Journal of Human Hypertension (2008) 22, 243–251

www.nature.com/jhh

ORIGINAL ARTICLE

Randomized study of traditional versus aggressive systolic blood pressure control (Cardio-Sis): rationale, design and characteristics of the study population

Cardio-Sis Study Group (see appendix)
Struttura Complessa di Cardiologia, Unità di Ricerca Clinica—Cardiologia Preventiva, Ospedale S Maria della Misericordia, Perugia, Italy

The hypothesis that a therapeutic strategy aimed at lowering systolic blood pressure (SBP) below 130 mm Hg is superior to a conventional strategy targeted at below 140 mm Hg in hypertensive subjects has never been tested in randomized intervention studies. The Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica (Cardio-Sis) is a multicentre study in non-diabetic, treated hypertensive subjects aged >55 years with uncontrolled SBP (⩾150 mm Hg) and at least one additional cardiovascular risk factor (ClinicalTrials.gov identifier: NCT00421863). Subjects are randomized to an SBP goal <140 mm Hg (conventional) or <130 mm Hg (aggressive), independently of baseline and achieved diastolic blood pressure (BP). Anti-hypertensive drugs dispensed for the study are restricted to a list of specific drugs. The primary outcome of the study is based on regression of left ventricular hypertrophy (LVH) using electrocardiography (ECG). The hypothesis is that subjects without LVH regression or with new development of LVH 2 years after randomization are 19% with conventional strategy and 12% with aggressive strategy. Secondary outcome is a composite pool of pre-specified fatal and non-fatal events. Randomization of 1111 subjects was completed by February 2007. Mean age of subjects (41% men) at entry was 67 years. BP was 158/87 mm Hg (systolic/diastolic) and prevalence of LVH by ECG was 21.0%. Cardio-Sis is the first randomized study specifically designed to compare two different SBP goals. Results will be broadly applicable to subjects with uncontrolled SBP under anti-hypertensive treatment.
Journal of Human Hypertension (2008) **22,** 243–251;
doi:10.1038/sj.jhh.1002313; published online 29 November 2007

Keywords: systolic blood pressure; prognosis; left ventricular hypertrophy; electrocardiography

Introduction

Only a minority of treated hypertensive subjects achieve adequate blood pressure (BP) control as suggested by guidelines,[1–4] although it is well established that poor BP control identifies subjects at increased cardiovascular risk.[5–7] The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure suggests that the goal of anti-hypertensive treatment should be the reduction of BP to <140/90 mm Hg, and to <130/80 mm Hg in patients with diabetes and chronic renal disease.[1] The 2007 European Society of Hypertension/European Society of Cardiology Guidelines suggest that BP goal should be <140/90 mm Hg in all hypertensive patients, and <130/80 mm Hg in diabetics and high or very high risk patients.[2] However, despite the epidemiological evidence of a continuous relation between BP and cardiovascular risk starting from 115/75 mm Hg[8] and retrospective analyses of available trials,[9–12] there are no randomized prospective intervention studies showing that a systolic blood pressure (SBP) goal <130 mm Hg is superior to a conventional goal (<140 mm Hg) in terms of cardiovascular protection in high-risk hypertensive subjects. Table 1 shows the available randomized trials that compared different BP goals. None of these studies compared different SBP targets in non-diabetic hypertensive subjects.

Consequently, The Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica (Italian Study on Cardiovascular Effects of Systolic Blood Pressure Control, Cardio-Sis) was planned to test the hypothesis that a therapeutic strategy based solely on reduction of SBP <130 mm Hg is superior to a traditional strategy based on SBP reduction <140 mm Hg in non-diabetic hypertensive subjects. The primary end point is based on the hypothesis that the

Correspondence: Dr P Verdecchia, Struttura Complessa di Cardiologia, Unità di Ricerca Clinica—Cardiologia Preventiva, Ospedale S Maria della Misericordia, Piazzale G Menghini, Perugia 06132, Italy.
E-mail: verdec@tin.it
Received 27 July 2007; revised 22 October 2007; accepted 27 October 2007; published online 29 November 2007

Table 1 Comparison between different blood pressure goals in randomized studies

Trial	*Targets compared*	*Number of patients*	*Design*	*Clinical setting*	*Duration of follow-up (years)*
African-American study of hypertensive kidney disease and hypertension	MBP $\leqslant$92 mm Hg vs 102–107 mm Hg	1094	Open	Hypertension+nephropathy (African-Americans)	3.8
Appropriate blood pressure control in diabetes trial (hypertension)	DBP $\leqslant$75 mm Hg vs $\leqslant$90 mm Hg	470	Open	Hypertension+diabetes	5.3
Appropriate blood pressure control in diabetes trial (normotension)	DBP 10 mm Hg below baseline vs 80–89 mm Hg	480	Open	Diabetes	5.3
Hypertension optimal treatment study	DBP $\leqslant$80 vs $\leqslant$85 vs $\leqslant$90 mm Hg	18 790	Open	Hypertension	3.8
UK prospective diabetes study—hypertension in diabetes study	DBP $<$85 mm Hg vs $<$105 mm Hg	1148	Open	Hypertension+diabetes	8.4

