

Outcome Results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in Patients With Hypertension and NIDDM

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OBJECTIVE — ACE inhibitors and calcium antagonists may favorably affect serum lipids and glucose metabolism. The primary aim of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) was to compare the effects of fosinopril and amlodipine on serum lipids and diabetes control in NIDDM patients with hypertension. Prospectively defined cardiovascular events were assessed as secondary outcomes.

RESEARCH DESIGN AND METHODS — Inclusion criteria included a diagnosis of NIDDM and hypertension (systolic blood pressure of >140 mmHg or diastolic blood pressure of >90 mmHg). Exclusion criteria included a history of coronary heart disease or stroke, serum creatinine >1.5 mg/dl, albuminuria >40 µg/min, and use of lipid-lowering drugs, aspirin, or antihypertensive agents other than beta-blockers or diuretics. A total of 380 hypertensive diabetics were randomly assigned to open-label fosinopril (20 mg/day) or amlodipine (10 mg/day) and followed for up to 3.5 years. If blood pressure was not controlled, the other study drug was added.

RESULTS — Both treatments were effective in lowering blood pressure. At the end of follow-up, between the two groups there was no significant difference in total serum cholesterol, HDL cholesterol, HbA_{1c}, fasting serum glucose, or plasma insulin. The patients receiving fosinopril had a significantly lower risk of the combined outcome of acute myocardial infarction, stroke, or hospitalized angina than those receiving amlodipine (14/189 vs. 27/191; hazards ratio = 0.49, 95% CI = 0.26–0.95).

CONCLUSIONS — Fosinopril and amlodipine had similar effects on biochemical measures, but the patients randomized to fosinopril had a significantly lower risk of major vascular events, compared with the patients randomized to amlodipine.

Hypertension is a common condition among diabetic patients, and hypertensive diabetic patients are about twice as likely to experience cardiovascular events as nondiabetic counterparts (1).

NIDDM is accompanied by changes in insulin sensitivity and lipid metabolism that increase cardiovascular risk. Several clinical trials suggested that, in addition to lowering blood pressure, the new antihy-

pertensive agents, ACE inhibitors and long-acting calcium antagonists, might exert direct beneficial metabolic effects on glucose tolerance and serum lipids in patients with hypertension, diabetes, or renal dysfunction (2–7). However, these findings have not been confirmed by others (8,9) and one comprehensive review suggested that ACE inhibitors, but not calcium antagonists, reduce serum lipids (10). The lipid effects associated with antihypertensive treatment in NIDDM patients remain controversial. It is not known which treatment might be most effective in improving the serum lipid profile and to what extent changes in laboratory measures may translate into clinical benefits.

The primary aim of the Fosinopril Amlodipine Cardiovascular Events Trial (FACET) was to assess treatment-related differences in serum lipids and diabetes control in hypertensive patients with NIDDM. The patients were randomly given an ACE inhibitor or a long-acting calcium antagonist as the first-line agent. If blood pressure was not controlled, the other study drug was added to the initial treatment. Cardiovascular events were collected as secondary outcomes. Additional outcomes were blood pressure control and renal function status.

RESEARCH DESIGN AND METHODS — The FACET was an open-label, randomized prospective trial comparing fosinopril to amlodipine in hypertensive people with NIDDM. Patients were men and women recruited from 1 January through 31 December 1992 from an outpatient diabetes clinic in Marino, Italy. NIDDM was defined as having fasting serum glucose >140 mg/dl when the patient was untreated and having no requirement of insulin as an initial treatment for diabetes. All patients were seen in the clinic three or more times during a 3-month period before randomization. Hypertension was diagnosed as systolic blood pressure (sBP) >140 mmHg or diastolic blood pressure (dbP) >90 mmHg measured in at least three consecutive visits,

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Abbreviations: ECG, electrocardiogram; FACET, Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial; HR, hazard ratio; PAI, plasminogen activator inhibitor; SHEP, Systolic Hypertension in the Elderly Program.

or sBP >160 mmHg or dBP >95 mmHg measured in at least two consecutive or nonconsecutive visits. Duration of hypertension was less than 1 year. Exclusion criteria included a history of coronary heart disease, stroke, or any other morbid condition with poor prognosis; a serum creatinine level of >1.5 mg/dl; a microalbuminuria level of >40 µg/min; and the use of lipid-lowering drugs, aspirin, or antihypertensive agents other than diuretics and beta-blockers. The patients treated with diuretics or beta-blockers were evaluated for blood pressure inclusion criteria after a washout period of 2 weeks. Diuretics or beta-blockers were not used in the trial.

