

# Current Treatment of Patients with Hypertension

## Therapeutic Implications of INSIGHT

*Stefano Taddei, Lorenzo Ghiadoni and Antonio Salvetti*

Department of Internal Medicine, University of Pisa, Pisa, Italy

### Abstract

When planning treatment for patients with hypertension, current guidelines emphasise the importance of risk stratification, based on blood pressure, the presence of end-organ damage and other cardiovascular risk factors. Because the beneficial effect of antihypertensive therapy seems to be linked to the degree of blood pressure reduction, guidelines recommend reducing blood pressure below 140/90mm Hg, with a lower target in patients who are young or who have diabetes mellitus (with or without nephropathy) or non-diabetic nephropathy.

Blood pressure reduction can be achieved with several classes of drugs, including diuretics,  $\beta$ -blockers, ACE inhibitors, angiotensin II antagonists and calcium channel antagonists. Calcium channel antagonists have been shown to reduce the risk of stroke and major cardiovascular events. However, it is still controversial whether different treatment regimens based on different drug classes can offer advantages beyond similar degrees of blood pressure control in preventing cardiovascular morbidity and mortality.

The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) was a controlled clinical trial aimed at comparing the efficacy of a long-acting calcium channel antagonist, nifedipine gastrointestinal-transport-system (GITS), versus co-amiloride, a combination of the diuretics hydrochlorothiazide (HCTZ) and amiloride, on morbidity and mortality in high-risk hypertensive patients. Nifedipine GITS and HCTZ/amiloride were equally effective at reducing blood pressure and the risk of primary outcomes (a composite of death from any cardiovascular or cerebrovascular cause, non-fatal stroke, myocardial infarction and heart failure). Results from other studies indicate that there may be greater benefits for stroke and smaller benefits for coronary artery disease with calcium channel antagonist-based regimens than with diuretic or  $\beta$ -blocker-based regimens. However, there is at present insufficient evidence to recommend a specific drug choice based on patient risk profile.

Thus, the choice of antihypertensive drug(s) should be according to efficacy and tolerability. In addition to the reductions in cardiovascular risk, two sub-studies of INSIGHT showed that nifedipine GITS was able to prevent the

progression of intima media thickness in the common carotid artery and slow the progression of coronary calcification. The clinical significance of this effect in the prevention of cardiovascular events still remains to be established.

Epidemiological studies have shown that both systolic and diastolic blood pressure values are directly and linearly related to the risk of cardiovascular events, and that this relationship is still detectable for blood pressure values within the normal range.<sup>[1,2]</sup> Although blood pressure values are strong determinants of the risk of cardiovascular events, the presence of end-organ damage as well as the association with other cardiovascular risk factors further increases the risk of cardiovascular events.<sup>[3,4]</sup> Therefore, when planning treatment for patients with hypertension, current guidelines emphasise the relevance of risk stratification, based on blood pressure values, the presence of end-organ damage or other cardiovascular risk factors.<sup>[3,4]</sup>

Controlled clinical trials have shown the benefit of blood pressure reduction, which is detectable in young, middle aged and elderly patients, both male and female, with severe, moderate and mild hypertension as well as in those with systo-diastolic and isolated systolic hypertension.<sup>[5,6]</sup> Because the beneficial effect of antihypertensive therapy seems to be linked to the degree of blood pressure reduction,<sup>[6,7]</sup> guidelines<sup>[3,4]</sup> recommend reducing blood pressure below 140/90mm Hg, with a lower target in young patients, in patients with diabetes mellitus with or without nephropathy, and in patients with non-diabetic nephropathy.

Clinical studies indicate that the benefit of blood pressure reduction can be achieved with several drugs, including conventional therapy (i.e. diuretics and  $\beta$ -blockers) or more recent drug classes, such as ACE inhibitors, angiotensin II antagonists or calcium channel antagonists.<sup>[6,7]</sup> Calcium channel antagonists, in particular, have been shown to reduce significantly the risk of stroke and major cardio-

vascular events, especially among elderly patients with isolated systolic hypertension<sup>[8,9]</sup> or systo-diastolic hypertension.<sup>[10]</sup> (although in reference 9 and 10 randomisation was performed according to an alternative scheme). Moreover, a recent overview of placebo-controlled trials with calcium channel antagonists has concluded that, although there is no clear evidence of reductions in coronary artery disease or heart failure, the estimates of treatment effects do not exclude the existence of a beneficial effect on these major cardiac outcomes and largely preclude the occurrence of adverse effects (including cancer or uncontrolled bleeding).<sup>[6,11]</sup> However, it is still controversial whether different treatment regimens based on different drug classes can offer additional advantages, beyond a similar degree of blood pressure control, in the prevention of cardiovascular morbidity and mortality.

