <80 mm Hg; $p=0.005$).⁶ The Afro-American Study of Kidney Disease and Hypertension (AASK)¹⁰ was undertaken in black hypertensive patients with nephropathy.

We powered our study on left ventricular hypertrophy as the primary outcome. Although usually described as an intermediate endpoint, electrocardiographic left ventricular hypertrophy is a powerful and independent predictor of outcome when diagnosed at one visit²² or as a trend over time.^{15,16,23} In the Framingham Heart study,¹⁵ patients with left ventricular hypertrophy at baseline and

Figure 5: Percentage of patients in the usual-control and tight-control groups treated at baseline and follow-up with various classes of antihypertensive drugs. Error bars denote 95% CIs. ACE=angiotensin-converting enzyme.

a serial increase over time in the electrocardiographic voltages were twice as likely to have a cardiovascular event during the subsequent 2 years than were those with a decrease in the voltages. The primary objective of the double-blind Heart Outcomes Prevention (HOPE) trial^{24,25} was to show benefit beyond blood-pressure lowering of the angiotensin-converting enzyme inhibitor ramipril, which was given in addition to usual treatment in high-risk patients with normal or modestly increased blood pressure. Systolic blood pressure was 3 mm Hg lower with ramipril than with placebo.²⁵ Electrocardiographic left ventricular hypertrophy was defined by voltage criteria,²³ and it was not one of the predefined outcomes.²⁴ Electrocardiographic left ventricular hypertrophy was present at baseline in 8% of patients (676/8281) and it was reduced by 17% with ramipril compared with placebo after 5 years of treatment (HR 0.83, 95% CI 0.72–0.95; $p=0.008$).²³ Prevalence of left ventricular hypertrophy at baseline was lower in HOPE than in Cardio-Sis, which was consistent with the lower blood pressure at baseline in patients in the HOPE trial.

In our present study, the use of antihypertensive drugs during follow-up increased equally in the two groups, indicating an aggressive therapeutic strategy. Furthermore, the use of aspirin and statins increased equally in the two groups. Diuretic drugs and, to a lesser extent, angiotensin-receptor blockers were more frequently used in the tight-control group than in the usual-control group. Since the use of specific classes of drugs was not driven by protocol but was left to the judgment of investigators, these findings could indicate a tendency towards the use of diuretic drugs and angiotensin-receptor blockers to achieve a tight control of systolic blood pressure.

Although the number of events of clinical outcome was small, coronary revascularisation and episodes of new-onset atrial fibrillation were significantly less frequent in the tight-control group than in the usual-control group. The lower risk of new-onset atrial fibrillation in the tight-control group is consistent with the reported association between the risk of atrial fibrillation and poor control of systolic blood pressure.²⁶

Our trial has to be interpreted within the context of its potential limitations and strengths. First, we based the diagnosis of left ventricular hypertrophy on the electrocardiogram, which is less sensitive than is echocardiography.²⁷ However, we centralised and standardised the reading of the electrocardiograms and based the diagnosis of electrocardiographic left ventricular hypertrophy on the validated Perugia score,^{17,18} which incorporates both voltages and repolarisation, rather than on simple voltage criteria. In a longitudinal study of hypertensive patients with left ventricular hypertrophy at baseline diagnosed by this score, patients with regression of left ventricular hypertrophy at follow-up had a 54% reduced risk of primary outcome events. In overweight and obese individuals randomly assigned in the Losartan Intervention For Endpoint Reduction (LIFE) study,²⁸ the diagnostic performance of the Perugia score^{17,18} was better than that of the Sokolow-Lyon index²⁹ and similar to that of the Cornell voltage-duration product.²⁷

Second, since this study was not double blind, awareness of the randomisation code could have affected the clinical decisions related to secondary outcome events, especially admission for heart failure and coronary revascularisation. Third, since the study has been entirely undertaken in white patients, extrapolation to other ethnic groups, such as African-Americans,¹⁰

might not be justified. Fourth, we did not include patients with diabetes mellitus—a group for which present guidelines based on the already available evidence^{6–9} recommend tight pressure control.^{3–5} Finally, although the secondary clinical outcome of our study was consistent with the primary outcome of left ventricular hypertrophy, few clinical events occurred because of the fairly small sample size and because the follow-up was limited to 2 years. Our outcome results should therefore be viewed as hypothesis generating, but might potentially be useful for planning large outcome trials focusing on clinical events. The Systolic Blood Pressure Intervention Trial (SPRINT), funded by the US National Institutes of Health, will test the notion that tight control of systolic blood pressure to less than 120 mm Hg is better than is usual control to less than 140 mm Hg for the prevention of cardiovascular disease.¹¹ This trial is still in the planning stage.¹¹

In conclusion, tight control of systolic blood pressure to less than 130 mm Hg in non-diabetic patients with at least one additional risk factor decreased the likelihood of electrocardiographic left ventricular hypertrophy and clinical events, compared with usual control to less than 140 mm Hg systolic. Because of the poor amount of blood-pressure control in the general population and clinical trials, and because of the direct relation between cardiovascular protection and blood-pressure lowering, the results of Cardio-Sis draw attention to the potential benefits of tight blood-pressure control in non-diabetic patients with hypertension.

Contributors

PV, JAS, FA, AA, GdS, AG, GM, SP, APM, DL, and GR contributed to the design of the study and to the collection and interpretation of the data. GR and FA did the statistical analysis. PV and JAS wrote the first draft of the report. All authors contributed to draft the report and read and approved the final version.

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Conflicts of interest

PV, FA, and GR received consulting and lecturing fees from Boehringer-Ingelheim and Sanofi-Aventis. AM and DL received research support from Boehringer-Ingelheim, Sanofi-Aventis, and Pfizer. JAS received consulting and lecturing fees and research support from AstraZeneca, Daiichi-Sankyo, Mitsubishi Tanabe Pharma, Novartis, Pfizer, and Sigma-Tau. GM, AA, GdS, AG, and SP declare that they have no conflicts of interest.

Acknowledgments

Cardio-Sis was an investigator-initiated study supported by Associazione Medici Cardiologi Ospedalieri (ANMCO) through grants from Boehringer-Ingelheim, Sanofi-Aventis, and Pfizer to ANMCO. We thank T Richart (Leuven, Belgium) for preparing the figures; and Sandra Covens and Ya Zhu (Leuven, Belgium) for their expert assistance in preparing the report for submission.

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