At baseline, a physical exam was performed by a single study physician (P.T.). Blood pressure was measured in the morning while the patient was sitting. Fasting blood samples were drawn by venipuncture with the patient in a sitting position and analyzed in the central clinic laboratory. The biochemical assays included fasting serum glucose, serum creatinine, plasma insulin, HbA_{1c}, total cholesterol, HDL cholesterol, triglycerides, fibrinogen, and microalbuminuria. Electrocardiograms (ECGs) were performed during the clinic visit. Medical history, review of medical charts, and ECGs were used to exclude patients with coronary heart disease.

By using a computer-generated random number sequence obtained from an investigator who was not involved in patient recruitment, patients were randomized to either fosinopril 20 mg/day given in the morning or amlodipine 10 mg/day given in the evening. The study drugs were administered open-label and were part of the patient's scheduled treatment. The goal blood pressure was defined as sBP ≤140 mmHg and dBP ≤90 mmHg, or a decrease ≥20 mmHg of blood pressure if sBP was >160 mmHg or dBP was >110 mmHg. If blood pressure was not controlled on monotherapy, the other study drug was added at full dose. Compliance with treatment was verified by self-report and by a pill count from the medication containers brought to the clinic by the participants. When the patients were on the study treatments, the compliance rate averaged >80% and was the same in both groups. Blood pressure control was used as an additional indicator for verifying compliance.

During the first 6 months after randomization, clinic visits and blood pressure measurements were scheduled monthly until blood pressure goals were reached.

The participants were followed for clinic visits every 6 months thereafter. Complete blood biochemical examination tests and urine assays for microalbuminuria were performed at least annually in the same clinic laboratory. The trial was completed on 30 June 1995. Events were monitored during the study by asking the patients if they were hospitalized or had any other events since the last visit. The patients who did not return to the clinic were contacted personally or through proxies. After the completion of the study, all patients or their proxies were recontacted to ensure the completeness of follow-up and event ascertainment in both arms of the trial. Hospital and medical records were obtained, and all events were independently adjudicated by an internist and a cardiologist who had no patient contact or any other role in the study and who were blinded to the assigned treatment. The adjudication process used predetermined standardized algorithms based on clinical history, laboratory exams, and procedures. Hospitalized angina was defined as follows: the patient must have been hospitalized overnight with an admission diagnosis of chest pain and either 1) electrocardiographic evidence or positive thallium-201 (or equivalent) myocardial stress test or new coronary angiographic findings of angiographic significant coronary disease or 2) chest pain was typical, reproducible, or similar to previous documented episodes of myocardial ischemia. Acute myocardial infarction was defined according to a standardized algorithm that used information from clinical history of the event, predefined electrocardiographic changes, cardiac enzymes, and autopsy. Stroke was defined according to a standardized algorithm that used information from clinical history of the event, computerized tomography scan, lumbar puncture, surgery, and autopsy. The prospectively defined events were categorized as follows: 1) all-cause mortality, 2) fatal or nonfatal stroke, 3) fatal or nonfatal acute myocardial infarction, 4) hospitalized angina, 5) any major vascular event described in 2, 3, or 4, 6) coronary artery bypass, 7) percutaneous transluminal coronary angioplasty, 8) any major vascular event or procedure described in 5, 6 or 7, 9) other cardiovascular events or procedures, and 10) cancer. Cancers were histologically documented.

Data analyses

The trial had 80% power ($\alpha = 0.05$) to detect a 10% difference in total cholesterol

between fosinopril and amlodipine. Stopping rules were not warranted. Analysis of variance (ANOVA) and the χ^2 test were used to assess differences between means and proportions, respectively. Data measured at the last scheduled annual visit when the patient was seen in the clinic were compared with baseline values and between treatments. Changes from baseline are given as 95% CIs. This change is significant at $P \leq 0.05$ when the CI does not contain zero.