The International Nifedipine GITS Study: Intervention as a Goal in Hypertension Treatment (INSIGHT) was a controlled clinical trial aimed at comparing the efficacy of a long-acting calcium channel antagonist, nifedipine gastrointestinal transport system (GITS), versus co-amlozide (a combination of the diuretics hydrochlorothiazide [HCTZ] and amiloride) on morbidity and mortality in high-risk hypertensive patients.<sup>[12]</sup> Moreover, two substudies of INSIGHT have assessed the antiatherosclerotic effects of nifedipine GITS by evaluating intima-media thickness (IMT) in the common carotid artery<sup>[13]</sup> and coronary calcification.<sup>[14]</sup> This represents another major issue because the evaluation of intermediate endpoints (mechanisms or lesions that lead to cardiovascular events) has been proposed as an alternative approach to study the benefit of antihypertensive treatment.

In the present commentary we review the results of INSIGHT and related substudies in the context of other similar outcome studies to evaluate the role of calcium channel antagonists in the treatment of patients with hypertension.

## 1. INSIGHT

### 1.1 Description

INSIGHT was a prospective, randomised, double-blind trial comparing the effects of nifedipine GITS once daily with those of the combination diuretic HCTZ/amiloride, on morbidity and mortality in patients with hypertension.<sup>[12]</sup> INSIGHT inclusion criteria were defined as age between 55 and 80 years, blood pressure at least 150/95 mm Hg or at least 160 mm Hg systolic, and at least one additional cardiovascular risk factor. The latter could include hypercholesterolaemia, smoking, family history of myocardial infarction, current left ventricular hypertrophy, coronary heart disease, left ventricular strain, peripheral vascular disease, proteinuria and diabetes mellitus. All patients received placebo for 2–4 weeks before starting with either nifedipine GITS 30 mg once daily or HCTZ 25 mg/amiloride 5 mg once daily; all patients received one active and one placebo tablet taken at the same time of day. In those patients whose blood pressure was reduced by less than 20/10 mm Hg or remained higher than 140/90 mm Hg, four additional dose-titration steps were performed by doubling the dose of the randomised drugs; adding atenolol 25 mg/day (or enalapril 5 mg/day if atenolol was contraindicated); doubling the dose of the additional drug; and addition of any other antihypertensive therapy (other than calcium channel antagonists or diuretics).

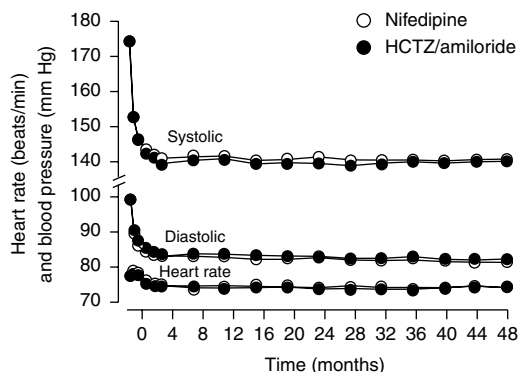
A total of 6321 patients (2929 men, mean age 65 years) were randomly assigned to treatment with nifedipine (3157) or HCTZ/amiloride (3164). The mean follow-up was 3.5 years with 4014 patients

(64% of randomised patients) completing the 4-year study.

The primary outcome variable in INSIGHT was a composite of death from any cardiovascular or cerebrovascular cause, together with non-fatal stroke, myocardial infarction or heart failure. Secondary variables were total mortality, death from a vascular cause, and non-fatal vascular events including transient ischemic attacks, angina pectoris (new or worsening) and renal failure. All events were assessed by an independent critical events committee (CEC) according to pre-specified criteria. No less than 28 and 41% of investigator-coded primary and secondary events, respectively, were re-classified by the CEC.<sup>[15]</sup>

### 1.2 Results

Nifedipine GITS and HCTZ/amiloride were equally effective at reducing blood pressure. Mean blood pressure was 173/99 mm Hg immediately after the placebo phase and had fallen by  $33 \pm 15/17 \pm 9$  mm Hg at the end of the titration phase, remaining close to 138/82 mm Hg in the two groups throughout the rest of the study (figure 1). At the 4-year follow-up, blood pressure was controlled (<140/90 mm Hg) in 58% of nifedipine GITS recipi-



**Fig. 1.** Mean systolic and diastolic blood pressures and heart rate response to study drugs in patients from the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT) [reproduced from Brown et al.,<sup>[12]</sup> with permission]. **GITS** = gastrointestinal-transport-system; **HCTZ** = hydrochlorothiazide.

ents and 57% of the HCTZ/amiloride recipients. Note that around 68% of patients received monotherapy in both groups for the entire study duration.