Abbreviations: DBP, diastolic blood pressure; MBP, mean blood pressure; UK, United Kingdom.
Modified from reference [29].

different strategies are associated with different changes in left ventricular hypertrophy (LVH) by electrocardiography (ECG), used as an intermediate outcome measure.[13–16]

Materials and methods

Cardio-Sis is a prospective multi-centre, randomized study with two parallel groups.

Study objectives

The primary objective of the study was the comparison between two SBP goals ($<$130 mm Hg, labelled as 'aggressive' and $<$140 mm Hg labelled as 'conventional') on the 2-year modification of ECG-LVH evaluated by the Perugia score,[17,18] which is defined by the presence of at least one of the following three criteria:

(1) A modified Cornell voltage ($SV_3 + RaVL > 2.4$ mV in men, >2.0 mV in women).
(2) A typical left ventricular (LV) strain (inverted T wave with asymmetric branches associated with flat or downsloping ST-segment with at least 0.05 mV depression 80 ms after the J point).
(3) A Romhilt–Estes score $\geqslant 5$.

The secondary objective of the study was the comparison between two SBP goals in the incidence of a composite pool of pre-specified fatal and non-fatal events (fatal and non-fatal myocardial infarction, fatal and non-fatal strokes, transient ischaemic attack, sudden cardiac death, death due to other cardiovascular causes, death due to non-cardiovascular causes, congestive heart failure, New York Heart Association (NYHA) stage III or IV requiring hospitalization, angina with objective evidence of myocardial ischaemia, new onset atrial fibrillation, coronary re-vascularization (bypass or angioplasty, peripheral occlusive arterial disease, renal failure requiring dialysis, aortic dissection). For patients with more than one event, the survival time up to the first event was used in the analysis. The comparison between the two groups in the serial changes in systolic and diastolic BP was another secondary end point of the study.

Patients

Eligible patients were men or women aged >55 years at randomization and with uncontrolled SBP (that is, $\geqslant$150 mm Hg) during prolonged (that is, $\geqslant$12-week duration) anti-hypertensive treatment. Inclusion criteria are detailed in Table 2. Exclusion criteria were diabetes, defined by fasting glucose $>125\,mg\,dl^{-1}$ in two samples or ongoing anti-diabetic treatment. Renal failure, defined by a serum creatinine $>2.0\,mg\,dl^{-1}$, chronic atrial fibrillation or flutter, clinically significant hepatic or haematological disorders, alcoholism, drug addiction, causes

precluding ECG interpretation for LVH (complete right or left bundle block, Wolff–Parkinson–White syndrome, previous Q-wave myocardial infarction), significant valvular heart disease, any disease causing reduced life expectancy. Patients with concomitant diabetes were excluded from the study because achievement of a tight BP control in these patients has already been suggested by current guidelines.[1,2]

Overview of study procedures

The study procedures are summarized in the Figure 1. During an initial run-in period, two qualifying visits 7–14 days apart were carried out to establish whether BP remains uncontrolled (SBP $\geqslant$ 150 mm Hg) under current treatment. At the end of the second visit, eligible patients were randomized to one of the two BP goals outlined above. Routine laboratory tests (total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, triglycerides, uric acid, aspartate aminotransferase, alanine aminotransferase, sodium, potassium, glucose, creatinine, uric acid and urinalysis) and a 12-lead ECG were carried out in this visit. Subsequent clinical visits were scheduled at 4-month intervals up to the end of the study (24 months after randomization). A complete clinical examination was carried out at each visit. ECG and routine laboratory tests were carried out at randomization and after 12 and 24 months.

Table 2 List of inclusion criteria

1. Current cigarette smoking
2. Total cholesterol $\geqslant 200\,mg\,dl^{-1}$, or HDL cholesterol $<40\,mg\,dl^{-1}$, or LDL cholesterol $\geqslant 130\,mg\,dl^{-1}$.
3. Family history of cardiovascular disease in male first degree relative <55 years or female first degree relative <65 years
4. Previous stroke or transitory ischaemic attack
5. Coronary artery disease defined by evidence of at least one of the following:
   a. Documentation of myocardial ischaemia by ECG, stress echocardiography or scintigraphy;
   b. Angiographic stenosis $>50\%$ in at least two major epicardial vessels;
   c. Prior aortocoronary bypass or percutaneous coronary angioplasty;
   d. Non-Q-wave myocardial infarction.
6. Peripheral occlusive arterial disease defined by evidence of claudication intermittents associated with angiographic or ecographic evidence of $>60\%$ arterial stenosis

Abbreviations: ECG, electrocardiography; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Blood pressure measurement

BP was measured by a physician through a standard mercury sphygmomanometer. Subjects were maintained in sitting position and relaxed for at least 10 min before measurements. SBP was taken at Korotkoff phase I and diastolic BP at phase V. Three office BP measurements 2–3 min apart were recorded.