In analyses of events, the time to the first event was used. Follow-up ended on 30 June 1995 or at the time of death, whichever occurred first. The Kaplan-Meier method was used to plot survival time free of events, and the log-rank test was used to test differences between survival curves (11). The Cox proportional hazards regression model was used to estimate the hazard ratio (HR) and 95% CI for the association of type of treatment with events and to adjust for potential baseline confounding variables (12). The assumption of proportionality of hazards was assessed with log-minus-log plots and by testing for an interaction between treatment and time (13). All P values were two-sided and all analyses were intention-to-treat, unless otherwise stated.

RESULTS — A total of 189 patients were randomized to fosinopril and 191 patients to amlodipine (Fig. 1). To control blood pressure, amlodipine was added in 30.7% of the fosinopril group patients (58/189), and fosinopril was added in 26.2% of the amlodipine group patients (50/191, $P > 0.1$). The patients randomized to fosinopril and amlodipine had similar demographic, blood pressure, and blood biochemical characteristics at baseline (Table 1). Microalbuminuria was slightly higher in the amlodipine group. A total of 55 patients in the fosinopril group and 66 patients in the amlodipine group were on diuretics, and 20 patients in the fosinopril group and 18 patients in the amlodipine group were on beta-blockers before the study. Diuretics and beta-blockers were not prescribed during the study.

Table 2 summarizes the measurements at the last annual visit, which occurred on average 2.5 years after randomization, and the change from baseline. Both treatments significantly decreased sBP and dBP. During follow-up in the fosinopril and amlodipine groups, the sBP goal was reached by 58.5 and 60.7% of the patients, respectively; the dBP goal was reached by 89.4 and 90.1%

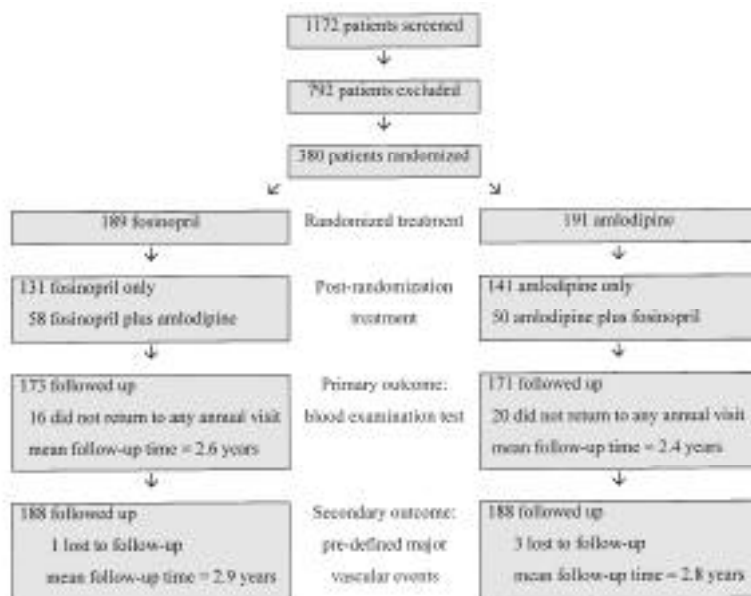


Figure 1—Trial profile.

of the patients, respectively; and both sBP and DBP goals were reached in 55.6 and 58.6% of the patients, respectively ($P > 0.1$). At the last annual visit, the sBP was 4 mmHg lower in the amlodipine group compared with foscipril ($P < 0.01$). This difference reflected the greater reduction in sBP over the follow-up period in patients treated with amlodipine than in those treated with foscipril (−19 and −13 mmHg, respectively). The two treatment groups had the same reduction in DBP compared with baseline (−8 mmHg).

In both treatment groups, serum creatinine, HbA_{1c}, and triglycerides did not vary significantly during follow-up. Fasting serum glucose, serum insulin, and microalbuminuria were significantly decreased at the last annual visit, compared with baseline values by a similar magnitude in the foscipril and amlodipine groups. Subcutaneous insulin was administered during the trial to 19.0% (36/189) of the patients in the foscipril group and 17.8% (34/191) of the patients in the amlodipine group ($P > 0.1$). During follow-up, total serum cholesterol increased slightly but significantly in both groups. The increase in total cholesterol was accompanied by a small increase in HDL cholesterol, which was significant only in the foscipril group. Compared with baseline levels, fibrinogen decreased significantly in the patients receiving foscipril and did not change significantly in those receiving amlodipine. The difference in fibrinogen levels at the

last annual visit between foscipril and amlodipine groups was not significant.

