Rates and predictors of risk of stroke and its subtypes in diabetes: a prospective observational study

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Key words

cerebrovascular disease; diabetes; predictors; prognostic factors; stroke

Abstract

Background

Small vessel disease is reported to be a more common cause of ischaemic stroke in people with diabetes than in others. However, population-based studies have shown no difference between those with and those without diabetes in the subtypes of stroke.We determined the rates and predictors of risk of stroke and its subtypes in the FIELD trial.

Methods

9795 patients aged 50–75 years with type 2 diabetes were followed up for a median of 5 years. Annual rates were derived by the Kaplan-Meier method and independent predictors of risk by Cox proportional-hazards regression analyses.

Results

The annual rate of stroke was 6.7 per 1000 person–years; 82% were ischaemic, and caused by small artery disease (36%), large artery disease (17%), and embolism from the heart (13%); 10% were haemorrhagic. Among the strongest baseline predictors of ischaemic or unknown stroke were age (60–65 years, hazard ratio (HR) 1.98; >65 years, HR 2.35) and a history of stroke or TIA (HR 2.06). Other independent baseline predictors were male sex, smoking, history of hypertension, ischaemic heart disease, nephropathy, systolic blood pressure, and blood LDL cholesterol, HbA_{1c}, and fibrinogen. A history of peripheral vascular disease, low HDL, age, and history of hypertension were associated with large artery ischaemic stroke. A history of diabetic retinopathy, LDL cholesterol, male sex, systolic blood pressure, smoking, diabetes

duration, and a history of stroke or TIA were associated with small artery ischaemic stroke.

Conclusions

Older people with a history of stroke were at highest risk of stroke, but the prognosis and prognostic factors of subtypes were heterogeneous. The results will help clinicians quantify the absolute risk of stroke and its subtypes for typical diabetes patients.

The major contributor to the burden and cost of diabetes is vascular disease of the brain, eye, heart, kidneys and peripheral nerves. The Emerging Risk Factors Collaboration's meta-analysis indicated that a history of diabetes increased the hazard for ischaemic stroke and haemorrhagic stroke.[1] The hazard ratios (HRs) for ischaemic stroke in people with diabetes, adjusted for baseline covariates, were higher in women, patients aged 40–59 years, and patients with above average body mass index (BMI); the HRs did not change significantly after additional adjustment for lipids, and fasting blood glucose concentration was not linearly related to the risk of ischaemic stroke.[1] The annual rate of stroke in a cohort of 41 799 people with diabetes in the UK was 11.9 per 1000 person–years, compared with 5.5 per 1000 person–years in 202 733 controls.[2]

The debate over which factors increase the risk of stroke in diabetic people is controversial. In the Diabetes and Informatics study of 14 432 people with type 2 diabetes, the rate of stroke was much higher among people with a history of cardiovascular disease than those with no history of cardiovascular disease.[3] The only other consistently significant and independent prognostic factor for stroke in people with diabetes is age, but some studies have shown that the risk of stroke decreases with age beyond 35–54 years[1, 2] and others that the risk increases with age.[3–6] Other adverse prognostic factors reported in some, but not all, studies include sex, smoking, obesity, atrial fibrillation, hypertension, systolic blood pressure, total-to-high-density-lipoprotein (HDL) cholesterol ratio, waist circumference, microvascular complications, duration of diabetes, and therapy with insulin plus oral agents.[2–6]

There also is uncertainty about the frequency with which the different aetiological subtypes of ischaemic stroke occur in diabetes patients. Ischaemic stroke caused by intracranial small-vessel disease (lacunar infarction) is reported to be more common in diabetic people than others, presumably because of their higher prevalence of microvascular disease.[7–9] However, the few population based studies of incident cases of stroke have shown no significant difference in the subtypes of stroke between diabetic and nondiabetic people.[10–14] Although the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study[15] was not a population based study, it provided an opportunity to determine the rate and predictors of risk of stroke in a large cohort of diabetes patients followed up over a long period, with outcome events systematically assessed by a panel of stroke experts. Our study design and data also allowed us to ascertain the risks of pathological and aetiological subtypes of stroke in this cohort.

Methods

The design and results of the FIELD study have been reported.[15,16] FIELD, a double blind, placebo controlled, randomised trial undertaken in 63 centres in Australia, New Zealand and Finland between 1998 and 2005, enrolled 9795 patients with type 2 diabetes mellitus. The study was designed to offer at least 80% power at 2*P*=0.05 to identify as significant a 22% reduction in coronary events among patients assigned fenofibrate. Participants were recruited from hospital clinics and community based sources. All patients gave written informed consent. The study protocol was approved by local and national ethics committees and was undertaken in accordance

with the Declaration of Helsinki and Good Clinical Practice guidelines. Results of this analysis are reported according to the STROBE guidelines (17).

Patients were aged 50–75 years and had an initial plasma total cholesterol concentration of 3.0–6.5 mmol/L, plus either a total-cholesterol-to-HDL-cholesterol ratio of at least 4.0 or a plasma triglyceride concentration of 1.0–5.0 mmol/L. The study had wide inclusion criteria in order to recruit patients across an extensive range of characteristics with regard to age, sex, location and clinical management. Exclusion criteria included renal impairment (plasma creatinine >130 μmol/L), known chronic liver disease or symptomatic gallbladder disease, and a cardiovascular event within 3 months before recruitment.

All patients were randomly allocated to once daily micronised fenofibrate 200 mg (n=4895) or matching placebo (n=4900) on a background of usual care. Planned follow-up was every 4–6 months over an average of 5 years. All the patients were treated according to the diabetic guidelines that were current at the time of the study. Decisions about changes in therapy for diabetes or comorbid conditions, including lipid lowering therapy, were at the discretion of the patient's primary care doctor or specialist physician.