Anti-hypertensive drugs

Anti-hypertensive therapy was open-label and tailored to the single subjects. Because achievement of optimal SBP control is expected to require additional drugs on top of those previously taken

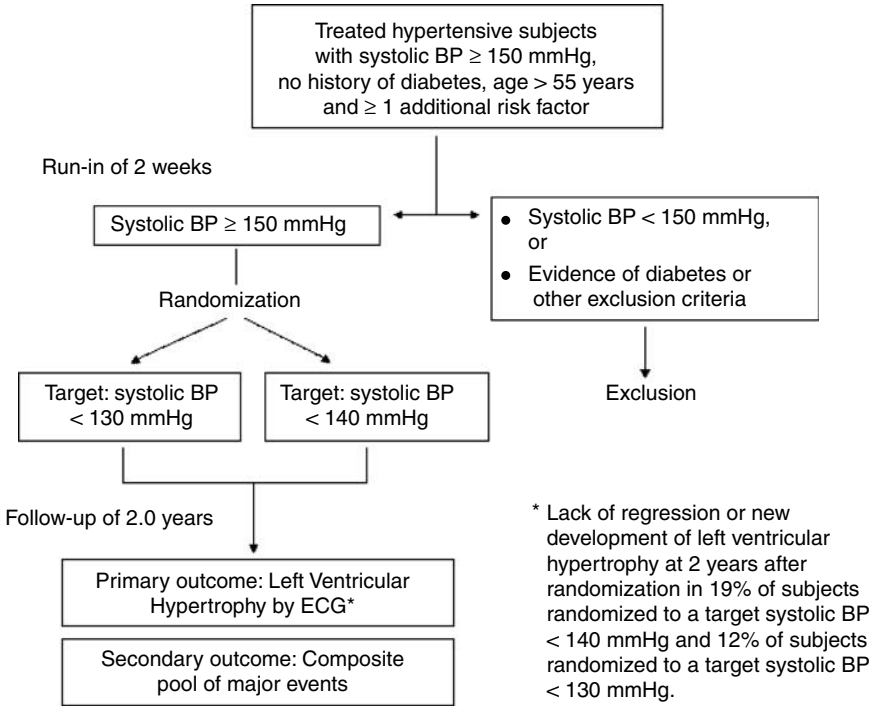

Figure 1 Study design and outcome. BP, blood pressure; ECG, electrocardiography.

Table 3 List of dispensed drugs

1. Diuretics: hydrochlorothiazide in fixed combination with ramipril[4] or telmisartan[5], furosemide (25 mg).
2. β-blockers: Bisoprolol (10 mg).
3. Calcium channel blockers: Amlodipine (10 mg).
4. Angiotensin-converting enzyme inhibitors: ramipril alone (10 mg) or in fixed combination with hydrochlorothiazide (5/25 mg).
5. Angiotensin II receptor antagonists: telmisartan alone (80 mg) or in fixed combination with hydrochlorothiazide (80/12.5 mg).
6. Centrally acting sympathetic inhibiting drugs: transdermal clonidine (2 mg).

by subjects, treatment included different combinations of prior drugs (background therapy) plus drugs dispensed for the present study. The list of antihypertensive drugs dispensed for the purpose of the study was restricted according to the list outlined in Table 3.

Adjustment of treatment
In the aggressive strategy group, even one single SBP measurement >130 mm Hg is enough to intensify treatment. In the conventional strategy group, achievement of SBP goal <130 mm Hg does not imply downtitration of treatment.

Sample size and data analysis
Sample size was calculated according to the following estimates:

(1) ECG LVH at randomization in 25% of subjects.
(2) ECG LVH at 2 years after randomization:
  (a) Target SBP <140 mm Hg: LVH regression plus persistent absence of LVH in 81% of subjects. Persistent LVH plus new development of LVH in 19% of subjects.
  (b) Target SBP <130 mm Hg: LVH regression plus persistent absence of LVH in 88% of subjects. Persistent LVH plus new development of LVH in 12% of subjects.
(3) Two-sided test: Type I error of 0.05. Type II error of 0.15 (85% power).
(4) Two-year dropout rate: 12%.