All patients had a complete follow-up for events through 30 June 1995, except for one patient in the foscipril group and

three patients in the amlodipine group who were lost to follow-up. The follow-up range was 2.5–3.5 years. A total of 69 participants experienced predefined events, including death, vascular events, procedures, and cancer. The patients randomized to foscipril were less likely to experience events than those randomized to amlodipine (Table 3). The proportion of patients reaching the prospectively defined combined end point of stroke, acute myocardial infarction, or hospitalized angina was significantly lower in the foscipril group compared with amlodipine ($P = 0.030$, Fig. 2; HR = 0.49, 95% CI = 0.26–0.95, Table 3). In a separate proportional hazards model adjusted for baseline albuminuria, the results were unchanged. The HR (95% CI) of the nonprospectively defined combined end point of fatal or nonfatal acute myocardial infarction or stroke for foscipril compared with amlodipine was 0.58 (0.30–1.13) ($P = 0.11$). The HR (95% CI) of major vascular events in men, women, people age <65 years, and in people age ≥65 years was 0.53 (0.17–1.62), 0.55 (0.25–1.22), 1.12 (0.43–2.90), and 0.24 (0.09–0.65), respectively. The P value for the interaction of treatment with sex was

Table 1—Patient characteristics at baseline

Characteristic	Foscipril	Amlodipine
<i>n</i>	189	191
Age (years)	62.8 ± 0.5	63.3 ± 0.4
Sex (% women)	36.5	44.5
Duration of diabetes (years)	10.7 ± 0.7	10.5 ± 0.6
Cigarette smoking (%)		
Never smoked	86.8	81.7
Current smoker	4.8	6.8
Former smoker	5.3	5.2
Passive smoker	3.2	6.3
BMI (kg/m ²)	30.7 ± 0.3	30.5 ± 0.4
Blood pressure		
Systolic (mmHg)	170 ± 1	171 ± 1
Diastolic (mmHg)	95 ± 1	94 ± 1
Blood examination		
<i>n</i>	189	191
Creatinine (mg/dl)	1.0 ± 0.01	1.0 ± 0.01
Glucose (mg/dl)	171 ± 3	174 ± 4
Insulin (mU/ml)	25 ± 2	22 ± 1
HbA _{1c} (%)	6.9 ± 0.1	7.0 ± 0.1
Total cholesterol (mg/dl)	222 ± 2	222 ± 2
HDL cholesterol (mg/dl)	47 ± 1	47 ± 1
Triglycerides (mg/dl)	153 ± 6	159 ± 5
Fibrinogen (mg/dl)	292 ± 5	291 ± 5
Albuminuria (μg/min)	20 ± 1	24 ± 1 *

Data are means ± SE or %. * $P < 0.05$ vs. foscipril.

Outcome results of the FACET

Table 2—Blood pressure and biochemical measures at last annual visit

Measure	Fosinopril		Amlodipine	
	Last visit	Change from baseline	Last visit	Change from baseline
Blood pressure				
<i>n</i>		179		178
Systolic (mmHg)	157 ± 1	-13 (-16 to -10)	153 ± 1†	-19 (-22 to -15)*
Diastolic (mmHg)	88 ± 1	-8 (-9 to -6)	86 ± 1	-8 (-9 to -6)
Blood examination				
<i>n</i>		173		171
Creatinine (mg/dl)	1.0 ± 0.01	-0.01 (-0.03 to 0.01)	1.1 ± 0.05	0.06 (-0.03 to 0.16)
Glucose (mg/dl)	153 ± 4	-17 (-28 to -7)	161 ± 5	-14 (-26 to -2)
Insulin (mU/ml)	19 ± 1	-5 (-8 to -3)	20 ± 1	-2 (-4 to -1)
HbA _{1c} (%)	6.8 ± 0.1	-0.1 (-0.3 to 0.1)	7.0 ± 0.1	0 (-0.2 to 0.1)
Total cholesterol (mg/dl)	226 ± 3	4 (0 to 9)	228 ± 3	6 (2 to 10)
HDL cholesterol (mg/dl)	49 ± 1	3 (1 to 4)	49 ± 3	2 (-0 to 3)
Triglycerides (mg/dl)	155 ± 5	1 (-8 to 11)	161 ± 5	1 (-7 to 10)
Fibrinogen (mg/dl)	283 ± 4	-9 (-16 to -1)	290 ± 4	2 (-4 to 8)
Albuminuria (µg/min)	13 ± 1	-8 (-11 to -5)	13 ± 1	-11 (-14 to -8)

