Rationale and Design of a Large Study to Evaluate the Renal and Cardiovascular Effects of an ACE Inhibitor and Vitamin E in High-Risk Patients With Diabetes

The MICRO-HOPE Study

HERTZEL C. GERSTEIN, MD, MSC, FRCPC
JACKIE BOSCH, BSC
JANICE POGUE, MSC
D. WAYNE TAYLOR, MA
BERNARD ZINMAN, MD, CM, FRCPC
SALIM YUSUF, MBBS, FRCP, DPHIL
THE HOPE STUDY INVESTIGATORS

OBJECTIVE — To describe the rationale and design of a large international study (microalbuminuria, cardiovascular, and renal outcomes [MICRO] in the HOPE [Heart Outcomes Prevention Evaluation] study) of an ACE inhibitor and vitamin E for the prevention of diabetic nephropathy (DN) and cardiovascular disease (CVD) in patients with diabetes and microalbuminuria (MA).

RESEARCH DESIGN AND METHODS — A total of 3,657 diabetic subjects, including 1,129 with MA, are randomly allocated to receive the ACE inhibitor ramipril (or placebo) and vitamin E (or placebo) for 4 years in a two-by-two factorial design. Diabetic subjects are a subset of the 9,541 subjects enrolled in the HOPE study.

RESULTS — The development of DN in microalbuminuric diabetic subjects and the development of MA in normoalbuminuric subjects, as well as cardiovascular death, myocardial infarction, and stroke, are the main outcomes. The correlation of changes in albuminuria with changes in carotid atherosclerosis documented in a subset of subjects will also be analyzed.

CONCLUSIONS — The effect of both an ACE inhibitor and vitamin E on the progression of renal and CVD in patients with diabetes is being assessed in the MICRO-HOPE study.

The Heart Outcomes Prevention Evaluation (HOPE) study is an international randomized double-blind placebo-controlled trial of 9,541 patients ≥55 years of age at high risk for cardiovascular disease (CVD), including 3,657 patients with diabetes (1). Subjects are randomized to receive the ACE inhibitor ramipril (or placebo) and vitamin E (or placebo) using a factorial design (Table 1); the primary endpoint is a major cardiovascular event (myocardial infarction [MI], stroke, or cardiovascular death). Carotid atherosclerosis progression is being measured in a substudy (Study to Evaluate Carotid Ultrasound Changes With Ramipril and Vitamin E [SECURE]). These studies provide an opportunity to assess if an ACE inhibitor (and/or vitamin E) can prevent diabetic renal disease in older diabetic patients. This opportunity is exploited in the MICRO-HOPE study (microalbuminuria, cardiovascular, and renal outcomes in the HOPE study), which is testing the hypothesis that the ACE inhibitor ramipril and/or vitamin E will prevent the development of diabetic nephropathy (DN) in patients with diabetes and microalbuminuria (MA) and the development of MA in normoalbuminuric patients with diabetes. This study will also explore the hypothesis that urinary albumin excretion (UAE) is a marker for atherosclerosis and that it reflects changes in carotid atherosclerosis.

MA and the risk of renal and CVD in people with diabetes

MA (a UAE rate of 20–200 μg/min) affects 30% of people with diabetes aged 55 or older (2–6). It is a risk factor for DN, which occurs in ~5% of affected NIDDM patients (7–9) and 7.5% of affected IDDM patients (10–12) annually. Once DN develops, NIDDM patients develop chronic renal failure (CRF) at ~1% per year (13,14); in young IDDM patients, the risk of CRF approaches 75% after 10 years (15–18).

Changes in UAE reflect changes in the severity of renal disease and the risk of renal failure. Moreover, interventions that decrease UAE, including low-protein diets, glycemic control, control of hypertension, and ACE inhibitors (17,19), also slow progression of renal disease and decrease the risk of renal failure. Hence, UAE reflects the impact of an intervention on the progression of diabetic renal disease.

MA may also reflect widespread vascular disease. First, MA independently predicts total and cardiovascular mortality in patients with both IDDM and NIDDM (20), as well as in patients with no evidence of diabetes (21,22). Patients with NIDDM and MA have an annual total and cardiovascular mortality of ~8 and 4% respectively (4,7,23–26); this is up to 4 times higher

From McMaster University (H.C.G., J.B., J.P., D.W.T., S.Y.), Hamilton; the University of Toronto (B.Z.), Toronto, Ontario, Canada; and the Canadian Cardiovascular Collaboration (HOPE Study investigators [1]).

Address correspondence to H.C. Gerstein, MD, MSc, FRCPC, Rm. 3V38, McMaster University Medical Centre, 1200 Main St. West, Hamilton, Ontario, Canada L8N 3Z5. E-mail: gerstein@fhs.csu.mcmaster.ca. Address reprint requests to H.C. Gerstein, MD, MSc, FRCPC, HOPE Project Office, HGH-McMaster Clinic, 237 Barton St. East, Hamilton, Ontario, Canada L8L 2X2.