The hypothesis that a 24% reduction in the frequency of LVH (that is from 25 to 19%) in the conventional strategy group is derived from previous observational data indicating a 27% reduction in the frequency of ECG LVH (estimated through the Perugia score[17,18]) during standard treatment.[19] We hypothesized a further absolute 7% reduction in association with a targeted SBP drop by further 10 mm Hg. According to the above points, 484 subjects per group (968 total) were needed to demonstrate the primary hypothesis. With a 2-year dropout rate set at 12%, 1100 patients were required for randomization.

Statistical analysis was based on the intention-to-treat principle. The primary objective of the study was evaluated by using the χ^2 distribution. For assessment of the secondary objective of the study, analysis was restricted to the first event in subjects with multiple events. Survival curves were estimated using Kaplan–Meier product-limit method and compared by the Mantel (log-rank) test. The effect of prognostic factors on survival was evaluated by stepwise Cox semi-parametric regression model.[20]

Organizational structure
Cardio-Sis is registered at the National Institute of Health (ClinicalTrials.gov identifier: NCT00421863). The sponsor of the study was the Heart Care Foundation (Fondazione Italiana per la Lotta alle Malattie Cardiovascolari), a non-profit independent institution, which is also the owner of the database. An international steering committee was responsible for the scientific integrity, conduct and publication policy of the study. An independent end point adjudication committee, unaware of randomization code, was responsible to review and adjudicate incident clinical events (secondary objective) on the basis of original documentation provided by local investigators (see Appendix for events definitions).

Cardio-Sis has its central administration and monitoring office at the research centre of the Italian Association of Hospital Cardiologists (ANMCO) in Florence, Italy. ECG tracings were coded and shipped to a central reading laboratory. ECG reading was carried out by expert readers unaware of randomization code and clinical characteristics of patients. The Cardio-Sis clinical record form (CRF) was developed by the ANMCO Research Centre and Clinical Research Technology S.r.l., Salerno, Italy (www.cr-technology.com). It runs entirely on the Web (www.cardio-sis.it). Drug supply to centres was automatically updated on the basis of local needs as resulting from CRF.

Ethics
Before beginning of the study, each participating centre received written approval from the competent ethics committee and university/hospital authorities.

Results

Baseline clinical characteristics of patients
Overall, 44 centres participated in the study. Randomization began on February 2005 and ended on February 2007. Table 4 shows the main clinical characteristics of patients at randomization. Mean age was 67 years and mean systolic and diastolic BP was 158/87 mm Hg. Prevalence of LVH at ECG[17,18] was 21%, that is 4% lower than expected. Increased Cornell voltage (>2.0 mV in women and >2.4 mV in men) was present in 15.7% of subjects, typical strain

Table 4 Clinical characteristics of subjects at randomization

Number of subjects	1111
Sex (% male)	41
Age (years)	67 (7)
Weight (kg)	74 (13)
Height (cm)	163 (8)
Body mass index ($kg\,m^{-2}$)	27.8 (4.1)
Waist circumference (cm)	98.4 (12)
Systolic blood pressure (mm Hg)	158 (8)
Diastolic blood pressure (mm Hg)	87 (8)
Pulse pressure (mm Hg)	71 (10)
Heart rate (beats per minute)	69 (10)
Total cholesterol ($mg\,dl^{-1}$)	217 (42)
HDL cholesterol ($mg\,dl^{-1}$)	58 (20)
LDL cholesterol ($mg\,dl^{-1}$)	130 (39)
Triglycerides ($mg\,dl^{-1}$)	140 (80)
Glucose ($mg\,dl^{-1}$)	98 (13)
Uric acid ($mg\,dl^{-1}$)	5.8 (1.4)
Na ($mEq\,l^{-1}$)	141 (11)
K ($mEq\,l^{-1}$)	4.8 (2.4)
Creatinine ($mg\,dl^{-1}$)	0.9 (0.2)
Subjects with ECG LVH[a] (%)	21.0
LVH criteria	
(1) Cornell voltage > 2.0 mV in women, or > 2.4 mV in men (%)	15.7
(2) Typical strain (%)	6.4
1 lead (%)	2.7
2 leads (%)	2.1
⩾3 leads (%)	1.6
(3) Romhilt–Estes point score	
1–3 (%)	62.6
4 (%)	15.3
⩾5 (%)	4.1

Abbreviations: ECG, electrocardiography; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LVH, left ventricular hypertrophy. Data expressed as mean (± s.d.).
[a]Composite of Cornell voltage > 2.0 mV in women or > 2.4 mV in men, typical strain or Romhilt–Estes score ⩾5 points.

pattern in 6.4% and a Romhilt–Estes point score ⩾5 in 4.1% subjects. The three components of the Perugia score were variously combined in some of the subjects.