Data are means ± SE or means (95% CI). Changes from baseline are significant at $P \leq 0.05$ when the CI does not contain 0. * $P < 0.05$; † $P < 0.01$ vs. fosinopril at last annual visit.

0.97 and for the interaction of treatment with age was 0.031.

In the worst-case scenario, in which the single fosinopril patient who was lost to follow-up had an event and none of the three amlodipine patients who were lost to follow-up had events, the difference in risk of major vascular events between fosinopril and amlodipine would still be significant ($P = 0.048$ with log-rank test). Incident cancer events tended to be less frequent in the fosinopril group, but the difference

between the two groups was not significant.

In crude analyses according to post-randomization treatment given to control blood pressure, the patients who received fosinopril only ($n = 131$), amlodipine only ($n = 141$), and the combination of fosinopril plus amlodipine ($n = 108$) experienced 10, 27, and 4 major vascular events, respectively. In the three post-randomization groups, the number of patients who experienced acute myocardial infarction was 7,

13, and 3, respectively; the number of patients who experienced hospitalized angina was 0, 4, and 0, respectively; and the number of patients who experienced stroke was 3, 10, and 1, respectively. Compared with use of amlodipine only, the risk of major vascular events was significantly decreased with the use of fosinopril only and with the combination treatment (HR 0.37, 95% CI 0.18–0.77, $P = 0.008$ and HR 0.17, 95% CI 0.06–0.50, $P = 0.001$, respectively). The event rates in the fosinopril

Table 3—Events during follow-up

Event	Fosinopril	Amlodipine	HR (95% CI)	<i>P</i> value
<i>n</i>	189	191	—	—
All-cause mortality	0.7 (4)	0.9 (5)	—	—
Fatal or nonfatal stroke	0.7 (4)	1.9 (10)	0.39 (0.12 to 1.23)	>0.1
Fatal or nonfatal acute myocardial infarction	1.8 (10)	2.4 (13)	0.77 (0.34 to 1.75)	>0.1
Hospitalized angina	0 (0)	0.7 (4)	‡	—
Any major vascular event	2.6 (14)	5.0 (27)	0.49 (0.26 to 0.95)	0.030
Coronary artery bypass	0.5 (3)	0.4 (2)	—	—
Percutaneous transluminal coronary angioplasty	0 (0)	0.2 (1)	—	—
Any major vascular event or procedure*	2.6 (14)	5.0 (27)	0.49 (0.26 to 0.95)	0.030
Other cardiovascular events or procedures†	0.7 (4)	0.9 (5)	—	—
Any death or any vascular event or any procedure	3.6 (20)	6.3 (34)	0.56 (0.32 to 0.97)	0.036
Nonfatal cancer	1.3 (7)	1.7 (9)	—	—
Fatal cancer	0.2 (1)	0.4 (2)	—	—
Any cancer	1.5 (8)	2.0 (11)	0.64 (0.25 to 1.65)	>0.1
Any event listed above	4.9 (27)	7.8 (42)	0.59 (0.37 to 0.97)	0.035

Data are rates expressed as number of events per 100 person-years (*n*). HR of fosinopril versus amlodipine calculated with proportional hazards models. *All coronary artery bypass and angioplasty procedures were performed in patients who previously have had a myocardial infarction; †include three transitory ischemic attacks, one pericarditis, and five pacemaker implants; ‡too few events to analyze.