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ACR, albumin-to-creatinine ratio; CRF, chronic renal failure; CVD, cardiovascular disease; DN, diabetic nephropathy; HOPE, Heart Outcomes Prevention Evaluation; MA, microalbuminuria; MI, myocardial infarction; MICRO, microalbuminuria, cardiovascular, and renal outcomes; SECURE, Study to Evaluate Carotid Ultrasound Changes With Ramipril and Vitamin E; UAE, urinary albumin excretion.

Table 1—*Factorial design of the overall HOPE study*

	n	Vitamin E (*n* = 4,761)	Vitamin E placebo (*n* = 4,780)
Ramipril	4,889	2,450	2,439
Ramipril placebo	4,652	2,311	2,341

In the study, 3,657 subjects have diabetes. Data are number of subjects receiving each combination.

than the rate in patients without MA. Comparable data for younger patients with IDDM (mean age, 40) and MA indicate that the annual total and cardiovascular mortality rates are ~2.7 and 2.1% respectively, which is up to two times higher than comparable patients without MA (27). Second, MA is associated with several biochemical risk factors for atherosclerosis such as atherogenic lipid profiles, and hyperinsulinemia in both diabetic (20,28) and nondiabetic patients (21). It is also associated with high levels of biochemical indexes of endothelial dysfunction such as von Willebrand factor (25), with increased platelet adhesiveness (2) and a prothrombotic profile including high fibrinogen and plasminogen activator inhibitor levels (2–4). Third, patients with MA have an increased red-cell sodium-lithium countertransport rate and lipoprotein(a) levels—genetically acquired traits associated with hypertension and CVD (29).

ACE inhibitors, and renal and CVD

In young patients with IDDM, ACE inhibitors decrease UAE in the presence of MA (10,30,31) and prevent CRF in the presence of DN (16). This effect has not been clearly demonstrated in older IDDM patients with a longer duration of diabetes who are less likely to develop DN (17). Although one trial (8) has demonstrated a nephroprotective effect of an ACE inhibitor in relatively young patients with NIDDM, the fact that 20–30% of renal disease in NIDDM is not due to diabetes (32) suggests the need for more research on the role of ACE inhibitors in older diabetic patients before concluding that nephroprotective effects of this drug class are similar in all patients with diabetes.

ACE inhibitors may also retard the progression of atherosclerosis. Indeed, demonstrated reductions in death, dialysis, and transplantation with captopril (16) may be explained by both a renal and cardiovascular effect of this drug.

ACE inhibitors decrease angiotensin II by decreasing the activity of ACE (located on vascular endothelium). Angiotensin II is a potent vasoconstrictor of both the systemic vasculature and the glomerular efferent arteriole. It is also a growth factor for glomerular and mesangial cells, as well as for vascular smooth muscle cells (33,34). Reduced systemic blood pressure and efferent arteriolar vasodilation as a result of decreased angiotensin II levels lead to decreased glomerular hypertension and hyperfiltration and a reduced UAE rate (17). Reduced mesangial and vascular growth, directly due to lower angiotensin II levels, and indirectly due to a lower systemic blood pressure, may also prevent renal damage and MA progression, as well as damage to the systemic vasculature (35,36).

Because ACE also inactivates bradykinin, ACE inhibitors increase bradykinin levels, which increases endothelial production of nitric oxide—a potent vasodilator (37). Finally, ACE inhibitors modestly increase insulin sensitivity (38). These are further mechanisms whereby ACE inhibitors may slow the progression of vascular disease, both in the kidney and elsewhere.

Potential role of vitamin E

Nephroprotective mechanisms of vitamin E may include reduced platelet aggregability (39), decreased insulin resistance (40,41), modified atherogenic lipid profiles (41), and decreased protein glycation (42,43) and advanced glycation end-product formation. Cardiovascular effects are reviewed elsewhere (44).

RESEARCH DESIGN AND METHODS

Randomized study population

Diabetic patients aged 55 years or older (96% diagnosed after age 30) with previous coronary, peripheral vascular, or cerebrovascular disease (1) or with dyslipidemia (total cholesterol >5.2 mmol/l or HDL cholesterol ≤0.9 mmol/), hypertension, MA (UAE 20–200 μg/min) or who currently smoke are recruited. Hypersensitivity to ACE inhibitors or vitamin E, significant renal disease (i.e., creatinine ≥200 mEq/l, UAE >200 μg/min or >300 mg/d, or urinary protein excretion >500 mg/d, random urine dipstick protein ≥1+, or renal artery stenosis), and hyperkalemia are key exclusion criteria (other criteria, see reference 1).