Concomitant risk factors

Overall, 20.4% of subjects were current smokers. The average waist girth was 98.4 cm (> 88 cm in 74% of women and > 102 cm in 45% of men). An impaired fasting glucose (> 110 $mg\,dl^{-1}$) was present in 40.1% of subjects. Overall, 75.9% of subjects had total cholesterol ⩾ 200 $mg\,dl^{-1}$ or HDL cholesterol < 40 $mg\,dl^{-1}$ or LDL cholesterol ⩾ 130 $mg\,dl^{-1}$, 27.5% family history of premature cardiovascular disease, 8.1% prior evidence of stroke or TIA, 11.5% prior evidence of coronary artery disease and 2.7% had prior evidence of occlusive peripheral arterial disease. Overall, 62, 31, 6 and 1% of subjects had 1, 2, 3 or ⩾4 concomitant risk factors, respectively. Metabolic syndrome by ATPIII criteria was present in 39.9% of subjects. When counting baseline ECG LVH as an additional risk factor, the prevalence of subjects with 1, 2, 3 or ⩾4 concomitant risk factors was 49, 39, 10 and 2%, respectively.

Discussion

Cardio-Sis is the first randomized study specifically designed to compare the effects of two different SBP goals (< 130 and < 140 mm Hg). The decision to base BP goals solely on SBP is supported by the strong evidence that, over age 55, SBP is the major determinant of cardiovascular risk[21,22] and the main target of anti-hypertensive treatment.[23]

Outcome measures

Cost reasons precluded the design of a study primarily targeted on major cardiovascular events. The decision of adopting ECG LVH as intermediate outcome measure was supported by evidence that ECG LVH is a potent and independent predictor of adverse outcome,[13] also when assessed in terms of serial changes during treatment[14–16] or before an incident event.[24] Indeed, consensus has been reported among experts that LVH regression may be considered as a surrogate outcome measure.[25] In the Framingham Heart Study,[14] subjects with baseline LVH and serial increase over time in the ECG voltages were twice as likely to suffer a cardiovascular event over the subsequent years than subjects with a decrease in the voltages. In a *post hoc* analysis of the Heart Outcome Prevention Evaluation study,[15] the primary study outcome occurred in 12.3% of subjects with absence of LVH or its regression during the study, and in 15.8% of subjects with development or lack of regression of LVH during the study ($P = 0.006$).

Among the available ECG indexes of LVH, the Perugia score showed the highest sensitivity[17] and population attributable risk.[18] In the Losartan Intervention For Endpoint study, the diagnostic performance of the Perugia score was superior to that of the Sokolow–Lyon index, and was comparable to that of the Cornell voltage-duration product, in overweight and obese individuals.[26] In the HEART Survey study, carried out in 711 hypertensive subjects with LVH at entry defined by the Perugia score, regression of ECG LVH at follow-up conferred a 54% lesser risk of primary outcome events (95% confidence interval 16–75).[16]

The secondary outcome measures in Cardio-Sis were all-cause mortality and a composite pool of pre-specified fatal and non-fatal events. Although the study is not powered to test the hypothesis of a different incidence of major events in relation to the achieved BP gradient between the two groups, some data suggest that an early aggressive control of BP may result in a consistent protection from cardiovascular events even in a relatively short term.[27]

Blood pressure goals

None of the available intervention studies was specifically designed to compare two different SBP targets in non-diabetic hypertensive individuals. In

the Hypertension Optimal Treatment study, a significant reduction in the incidence of major cardiovascular events in the target group $\leqslant 80$ mm Hg as compared to the target group $\leqslant 90$ mm Hg (51% reduction, $P=0.005$) was found only in the diabetic subset.[9] In the Afro-American study of kidney disease and hypertension,[10] 1094 African-Americans aged 18–70 years with hypertension and nephropathy were randomly assigned to a less aggressive (102–107 mm Hg) or more aggressive ($\leqslant 92$ mm Hg) target based on mean BP. Although achieved BP averaged 128/78 mm Hg in the more aggressive arm and 141/85 mm Hg in the less aggressive arm, neither the progression of renal function nor the incidence of a composite pool of cardiovascular events differed between the groups.[10]

The Appropriate Blood Pressure Control in Diabetes Trial compared a diastolic BP goal 80–89 mm Hg with a more aggressive goal (75 mm Hg) in a sample of 470 subjects with type 2 diabetes and baseline diastolic BP $\geqslant 90$ mm Hg.[11] The mean BP achieved during a 5.6-year follow-up period was 132/78 mm Hg in the more aggressive arm and 138/86 mm Hg in the less aggressive arm. Death rate was less frequent in the more aggressive than in the less aggressive arm (5.5 versus 10.7%, $P=0.037$), but no differences were found between the two arms in terms of progression of diabetic nephropathy, neuropathy and retinopathy.[11]