The incidence of total adverse events was greater in the nifedipine group than in the HCTZ/amiloride group (49 vs 42%;  $p < 0.0001$ ), but the incidence of serious adverse events (defined as life-threatening, disabling or leading to hospitalisation) was smaller in the nifedipine group than in the HCTZ/amiloride group (25 vs 28%;  $p = 0.02$ ). Adverse events were those expected to be associated with drug treatment. Thus, mainly peripheral oedema ( $p < 0.0001$ ), but also headache and flushing ( $p = 0.0002$  and  $p < 0.001$ , respectively), were more frequent in the nifedipine group, while syncope ( $p = 0.0004$ ), dizziness ( $p = 0.006$ ), depression ( $p = 0.0009$ ) and peripheral vascular disorders ( $p < 0.0001$ ) had a greater association with the HCTZ/amiloride group. More patients receiving HCTZ/amiloride than nifedipine presented with metabolic disorders, such as hypokalaemia ( $p < 0.0001$ ), hyponatraemia ( $p < 0.0001$ ), hyperuricaemia ( $p < 0.0001$ ), hyperglycaemia ( $p = 0.001$ ) and hyperlipidaemia ( $p < 0.0001$ ). Furthermore, the incidence of gout ( $p = 0.01$ ) and diabetes ( $p = 0.02$ ), as well as impaired renal function ( $p < 0.0001$ ), was greater in the HCTZ/amiloride group. In contrast, HCTZ/amiloride determined a lower rate of non-fatal congestive heart failure, a finding which can be explained by the positive effect of diuretic treatment on symptoms due to pulmonary congestion.

There was no significant difference in the total number of primary outcomes between the nifedipine and the HCTZ/amiloride recipients. By the end of the 4-year follow-up period, 200 nifedipine recipients (6.3%) and 182 HCTZ/amiloride recipients (5.8%) had had primary outcomes (18.2 vs 16.3 events per 1000 patients/year) [table I]. Similarly, there was no significant difference between the treatment groups for secondary outcomes, combined primary and secondary outcomes, all-cause mor-

talidity and cardiovascular mortality, and non-fatal cardiovascular events (table I). Event rates were found to be greater in the five northern European countries than in the three Mediterranean countries and, as expected, were influenced by most of the risk factors, including smoking, hypercholesterolaemia, diabetes, age, gender, systolic blood pressure, angina, peripheral vascular disease, left ventricular strain or hypertrophy, previous myocardial infarction and proteinuria. However, in a separate analysis of treatment interaction with each risk factor, no significant interaction was found.<sup>[12]</sup> Finally, in patients with diabetes the incidence of primary outcomes was similar in the nifedipine (8.3%) and HCTZ/amiloride (8.4%) groups.

Subgroup analysis (which should be considered with caution because of the low number of events) revealed that fatal myocardial infarction and non-fatal heart failure occurred more frequently in the nifedipine group (table I). However, the incidence of sudden death deserves a special comment. According to the pre-specified criteria, the CEC defined sudden deaths as those that occurred with documented cardiac symptom onset in the previous 24 hours. People who are found dead are commonly classified as sudden deaths. Thus, 56 patients (22 and 34 in the nifedipine and HCTZ/amiloride groups, respectively) who were found dead were classified as deaths from unknown cause. When the CEC (still blind to trial results as well as treatment group) re-examined these deaths, the cause was re-classified as 'unknown, probably cardiovascular' in 28 cases.<sup>[12,15]</sup> If these events had been included among primary events as sudden deaths, the incidence would have been lower in the nifedipine group (39 cases, 1.2%) than in the HCTZ/amiloride group (57 cases, 1.8%).

To address the clinical impact of treatment in INSIGHT, the expected incidence of primary endpoints was calculated according to the Framingham risk equations and compared with the observed incidence. The calculated expected value was 34.5 pri-