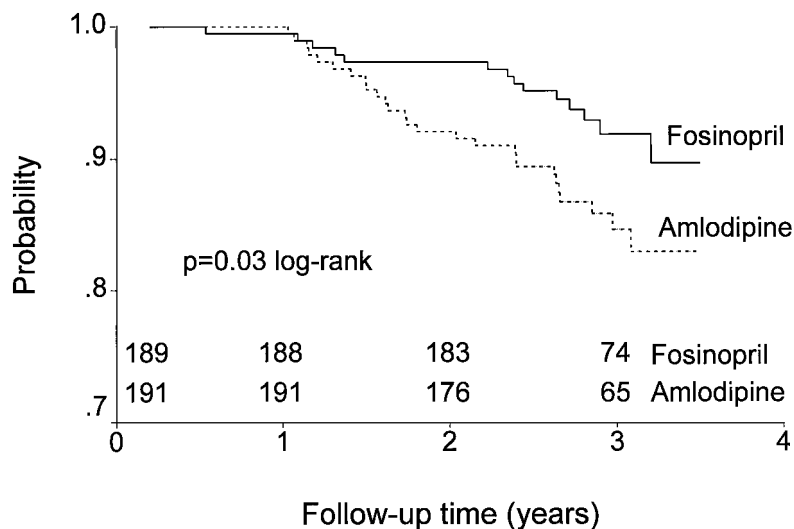


Figure 2—Probability of remaining free of stroke, acute myocardial infarction, or hospitalized angina according to treatment. The number of participants at each time point according to treatment is indicated at the bottom of the graph.

only and in the fosinopril plus amlodipine groups were not significantly different ($P = 0.19$). It is important to note that the post-randomization analyses shown above break the intention-to-treat principle (14).

A total of 36 and 52 patients dropped out from treatment before the end of follow-up in the fosinopril and amlodipine group, respectively (19.0 and 27.2%, respectively, $P = 0.06$). Among the patients who dropped out, only one event occurred in the amlodipine group and no events occurred in the fosinopril group. In on-treatment analysis, the risk of major cardiovascular events with fosinopril compared with amlodipine was virtually unchanged, with respect to the intention-to-treat analysis (HR = 0.45, 95% CI 0.24–0.86, $P = 0.016$).

CONCLUSIONS — The FACET did not demonstrate significant differences between fosinopril and amlodipine in the primary outcome measures of lipid profile and glucose metabolism. A greater SBP reduction was observed with amlodipine. Despite this blood pressure difference, patients randomized to fosinopril were about 50% less likely to experience major cardiovascular events, a secondary outcome, than those randomized to amlodipine. These findings illustrate again the limitations of blood pressure lowering as a surrogate marker of clinical efficacy of antihypertensive therapy.

No significant differences were found between fosinopril and amlodipine in absolute values or changes in biochemical

measures. These findings are in agreement with a recent study that compared cilazapril with amlodipine in patients with NIDDM (9). Although the interpretation of changes compared with baseline is limited by lack of a placebo reference group, the present results indicate that both fosinopril and amlodipine may favorably affect fasting serum glucose, plasma insulin levels, HDL cholesterol, and urinary protein excretion. These findings are in agreement with other studies conducted in patients with hypertension, renal dysfunction, or NIDDM (2–4,15). Some trials have shown that ACE inhibitors and amlodipine tend to decrease total serum cholesterol and triglycerides (3–7). However, this association was not seen in the FACET.

A plausible explanation for the greater decrease in SBP found in the amlodipine group compared with the fosinopril group is that, to reduce side effects, amlodipine was given in the evening and fosinopril in the morning. Therefore, because blood pressure was always measured in the morning and both drugs are long-acting agents (16,17), the time of the blood pressure measurement was likely to be close to the peak effect of amlodipine and to the trough effect of fosinopril. Alternative explanations are that the relative dose of amlodipine was greater than that of fosinopril, or that amlodipine was more effective than fosinopril in lowering blood pressure. In some studies, calcium antagonists tended to achieve a greater blood pressure reduction than ACE inhibitors (10,15,18).

To our knowledge, this is the first randomized trial comparing major clinical events in NIDDM patients receiving an ACE inhibitor or a long-acting calcium antagonist for hypertension. The reduction in risk of major vascular events in patients randomized to fosinopril compared with amlodipine was statistically significant and was consistent when all prespecified events were included. Such an effect remained unchanged in analyses adjusted for potential baseline confounders, in analyses according to treatment given after randomization, and in worst-case scenario analyses that account for patients lost to follow-up. Follow-up and ascertainment of events was virtually complete in both groups, and the prospectively defined events were adjudicated according to objective criteria by an independent blinded committee. Nonetheless, these results should be interpreted with caution. This trial was not designed and powered to assess a difference between the two treatments in vascular events. Additional methodological limitations are the open-label and single-site design of the study and the 6-month interval of the follow-up visits. The intriguing findings of FACET on vascular events need to be confirmed in large prospective long-term trials, such as for example, the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) (19).