In the United Kingdom Prospective Diabetes Study 38[12] of 1148 hypertensive patients with type 2 diabetes were randomized to a more tight ($<150/85$ mm Hg) or less tight ($<180/105$ mm Hg) BP target. During a follow-up period of 8.4 years, mean achieved BP was lower ($P<0.0001$) in the more aggressive (144/82 mm Hg) than in the less aggressive (154/87 mm Hg) strategy group. Despite the relatively high-achieved BP values, individuals randomized to the more aggressive strategy showed a significantly lesser incidence of diabetes related end points, deaths related to diabetes, stroke and microvascular end points.[12]

Taken together, the available intervention studies either addressed BP targets based on diastolic or mean BP, or examined specific populations composed by diabetic patients or patients with hypertension and nephropathy. Although the most recent European Society of Hypertension/European Society of Cardiology guidelines presented a list of clinical conditions defining an increased cardiovascular risk in hypertensive subjects for reasons different from diabetes,[2] randomized trials comparing different SBP targets were not available in those conditions.

Limitations of the study

The main limitation of Cardio-Sis is that major cardiovascular events are a secondary, although pre-specified, end point of the study. Furthermore, lack of ambulatory BP measurements could lead to inclusion of a number of subjects with white-coat, or isolated clinic, hypertension. However, since SBP had to be >150 mm Hg in two visits before randomization and subjects had to be treated in both visits, such a possibility was unlikely in most subjects.[28]

What is known about the topic

- Hypertension guidelines suggest that the goal of antihypertensive treatment should be the reduction of BP to $<130/80$ mm Hg in patients with diabetes or chronic renal disease, and to $<140/90$ mm Hg in the other patients.
- Systolic blood pressure is the main determinant of cardiovascular risk and target of treatment after the age of 55.
- There are no randomized intervention trials demonstrating that a systolic blood pressure goal <130 mm Hg is superior to a conventional goal (<140 mm Hg) in terms of cardiovascular protection in high-risk hypertensive subjects without diabetes.

What this study adds

- Cardio-Sis is the first randomized study specifically designed to compare two different systolic blood pressure goals.
- The primary end point is based on left ventricular hypertrophy regression, an established surrogate outcome measure. A composite pool of pre-specified events will be evaluated as a secondary end point.
- Conclusions of Cardio-Sis will be useful in the management of hypertensive subjects with uncontrolled systolic blood pressure under treatment.

Abbreviation: BP, blood pressure.

Acknowledgements

The study was partially supported by an unrestricted grant from Boehringer-Ingelheim, Sanofi-Aventis and Pfizer. Study drugs were provided by Boehringer-Ingelheim, Sanofi-Aventis, Pfizer, Bayer and Merk (Darmstadt).

References

1 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JLJ, *et al.*, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003; **42**: 1206–1252.

2 Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G *et al.* Guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25**: 1105–1187.

3 Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B *et al.* Inadequate management of blood pressure in a hypertensive population. *N Engl J Med* 1998; **339**: 1957–1966.