**Table 1.** Primary and secondary outcomes in INSIGHT (reproduced from Brown et al.,<sup>[12]</sup> with permission)

Outcome	Nifedipine GITS (%)	HCTZ/amiloride (%)	Odds ratio (95% CI)	p-Value
<b>Primary</b>				
Composite <sup>a</sup>	200 (6.3%)	182 (5.8)	1.11 (0.90–1.36)	0.34
Myocardial infarction				
Non-fatal	61 (1.9%)	56 (1.8)	1.09 (0.76–1.58)	0.52
Fatal	16 (0.5%)	5 (0.2)	3.22 (1.18–8.80)	0.017
Sudden death	17 (0.5%)	23 (0.7)	0.74 (0.39–1.39)	0.43
Stroke				
Non-fatal	55 (1.7%)	63 (2.0)	0.87 (0.61–1.26)	0.52
Fatal	12 (0.3%)	11 (0.3)	1.09 (0.48–2.48)	0.84
Heart failure				
Non-fatal	24 (0.8%)	11 (0.3)	2.20 (1.07–4.49)	0.028
Fatal	2 (0.1%)	1 (<0.1)	2.01 (0.18–22.13)	0.63
Other CV death	13 (0.4%)	12 (0.4)	1.09 (0.50–2.38)	0.85
<b>Secondary</b>				
Composite <sup>b</sup>	383 (12.1%)	397 (12.5)	0.96 (0.83–1.12)	0.62
Death				
All (first event) <sup>c</sup>	153 (4.8%)	152 (4.8)	1.01 (0.80–1.27)	0.95
Non-CV	71 (2.2%)	66 (2.1)	1.08 (0.77–1.52)	0.67
Unknown cause	22 (0.7%)	34 (1.1)	0.65 (0.80–1.69)	0.14
CV	60 (1.9%)	52 (1.6)	1.16 (0.80–1.69)	0.45
Non-fatal CV events	230 (7.3%)	245 (7.7)	0.94 (0.78–1.13)	0.50
Primary events	140 (4.4%)	130 (4.1)	1.08 (0.85–1.38)	0.53
Angina (worsening or new) CV events	57 (1.8%)	77 (2.4)	0.74 (0.52–1.04)	0.10
Transient ischemic attacks	25 (0.8%)	25 (0.8)	1.00 (0.57–1.75)	1.0
Renal failure	8 (0.3%)	13 (0.4)	0.62 (0.26–1.49)	0.38

a Myocardial infarction, stroke, heart failure and cardiovascular death.

b Primary outcomes plus non-CV deaths, renal failure, angina and transient ischemic attacks.

c As a first event (23 additional deaths occurred after a previous event in the nifedipine GITS group and 20 in the co-amiloride group).

**CV** = cardiovascular; **GITS** = gastrointestinal-transport-system; **HCTZ** = hydrochlorothiazide; **INSIGHT** = International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment.

mary endpoints per 1000 patient-years, which is twice the observed INSIGHT incidence.<sup>[12,16]</sup> Moreover, when the World Health Organization-Monitor trends in Cardiovascular diseases (WHO-MONICA) Project<sup>[17]</sup> was considered, a 35% reduction in predicted primary endpoints, adjusted for the proportion of Mediterranean patients, was still detectable with the two study drugs.<sup>[12]</sup> However, it is important to observe that the previous analysis compares an intervention trial with population-based experiences. Therefore, although interesting and suggestive, such findings need to be considered with great caution.

Finally, the frequency of cancers and gastric bleeding did not differ significantly between the two treatment groups and, as already stated in section 1.2, new diabetes occurred less frequently in patients receiving nifedipine than in those receiving HCTZ/amiloride (4.3 vs 5.6%,  $p = 0.02$ ).

### 1.3 Implications

The main implication of the INSIGHT trial is that effective blood pressure reduction reduces cardiovascular events in high-risk hypertensive patients. In such patients, blood pressure was well controlled; in particular, systolic blood pressure was reduced be-

low 140mm Hg. Such a target was not reached in either of the two previous studies comparing the efficacy of calcium channel antagonists and conventional therapy,<sup>[18,19]</sup> or in two of the three trials designed to evaluate the benefit of aggressive blood pressure reduction.<sup>[7,20]</sup> It is worth noting that this target was reached with monotherapy in around 68% of the treated patients. The benefit of blood pressure lowering was similar in nifedipine and HCTZ/amiloride recipients, a finding that reinforces the concept that the strategy of lowering blood pressure to the proposed target<sup>[3,4]</sup> is currently the main purpose of antihypertensive therapy.

Two other controlled studies have compared the efficacy of calcium channel antagonists with conventional therapy (diuretics,  $\beta$ -blockers or both) in elderly hypertensive patients<sup>[18]</sup> and middle-aged aged hypertensive patients.<sup>[19]</sup> In both studies the incidence of primary endpoints, fatal or non-fatal stroke and myocardial infarction and other cardiovascular death, did not differ between calcium channel antagonists and conventional drugs. In the Swedish Trial in Old Patients with hypertension (STOP)-2 trial, given the same blood pressure reduction, patients treated with calcium channel antagonists and conventional drugs showed non-significant trends towards a lower incidence of stroke and a higher incidence of myocardial infarction.<sup>[18]</sup> In the Nordic Diltiazem (NORDIL) trial, patients treated with diltiazem had a significantly lower incidence of stroke (-20%) and a non-significant increase in the occurrence of myocardial infarction, despite the presence of a smaller blood pressure reduction (+3mm Hg vs conventional therapy).<sup>[19]</sup> Moreover, a recent meta-analysis, including INSIGHT, the two studies mentioned above<sup>[12,18,19]</sup> and two minor trials,<sup>[21,22]</sup> suggested a lower risk of stroke and a greater risk of coronary artery disease in patients assigned to calcium channel antagonists, compared with those receiving conventional therapy.<sup>[6]</sup> Similar conclusions have been reached in

another recent meta-analysis,<sup>[23]</sup> which included three major<sup>[12,18,19]</sup> and three minor studies.<sup>[21,22,24]</sup> In contrast, another meta-analysis indicates that calcium channel antagonists as initial antihypertensive therapy increase the risk of myocardial infarction.<sup>[25]</sup> However, the apparently conflicting results can be explained by inclusion and exclusion bias.<sup>[26]</sup>