Recent studies have raised questions about long-term safety of calcium antagonists (20–24). Two observational studies in hypertension (21,22) and one meta-analysis of placebo-controlled trials in coronary heart disease (20) have found excess mortality or occurrence of coronary events with the use of certain short-acting calcium antagonists. One recent case-control study in hypertensive subjects has found an increased risk of coronary events primarily in patients using short-acting calcium antagonists, but only a small nonsignificant increase in those using long-acting formulations (25). In a randomized placebo-controlled trial in patients with severe heart failure, amlodipine did not affect the primary outcome of mortality or hospitalization for heart failure, but it increased the risk of pulmonary edema (25). More recent secondary analyses suggest that the excess risk of adverse events associated with the use of calcium antagonists may be particularly important in diabetic patients (26).

The results of the FACET on vascular events may be due to a special benefit of fosinopril in patients with NIDDM. This

interpretation is suggested by the analyses according to the treatment that was given post randomization. In these analyses, the risk of events was not increased among those receiving fosinopril plus amlodipine, compared with those receiving fosinopril only. About a third of the participants were using the combination treatment of fosinopril plus amlodipine, and as a result, in the intention-to-treat analyses, any treatment effect would be diluted. In crude analyses that compare those who received fosinopril only to those who received amlodipine only, the relative risk of major cardiovascular events was lower and more significant than in intention-to-treat analyses (HR 0.37, 95% CI 0.18–0.77, $P = 0.008$ and HR 0.49, 95% CI 0.26–0.95, $P = 0.030$, respectively). The findings according to post-randomization treatment may reflect more closely the real-life clinical practice. However, such post hoc analyses should be interpreted with caution because they break the intention-to-treat principle (14).

If fosinopril is truly more effective than amlodipine in preventing major vascular events in NIDDM, what are the potential mechanisms? The present findings are not explained by differences in blood pressure control, diabetes control, renal function, or lipid profile. It is unlikely that the evening versus morning dosage might have impacted on the results of cardiovascular events. Potential sympathetic stimulation with amlodipine might have accounted for the increased risk in cardiovascular events compared with fosinopril (27). However, it has been reported that adrenergic cardiovascular response is reduced in diabetic patients who often have sympathetic neuropathy and consequent regional autonomic denervation (28,29). In theory, ACE inhibitors might be more beneficial than other antihypertensive treatments in diabetic patients. The greater propensity to thrombotic events in people with diabetes has been linked to increased levels of plasminogen activator inhibitor-1 (PAI-1) (30). Recent evidence has shown that the ACE plays a key role in the activation of PAI-1 (31). It has been shown that ACE inhibitors can suppress the expression of PAI-1 (32) and thus, facilitate fibrinolysis. This mechanism may account for the beneficial effect of fosinopril on both stroke and coronary events.

There is growing evidence that ACE inhibitors prevent major complications in diabetic patients, including those with nephropathy (33), myocardial infarction

(34), or noncomplicated hypertension as shown in the FACET. Secondary analyses in the Systolic Hypertension in the Elderly Program (SHEP) have shown that diuretic-based treatment is more effective than placebo in preventing cardiovascular events in both diabetic and nondiabetic patients (1). These new findings in SHEP highlight the primary importance of blood pressure lowering in diabetic hypertensives. However, to optimize treatment, long-term trials comparing active agents are needed to assess which treatment is most effective in preventing major complications. The results of FACET are in agreement with those of the Multicenter Isradipine Diuretic Atherosclerosis Study (MIDAS) (35). In both trials, hypertensive patients with diabetes or impaired glucose metabolism who received alternative treatments had a significantly lower risk of cardiovascular events, compared with those who received a calcium antagonist. The FACET shows that both fosinopril and amlodipine effectively lowered blood pressure and had comparable effects on surrogate biochemical measures, but the patients randomized to fosinopril had a significantly lower risk of major vascular events, compared with those randomized to amlodipine.

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