4 Mancia G, Sega R, Milesi C, Cesana G, Zanchetti A. Blood-pressure control in the hypertensive population. *Lancet* 1997; **349**: 454–457.
5 The IPPPSH Collaborative Group. Cardiovascular risk and risk factors in a randomized trial of treatment based on the beta-blocker oxprenolol in the International Prospective Primary Prevention Study in Hypertension (IPPPSH). *J Hypertens* 1985; **3**: 379–392.
6 Isles CG, Waker LM, Beevers GD, Brown I, Cameron HL, Clarke J *et al.* Mortality in patients in the Glasgow blood pressure clinic. *J Hypertens* 1986; **4**: 141–156.
7 Bulpitt CJ, Bevers DG, Butler A, Coles EC, Fletcher AE, Hunt D *et al.* Treated blood pressure, rather than pretreatment, predicts survival in hypertensive patients. A report from the DHSS Hypertension Care Computing Project. *J Hypertens* 1988; **6**: 627–632.
8 Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**: 1903–1913.
9 Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S *et al.* Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; **351**: 1755–1762.
10 Wright Jr JT, Bakris G, Greene T, Agodoa LY, Appel LJ, Charleston J, *et al.*, African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; **288**: 2421–2431.
11 Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care* 2000; **23**(Suppl 2): B54–B64.
12 UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. UKPDS38. *BMJ* 1998; **317**: 703–713.
13 Kannel WB, Gordon T, Castelli WP, Margolis JR. Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease: the Framingham Study. *Ann Intern Med* 1970; **72**: 813–822.
14 Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB. Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy. *Circulation* 1994; **90**: 1786–1793.
15 Mathew J, Sleight P, Lonn E, Johnstone D, Pogue J, Yi Q, *et al.*, Heart Outcomes Prevention Evaluation (HOPE) Investigators. Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril. *Circulation* 2001; **104**: 1615–1621.
16 Verdecchia P, Reboldi GP, Angeli F, Avanzini F, de Simone G, Pede S *et al.*, on behalf of the HEART Survey Study Group. Prognostic value of serial electrocardiographic voltage and repolarization changes in essential hypertension. The HEART Survey Study. *Am J Hypertens* 2007; **20**: 997–1004.
17 Schillaci G, Verdecchia P, Borgioni C, Ciucci A, Guerrieri M, Zampi I *et al.* Improved electrocardiographic diagnosis of left ventricular hypertrophy. *Am J Cardiol* 1994; **74**: 714–719.
18 Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I *et al.* Prognostic value of a new electrocardiographic method for diagnosis of left ventricular hypertrophy in essential hypertension. *J Am Coll Cardiol* 1998; **31**: 383–390.
19 Verdecchia P, Reboldi G, Angeli F, Borgioni C, Gattobigio R, Filippucci L *et al.* Adverse prognostic significance of new diabetes in treated hypertensive subjects. *Hypertension* 2004; **43**: 963–969.
20 Cox DR. Regression models and life-tables. *J R Stat Soc (B)* 1972; **34**: 187–220.
21 Lloyd-Jones DM, Evans JC, Larson MG, O'Donnell CJ, Rocella EJ, Levy D. Differential control of systolic and diastolic blood pressure. Factors associated with lack of blood pressure control in the community. *Hypertension* 2000; **36**: 594–599.
22 Rutan G, McDonald RH, Kuller RH. A historical perspective of elevated systolic versus diastolic blood pressure from an epidemiological and clinical trial viewpoint. *J Clin Epidemiol* 1989; **42**: 663–673.
23 Ramsay LE, Williams B, Johnston GD, MacGregor GA, Poston L, Potter JF *et al.* Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. *J Hum Hypertens* 1999; **13**: 569–592.
24 Okin PM, Devereux RB, Jern S, Kjeldsen SE, Julius S, Nieminen MS, *et al.*, LIFE Study Investigators. Regression of electrocardiographic left ventricular hypertrophy during antihypertensive treatment and the prediction of major cardiovascular events. *JAMA* 2004; **292**: 2343–2349.
25 Devereux RB, Agabiti Rosei E, Dahlof B, Gosse P, Hahn RT, Okin PM, Roman MJ. Regression of left ventricular hypertrophy as a surrogate end-point for morbid events in hypertension treatment trials. *J Hypertens Suppl* 1996; **14**: S95–S101.
26 Okin PM, Jern S, Devereux RB, Kjeldsen SE, Dahlöf B, for the LIFE Study Group. Effect of obesity on electrocardiographic left ventricular hypertrophy in hypertensive patients. The Losartan Intervention For Endpoint (LIFE) reduction in hypertension study. *Hypertension* 2000; **35**: 13–18.
27 Julius S, Kjeldsen SE, Weber M, Brunner HR, Ekman S, Hansson L, *et al.*, VALUE Trial Group. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet* 2004; **363**: 2022–2031.
28 Verdecchia P, Palatini P, Schillaci G, Mormino P, Porcellati C, Pessina AC. Independent predictors of isolated clinic ('white-coat') hypertension. *J Hypertens* 2001; **19**: 1015–1020.
29 Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus. Results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005; **165**: 1410–1419.

Appendix

Steering committee
Paolo Verdecchia (Chairman), Jan A Staessen, Augusto Achilli, Giovanni de Simone, Antonello Ganau, Gianfrancesco Mureddu, Sergio Pede.

Adjudication committee
Carlo Porcellati and Giovanni Fornari.

Coordinating centre
ANMCO Research Centre (Aldo P Maggioni, Martina Ceseri, Donata Lucci, Andrea Lorimer)

ECG reading centre
Associazione Umbra Cuore e Ipertensione (Salvatore Repaci, Claudia Castellani, Paola Achilli, Carla Jaspers).

Clinical record from online management
Clinical Research Technology (Giovanni Cucchiara, Carlo Panzano).

Clinical help online
Fabio Angeli.