However, although overall data are suggestive of greater benefits for stroke and a smaller benefits for coronary artery disease with calcium channel antagonist-based regimens, compared with diuretic or  $\beta$ -blocker-based regimens, the evidence is not sufficiently reliable to recommend a specific drug choice according to patient risk profile.<sup>[6]</sup> Thus, results from ongoing trials, as well as future prospectively designed overviews of all available data, are needed to solve this crucial issue.<sup>[6]</sup> Until then, the choice of antihypertensive drugs cannot be restricted to only a few drug classes: rather, individual treatment should be planned according to efficacy and tolerability, the latter including metabolic effects, compelling indications and contraindications.<sup>[4,26]</sup>

On this regard, it is important to address that calcium channel antagonist therapy is associated with a documented improvement in the quality of life, including physical and emotional state, intellectual function and a general subjective perception of well-being or life satisfaction.<sup>[27]</sup>

## 2. INSIGHT Substudies

The efficacy of nifedipine GITS in slowing the progression of atherosclerosis was investigated in two substudies of INSIGHT.<sup>[13,14]</sup>

The IMT substudy included 439 patients who participated in INSIGHT.<sup>[13]</sup> In addition to the outcomes assessed in all INSIGHT participants, these patients underwent carotid ultrasonography at baseline, 4 months and then every year for 4 years. The primary outcome was the IMT progression rate, calculated as the slope of the IMT-time regression in the right common carotid artery 3cm before the

**Table II.** Effect of calcium antagonists on carotid intima-media thickness (IMT) in randomised, double-blind trials

Study	Patients	Treatment	Follow-up (y)	IMT progression rate (mm/y) [mean difference from baseline]
MIDAS <sup>[24]</sup>	HT	Isradipine vs HCTZ	3	-0.010
VHAS <sup>[22]</sup>	HT	Verapamil vs chlorthalidone	4	-0.010
INSIGHT <sup>[13]</sup>	HT	Nifedipine vs HCTZ/amiloride	4	-0.008 <sup>a</sup>
ELSA <sup>[32]</sup>	HT	Lacidipine vs atenolol	4	-0.009 <sup>a</sup>
PREVENT <sup>[31]</sup>	CAD	Amlodipine vs placebo	3	-0.015 <sup>a</sup>

<sup>a</sup> Significant reduction versus control group.

**CAD** = patients with coronary artery disease; **ELSA** = European Lacidipine Study on Atherosclerosis; **HCTZ** = hydrochlorothiazide; **HT** = patients with hypertension; **INSIGHT** = International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment; **MIDAS** = Multicenter Isradipine Diuretic Atherosclerosis Study; **PREVENT** = Prospective Randomised Evaluation of the Vascular Effects of Norvasc Trial; **VHAS** = Verapamil in Hypertension and Atherosclerosis Study.

bifurcation. Secondary outcomes included absolute changes from baseline (last value during treatment minus baseline value) of IMT and the cross-sectional area of IMT (CSA-IMT; an estimate of arterial wall mass) and diameter.

Among patients treated for the entire 4-year study duration, the mean rate of IMT progression was significantly less in nifedipine GITS recipients than in the group of patients who received HCTZ/amiloride.<sup>[13]</sup> However, there was no significant difference on intent-to-treat (ITT) analysis. This lack of significance for the ITT population can probably be attributed to results in patients who received only 1 year of treatment, which is an inadequate period of time for assessment of IMT progression. This conclusion is supported by analyses in patients in the ITT population who received  $\geq 2$ ,  $\geq 3$  or  $\geq 4$  years of treatment. In all three of these groups, the differences in IMT progression rates between the nifedipine and HCTZ/amiloride groups were statistically significant.<sup>[13]</sup> Changes in IMT and CSA-IMT differed significantly between treatments, as IMT and CSA-IMT increased in patients receiving HCTZ/amiloride but not in those receiving nifedipine. Therefore, this study indicated that despite a similar reduction in blood pressure, treatment with nifedipine is able to prevent the progression of IMT in the common carotid artery, a lesion that can reflect either medial hypertrophy due to hyperten-

sion (a nonatherosclerotic process) or intimal thickening due to atherosclerosis, or both.<sup>[28-30]</sup>

The results obtained from this INSIGHT sub-study are in agreement with those of other studies showing the beneficial effects of calcium channel antagonists versus placebo on IMT of carotid arteries in patients with angiographically documented coronary artery disease,<sup>[31]</sup> and versus diuretic<sup>[22,24]</sup> or  $\beta$ -blocker<sup>[29,32]</sup> treatment in patients with essential hypertension (table II).