Subjects are randomized within centers to receive ramipril (2.5 mg/day for 1 week, 5 mg/day for 3 weeks, and then 10 mg/day thereafter) or ramipril placebo and vitamin E (400 IU/day) or vitamin E placebo in a factorial design. Visits are scheduled semiannually. Compliance at 1 year exceeds 85%.

Outcome measures and analysis

The primary outcome is the development of DN in patients with baseline MA and the development of MA in patients without baseline MA. Other analyses will include the risk of cardiovascular death, stroke, or MI (silent infarcts are detected with electrocardiograms at the baseline, 2-year, and final visit) in patients with baseline MA and the relationship of UAE to carotid intimal media thickness for subjects also in the SECURE substudy.

The albumin-to-creatinine ratio (ACR) in a first morning urine is used to measure UAE and screen for DN. It is assayed on three occasions (Table 2) in one of four locations (Table 3). The sensitivity and specificity of an ACR >36 mg/mmol for the

Table 2—*Tests to detect overt nephropathy in subjects with diabetes*

Visit	Screening test (first A.M. urine)	Confirmatory test
Initial	ACR and protein dipstick	Not applicable
1 year	ACR and protein dipstick	24-h or timed urine albumin or protein
2 years	Protein dipstick	Same as above
3 years	Protein dipstick	Same as above
End of study	ACR and protein dipstick	Same as above

ACR is considered to be a positive screen if it is >36 mg/mmol. Protein dipstick is positive if ≥1+ in the absence of a urinary tract infection. Diabetic nephropathy will be diagnosed if the locally measured albumin excretion rate is >200 μg/min, or if >300 mg albumin or >500 mg of protein are excreted/day (i.e., if there is evidence of clinical proteinuria).

Table 3—*International urinary albumin assays*

Country	Method	Assay name	Company	Inter-run coefficient of variation (mg/l: %)
Canada	Radioimmunoassay	Albumin double antibody	Diagnostic Products Corporation	10: 7 25: 6
U.K.	Radioimmunoassay	Albumin double antibody	Diagnostic Products Corporation	10.1: 7.1
Brazil	Immunoturbidimetry	Turbiquant	Behringwerke AG Diagnostica	22.8: 3.7 244: 4.3
Argentina	Immunoturbidimetry	Tina-quant albumin in urine	Boehringer Mannhein GmbH Diagnostica	100: 4.3

Urinary albumin/creatinine results in each lab are compared with the North American lab by periodic exchange and duplicate assay of up to 100 urine specimens and calculation of correlations and kappa values during the study; baseline urinary albumin/creatinine results in North America and other labs were well correlated ($r > 0.76$). Urinary creatinine (used to calculate the ACR) is assayed using a kinetic alkaline picrate (Jaffe) method.

detection of DN are 93 and 98% respectively (45–48), and of a urinary protein dipstick ≥1+ for DN are >70 and >90% respectively (49). The dipstick will be used to screen for DN at the 2nd and 3rd year visits. Confirmatory testing for DN (Table 2) will be done if the ACR is >36 mg/mmol or the urinary protein dipstick is ≥1+.

Safety considerations

As ACE inhibitors are indicated in DN in IDDM (8,16) and possibly NIDDM patients (31), these subjects are excluded; subjects developing DN during the study may be given an open-label ACE inhibitor. Subjects developing congestive heart failure will also be given an open-label ACE inhibitor. All serious adverse experiences, as well as annual interim analyses, are reviewed by the independent external Data Safety and Monitoring Board in strict confidence.

Power calculations

Baseline ACRs in 3,512 of the 3,657 randomized patients with diabetes (96% diagnosed after age 30) showed MA in 1,129 (32%). Thus there is 85% power to detect a 40% decrease in DN (50) in MA patients and 97% power to detect a 35% decrease in MA development in patients without baseline MA (Table 4). There is 90% power to detect a 26% decrease in cardiovascular mortality in the 3,657 patients with diabetes.

CONCLUSIONS — Middle-aged diabetic patients are at high risk for renal and CVD, especially if they have MA. Evidence suggests, but does not yet prove, that ACE inhibitors and/or vitamin E may decrease this risk. Thus, this trial will have an important impact on the care of people with diabetes.

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Table 4—*Power (1-β) to detect a 35–40% decrease in renal outcomes*

		Decrease in DN (%)				Decrease in MA (%)	
n	Control rate	35	40	*n*	Control rate	35	40
1,130	0.14	74	85	2,482	0.14	97	99
	0.16*	80	90		0.16	98	99
	0.18	85	93		0.18	99	99

The decrease in development of diabetic nephropathy is for subjects with baseline microalbuminuria. The decrease in development of microalbuminuria is for normoalbuminuric subjects. *Based on a constant risk for the development of overt nephropathy of 5% per year; 16.3% of patients with diabetes and MA will develop diabetic nephropathy during the initially planned mean follow-up period of 3.5 years (two-sided; $\alpha = 0.05$).

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