Participating centres
Aosta (C Aillon, MG Sclavo), Benevento (M Scherillo, D Raucci, M Di Donato), Brescia (L Dei Cas, P Faggiano), Cagliari Brotzu (M Porcu, R Calamida, L Pistis), Caltanissetta (F Vancheri, M Alletto, M Curcio), Casarano (G Pettinati, M Ieva, A Muscella), Castiglione del Lago (M Guerrieri, C Denbek), Catania Garibaldi-Nesima (M Gulizia, GM Francese), Catanzaro (F Perticone, G Iemma), Chiari (R Fariello, N Sala), Chieti (A Mezzetti, SD Pierdomenico, M Bucci), Città della Pieve (G Benemio, R Gattobigio, N Sacchi), Città di Castello Cardiologia (M Cocchieri, L Prosciutti), Città di Castello Medicina (P Battocchi, O Garognoli, G Arcelli), Cremona (S Pirelli, C Emanuelli), Erice (GB Braschi, M Abrignani), Genova DIMI (G De Ferrari, R Pontremoli), Gorizia (D Igidbashian, R Marini, L Scarpino), Gubbio (S Mandorla, M Buccolieri, L Picchi), Lido di Camaiore (G Casolo, M Pardini, G Marracci), Napoli Policlinico Federico II (P Strazzullo, F Galletti, A Barbato), Perugia (C Cavallini, C Borgioni), Pistoia (G Seghieri, F Cipollini, E Arcangeli), Poggibonsi (W Boddi, C Palermo, F Savelli), Pozzilli (G Lembo, C Vecchione), Ragusa (L Malatino, P Belluardo), Reggio Calabria (C Zoccali, D Leonardis, F Mallamaci), Roma San Camillo (A Lacchè, C Gentile), Roma San Giovanni (A Boccanelli, GF Mureddu), Roma San Filippo Neri (M Santini, F Colivicchi, S Ficili), Roma CTO (M Uguccioni, C Nardozi, A Tedeschi), Sacile (G Martin, G Zanata), San Daniele del Friuli (L Mos, V Dialti, S Martina), San Pietro Vernotico (S Pede, A Renna), Sassari (A Ganau, G Farina), Scilla (E Tripodi, B Miserrafiti, R Scali), Siracusa (M Stornello, E Valvo), Terni (M Bernardinangeli, G Proietti), Thiesi (G Poddighe), Todi (B Biscottini, R Panciarola, A Boccali), Torino (F Veglio, F Rabbia, M Caserta), Trebisacce (M Chiatto), Trento (C Stefenelli, G Cioffi, G Bonazza) and Viterbo (EV Scabbia, A Achilli, D Bottoni).

Definition of secondary outcome events
Myocardial infarction (MI) is defined as follows:

(1) Q-wave or ST-elevation MI: new significant Q-wave ($>0.\ 04$ s duration or 3 mm in depth and loss in height of ensuing R wave or new significant R waves in V_1–V_2) in at least 2 leads on the standard 12-lead ECG. ST elevation is defined as 0.1 mV new ST elevation of 0.1 mV in peripheral leads or 0.2 mV in precordial leads. New onset left bundle branch block during MI is equivalent to a 'Q-Wave MI'. There must be at least one of the following criteria: (1) typical chest pain, or increase of CK-MB above the upper limit of normal within 36 h of onset of acute symptoms, (2) serum glutamic oxaloacetic transaminase or LDH at least twice the laboratory upper limit and (3) elevated troponin T or I level above the normal laboratory range.
(2) 'Non-Q-wave' or 'non-ST elevation' MI: new and persistent (>24 h) ST-segment or T wave changes in addition to cardiac enzymes/markers elevation (see above) and/or typical symptoms of chest pain.
(3) MI without significant ECG changes: typical symptoms with significant elevation of cardiac enzymes (see above).

'Stroke' is defined by acute focal neurological deficit thought to be of vascular origin and signs or symptoms lasting >24 h. On the basis of symptoms and laboratory tests (computed tomography/magnetic resonance imaging) and/or necropsy results, stroke is classified as (1) definite or probable ischaemic stroke or (2) definite or probable haemorrhagic stroke or (3) sub-arachnoid haemorrhage or (4) uncertain or unknown stroke.

'Transient ischaemic attack' is defined by focal neurological or monocular defect with associated symptoms lasting <24 h and thought to be due to occlusive (embolic or thrombotic) vascular origin.

'Atrial fibrillation' is defined by absence of P waves before each QRS complex on the surface ECG with irregular atrial electrical activity and f waves varying in size, shape and timing. All cases of AF must be documented by ECG tracings for adjudication. Paroxysmal AF is defined by a single or multiple occurrence of AF that resolved spontaneously or by treatment.

'Sudden cardiac death' is defined by a sudden, unexpected and witnessed death that occurred

within 1 h from onset of symptoms, in the absence of any known relation with traumatic or violent causes.

'Death due to other cardiovascular causes' is defined by a cardiovascular death different from myocardial infarction or stroke (for example, death due to heart failure or aortic dissection).

'Congestive heart failure' NYHA stage III or IV is defined by congestive heart failure with dyspnoea induced by a lesser than usual physical activity (stage III) or at rest (stage IV) associated with hospitalization and treatment of the patient.

'Angina with objective evidence of myocardial ischaemia' is defined by new onset chest pain associated with objective evidence of myocardial ischaemia at ECG, radionuclide study or stress echocardiography, or with angiographic evidence of at least 50% stenosis in $>=$ 2 major epicardial vessels.

'Peripheral occlusive arterial disease' is defined by intermittent claudication associated with angiographic or ecographic evidence of arterial stenosis $>60\%$.