The coronary calcification substudy of INSIGHT included 201 patients with total calcium scores of at least 10 at baseline.<sup>[14]</sup> Total calcium score was assessed annually for 3 years using double-helix computed tomography. Progression of coronary calcification was significantly lower in the nifedipine GITS group than the HCTZ/amiloride recipients, during the first and third years, but not during the second year (table III). These findings suggest that nifedipine-GITS can slow the progression of coro-

**Table III.** Progression of coronary calcification in the INSIGHT calcification substudy<sup>[14]</sup>

Time from baseline	Increase in total calcium score from baseline (%)		p-Value
	nifedipine GITS	HCTZ/amiloride	
Year 1	3.2	27.0	0.02
Year 2	28.5	46.8	0.14
Year 3	40	78.0	0.02

**GITS** = gastrointestinal-transport-system; **HCTZ** = hydrochlorothiazide; **INSIGHT** = International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment.

nary calcification and are supportive of the antiatherosclerotic properties observed in the IMT sub-study.<sup>[13]</sup> In this regard, it is important to observe that coronary calcifications and their progression are not exclusively influenced by traditional cardiovascular risk factors, but also by specific factors related to bone mineralisation (including osteopontin and osteoclastin).<sup>[33,34]</sup> Therefore, it is possible that calcium channel antagonists may additionally interact with mechanisms different from those involved in atherosclerosis.

Other studies have also suggested that calcium channel antagonists can have a favourable effect on coronary atherosclerosis. The International Nifedipine Trial on Antiatherosclerotic Therapy (IN-TACT) showed that nifedipine reduced the incidence of new lesions on arteriography by 28% in patients with mild coronary artery disease.<sup>[35]</sup> Moreover, nicardipine reduced the progression of minimal lesions in patients with 5–75% stenoses in at least four coronary artery segments.<sup>[36]</sup> However, in the recent Prospective Randomised Evaluation of Norvasc Trial (PREVENT), treatment with amlodipine had no effect on angiographic progression of coronary atherosclerosis.<sup>[31]</sup>

Taken together, the data presented in this commentary indicate that nifedipine can exert an antiatherosclerotic effect on both the carotid and coronary arteries. This result can tentatively be explained by the favourable effect of this drug on endothelial dysfunction.<sup>[37]</sup> Thus, in patients with essential hypertension, treatment with nifedipine GITS increased forearm vasodilation to acetylcholine, an endothelium-dependent vasodilator, by restoring nitric oxide availability.<sup>[38]</sup> Moreover in the Evaluation of Nifedipine and Cerivastatin On the Recovery of Endothelial function (ENCORE) study, coronary endothelial function improved by 88% after 6 months in patients with coronary artery disease who received nifedipine GITS, compared with placebo.<sup>[39]</sup>

On the other hand, the findings from the entire INSIGHT study did not reveal a significant difference in the incidence of cardiovascular events between patients given nifedipine GITS and those who received HCTZ/amiloride.<sup>[12]</sup> Moreover, analysis of other studies assessing the effect of drug treatment on carotid lesions revealed no convincing relationship between carotid lesion regression and reduction in cardiovascular events.<sup>[40]</sup>

Several arguments can be put forward to explain the apparent discrepancy between the antiatherosclerotic effect on carotid arteries and the lack of reduction in cardiovascular events: (i) the effect on early pre-intrusive carotid lesions;<sup>[13,40]</sup> (ii) dissociation between the antiatherosclerotic effect on carotid and coronary arteries;<sup>[31,40]</sup> and, (iii) the possibility that the beneficial effect on cardiovascular events could be detected in a longer follow-up period. Therefore, although carotid arterial IMT seems to be a strong predictor of clinical events,<sup>[28]</sup> it remains to be established whether an improvement in carotid IMT could be translated into a reduced risk of cardiovascular events.

The same line of reasoning could be applied to the antiatherosclerotic effect of calcium channel antagonists in the coronary arteries and their lesser benefit on coronary events. Moreover, the relationship between coronary calcification and the risk of cardiovascular events is not well defined, especially considering that vulnerable plaques are predominantly composed of soft lipid and contain little or no calcium.<sup>[41]</sup> Nevertheless, the results of A Coronary disease Trial Investigating Outcome with Nifedipine GITS (ACTION) will provide additional information on the clinical relevance of these antiatherosclerotic effects.<sup>[42]</sup> ACTION is a multicentre, double-blind study with 7000 patients with stable angina randomised to either nifedipine GITS or placebo with follow up for at least 4 years. Results from ACTION are likely to be available in autumn 2003.

### 3. Conclusions

A key finding of INSIGHT is that an efficient reduction in blood pressure was able to reduce the risk of cardiovascular events in hypertensive patients with additional risk factors. Furthermore, nifedipine GITS monotherapy was as effective as the diuretic combination (HCTZ/amiloride) in reducing blood pressure and preventing cardiovascular complications. In addition, the INSIGHT study demonstrated that the incidence of serious adverse effects was lower in the nifedipine GITS recipients, who also had a better metabolic profile than patients receiving the diuretic combination. Overall, these data indicate that nifedipine GITS is an appropriate first-line treatment for hypertensive patients with additional risk factors.

Finally, the two INSIGHT substudies show that nifedipine GITS exerts an antiatherosclerotic effect in the carotid and coronary arteries. The clinical contribution of this effect in the prevention of cardiovascular events still remains to be established.

### Acknowledgements

The authors have provided no information on sources of funding or on conflicts of interest directly relevant to the content of this review.

### References

- MacMahon S, Peto R, Cutler J, et al. Blood pressure, stroke, and coronary heart disease. Part 1: prolonged differences in blood pressure: prospective observational studies corrected for the regression dilution bias. *Lancet* 1990; 335: 765-74
- Vasan RS, Larson MG, Leip EP, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. *N Engl J Med* 2001; 345: 1291-7
- Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure. The sixth report of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (JNC VI). *Arch Intern Med* 1997; 157: 2413-46
- Guidelines Subcommittee. 1999 World Health Organization-International Society of Hypertension guidelines for the management of hypertension. *J Hypertens* 1999; 17: 151-83
- Collins R, McMahon S. Blood pressure, antihypertensive drug treatment and the risk of stroke and of coronary artery disease. *Br Med Bull* 1994; 50: 272-98
- Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood pressure-lowering drugs: results of prospectively designed overviews of randomized trials. *Lancet* 2000; 356: 1955-64
- Hansson L, Zanchetti A, Carruthers SG, 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: HOT Study Group. *Lancet* 1998; 351: 1755-62
- Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension: the Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997; 350: 757-64
- Liu L, Wang JG, Gong L, et al. Comparison of active treatment and placebo in older Chinese patients with isolated systolic hypertension: Systolic Hypertension in China (Syst-China) Collaborative Group. *J Hypertens* 1998; 16: 1823-9
- Gong L, Zhang W, Zhu Y, et al. Shanghai trial of nifedipine in the elderly (STONE). *J Hypertens* 1996; 14: 1237-45
- Ad Hoc Subcommittee of the Liaison Committee of the World Health Organisation and the International Society of Hypertension. Effects of calcium antagonists on the risks of coronary heart disease, cancer and bleeding. *J Hum Hypertens* 1997; 11: 331-42
- Brown MJ, Palmer CR, Castaigne A, et al. Morbidity and mortality in patients randomised to double-blind treatment with a long-acting calcium-channel blocker or diuretic in the International Nifedipine GITS study: Intervention as a Goal in Hypertension Treatment (INSIGHT). *Lancet* 2000; 356: 366-72
- Simon A, Gariepy J, Moyse D, et al. Differential effects of nifedipine and co-amilofide on the progression of early carotid wall changes. *Circulation* 2001; 103: 2949-54
- Motro M, Shemesh J. Calcium channel blocker nifedipine slows down progression of coronary calcification in hypertensive patients compared with diuretics. *Hypertension* 2001; 37: 1410-3
- Haegerty A, Deverly A, Funck-Bretano C, et al. The role of the Critical Event Committee in a major cardiovascular outcome study. *Blood Press* 2003; 11: 339-44
- Dobson AJ, Evans A, Ferrario M, et al. Changes in estimated coronary risk in the 1980s: data from 38 populations in the WHO MONICA Project. World Health Organization. Monitoring trends and determinants in cardiovascular diseases. *Ann Med* 1998; 30: 199-205
- Kuulasmaa K, Tunstall-Pedoe H, Dobson A, et al. Estimation of contribution of changes in classic risk factors to trends in coronary-event rates across the WHO MONICA Project populations. *Lancet* 2000; 355: 675-87
- Hansson L, Lindholm LH, Ekblom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999; 354: 1751-6
- Hansson L, Hedner T, Lund-Johansen P, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in

- hypertension: the Nordic Diltiazem (NORDIL) study. *Lancet* 2000; 356: 359-65
20. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ* 1998; 317: 703-13
  21. National Intervention Cooperative Study in Elderly Hypertensives Study Group. Randomized double-blind comparison of a calcium antagonist and a diuretic in elderly hypertensives. *Hypertension* 1999; 34: 1129-33
  22. Zanchetti A, Rosei EA, Dal Palu C, et al. The Verapamil in Hypertension and Atherosclerosis Study (VHAS): results of long-term randomized treatment with either verapamil or chlorthalidone on carotid intima-media thickness. *J Hypertens* 1998; 16: 1667-76
  23. Opie LH, Schall R. Evidence-based evaluation of calcium channel blockers for hypertension: equality of mortality and cardiovascular risk relative to conventional therapy. *J Am Coll Cardiol* 2002; 39: 315-22
  24. Borhani NO, Mercuri M, Borhani PA, et al. Final outcome results of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS): a randomized controlled trial. *JAMA* 1996; 276: 785-91
  25. Pahor M, Psaty BM, Alderman MH, et al. Health outcome associated with calcium antagonists compared with other first-line antihypertensive therapies: a meta-analysis of randomized controlled trials. *Lancet* 2000; 356: 1949-54
  26. Opie LH. Calcium channel blockers in hypertension: reappraisal after new trials and major meta-analyses. *Am J Hypertens* 2001; 14: 1074-81
  27. Pessina AC, Boari L, De Dominicis E, et al. Efficacy, tolerability and influence on quality of life of nifedipine GITS versus amlodipine in elderly patients with mild-moderate hypertension. *Blood Press* 2001; 10: 176-83
  28. Hodis HN, Mack WJ, LaBree L, et al. The role of carotid arterial intima-media thickness in predicting clinical coronary events. *Ann Intern Med* 1998; 128: 262-9
  29. Zanchetti A, Bond MG, Hennig M, et al. Risk factors associated with alterations in carotid intima-media thickness in hypertension: baseline data from the European Lacidipine Study on Atherosclerosis. *J Hypertens* 1998; 16: 949-61
  30. Chobanian AV. 1989 Corcoran lecture: adaptive and maladaptive responses of the arterial wall to hypertension. *Hypertension* 1990; 15: 666-74
  31. Pitt B, Byington RP, Furberg CD, et al. Effect of amlodipine on the progression of atherosclerosis and the occurrence of clinical events: PREVENT Investigators. *Circulation* 2000; 102: 1503-10
  32. Zanchetti A, Bond G, Henning M, et al. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double blind, long-term trial. *Circulation* 2002; 106: r47-52
  33. Fitzpatrick LA, Severson A, Edwards WD, et al. Diffuse calcification in human coronary arteries: association of osteopontin with atherosclerosis. *J Clin Invest* 1994; 94: 1597-604
  34. Canfield AE, Farrington C, Dziobon MD, et al. The involvement of matrix glycoproteins in vascular calcification and fibrosis: an immunohistochemical study. *J Pathol* 2002; 196: 228-34
  35. Lichtlen PR, Hugenholtz PG, Rafflenbeul W, et al. Retardation of angiographic progression of coronary artery disease by nifedipine: results of the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT). INTACT Group Investigators. *Lancet* 1990; 335: 1109-13
  36. Waters D, Lesperance J, Francetich M, et al. A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis. *Circulation* 1990; 82: 1940-53
  37. Taddei S, Virdis A, Ghiadoni L, et al. Effects of antihypertensive drugs on endothelial dysfunction: clinical implications. *Drugs* 2002; 62: 265-84
  38. Taddei S, Virdis A, Ghiadoni L, et al. Restoration of nitric oxide availability after calcium antagonist treatment in essential hypertension. *Hypertension* 2001; 37: 943-8
  39. The ENCORE investigators. Effect of nifedipine and cerivastatin on coronary endothelial function in patients with coronary artery disease: the ENCORE I study. *Circulation* 2003; 107: 422-8
  40. Kozakova M, Buralli S, Palombo C, et al. Surrogate end points of antihypertensive treatment: left ventricular hypertrophy and structural alteration of carotid arteries. *Heart Drugs* 2001; 1: 89-95
  41. Shemesh J, Stroth CI, Tenenbaum A, et al. Comparison of coronary calcium in stable angina pectoris and in first acute myocardial infarction utilizing double helical computerized tomography. *Am J Cardiol* 1998; 81: 271-5L
  42. Lubsen J, Poole-Wilson PA, Pocock SJ, et al. Design and current status of ACTION: a coronary disease trial investigating outcome with Nifedipine GITS. Gastro-Intestinal Therapeutic System. *Eur Heart J* 1998; 19 Suppl. I: I20-32

---

Correspondence and offprints: Dr *Stefano Taddei*, Department of Internal Medicine, University of Pisa, Via Roma 67, Pisa, 56100, Italy.  
E-mail: s.taddei@med.unipi.it