Outcomes

The primary outcome event for this substudy was stroke and its pathological and aetiological subtypes. All primary outcome events (and major cardiovascular disease events) were adjudicated by an outcomes assessment committee, unaware of treatment allocation, using definitions specified before the study began. Each primary outcome event was adjudicated by two members of the outcomes assessment

committee. When there was disagreement, the event was adjudicated by the third member. If there was still disagreement after the third evaluation, the event was discussed at a meeting of the full committee. The diagnosis of stroke and its pathological and aetiological subtype required agreement by at least two of the outcomes assessment committee.

Stroke was defined as an acute new disturbance of focal neurological function resulting in death or lasting more than 24 hours and thought to be due to brain infarction or intracranial haemorrhage.[18] Ischaemic stroke was defined as a definite stroke[18] in which computed tomography (CT) scans or magnetic resonance imaging (MRI) within three weeks of symptom onset showed an infarct in the clinically relevant area of the brain, or if the imaging was normal or showed a clinically irrelevant abnormality, or autopsy showed evidence of relevant brain infarction.

Large artery ischaemic stroke was defined as a nonlacunar ischaemic stroke with clinical, duplex ultrasound, or angiography evidence of occlusive disease of the extracranial or intracranial large artery supplying the ischaemic brain, (including the aortic arch, common and internal carotid artery, main stem of the middle cerebral artery, vertebral artery, and basilar artery). In addition, there was no major cardioembolic source (see below), and the clinical opinion of the outcomes assessment committee was that the most likely cause of the brain infarct was large artery disease.

Small-artery ischaemic stroke was defined as ischaemic stroke with either one of the classical lacunar syndromes (pure motor hemiparesis, pure hemisensory loss, pure

hemisensorimotor loss, ataxic hemiparesis or basilar branch artery syndrome), together with a CT or MRI that was normal or showed a small (<1.5 cm) infarct in the basal ganglia, internal capsule, or brainstem.

Cardioembolic ischaemic stroke was defined as nonlacunar ischaemic stroke with a major cardioembolic source (for example, atrial fibrillation, myocardial infarction in the preceding 6 weeks, echocardiographic evidence of left ventricular thrombus, endocarditis, or a prosthetic heart valve), plus no definite evidence of large artery disease (see above), and clinical opinion that the most likely cause of the brain infarct was embolism from the heart.

Ischaemic stroke of unknown or uncertain cause was defined as a definite ischaemic stroke that did not meet the above criteria, or where there was more than one possible explanation (for example, in a patient with atrial fibrillation and carotid stenosis).

Haemorrhagic stroke was defined as an intracerebral or subarachnoid haemorrhage. Intracerebral haemorrhage was defined as a definite stroke [18] in which CT, MRI or autopsy showed haemorrhage into the clinically relevant area of the brain, excluding haemorrhagic transformation of infarction, haemorrhage into a tumour, and haemorrhage secondary to trauma. Subarachnoid haemorrhage was defined as a typical clinical syndrome of sudden onset of headache, with or without neck stiffness and focal neurological signs, and with CT, cerebrospinal fluid, or autopsy evidence of bleeding primarily in the subarachnoid space.

Stroke of unknown pathological type was a definite stroke [18] in which there was no documentation of the pathological type (infarction or haemorrhage) by CT, MRI, or autopsy. Transient ischaemic attack (TIA) of the brain or eye was defined as an acute

new disturbance of focal neurological or monocular function with symptoms lasting less than 24 hours and thought to be due to brain or ocular ischaemia.[19]

Cause specific mortality was classified into major categories of coronary, other vascular, cancer, and other noncardiovascular disease subtypes. Cardiovascular disease events comprised, as well as stroke, coronary heart disease death, cardiovascular disease death, nonfatal myocardial infarction, and coronary and carotid revascularisation. Major cardiovascular events were coronary death, cardiovascular death, and stroke.

Statistical analysis

Categorical baseline characteristics were analyzed with chi squared tests. For continuous variables, groups were compared with analysis of variance when data could be assumed to be normally distributed. Otherwise, the Kruskal–Wallis test was used. A small number of missing values at baseline were imputed. Missing values for homocysteine (273) were estimated on the basis of linear regression for values of all other baseline variables. For other variables, the median was imputed (urinary albumin (27), urinary creatinine (27), albuminuria (27), diabetes duration (17), BMI (7), waist–hip ratio (13), fibrinogen (1)). Sex specific medians were used for BMI and waist-hip ratio. Ethnicity was not considered in the analysis.

Cumulative risk curves derived by the Kaplan–Meier method were plotted. The average annual stroke rate was calculated according to the formula $1–((1–I_c)1/n)$, where I_c is the cumulative incidence rate at n years of follow-up. The 95% confidence interval for the average annual rate was obtained using the upper and lower 95% confidence limits of I_c instead of I_c in the above formula.[20]

Cox proportional hazards models were used to develop risk models for the most common pathological subtype of stroke (ischaemic or unknown pathological subtypes) and two of its aetiological subtypes (large artery and small artery disease), as well as for the less common pathological subtype—haemorrhagic stroke. The proportional hazards assumption was checked with the Harrell-Lee test.[21] All models were stratified on treatment allocation. All continuous variables were standardised by dividing them by their standard deviation. Selection of predictor variables used the backward elimination method. The same results were obtained with the exhaustive search method.[22] Discrimination was assessed with the *c* statistic, which shows the ability of the model to discriminate subjects with the outcome from those without the outcome. A risk of using the same data for the modelling process and model performance is to obtain an overoptimistic estimate of performance. Therefore, the optimism corrected *c* statistic, a nearly unbiased estimate of predictive accuracy, was calculated by using bootstrapping with 200 bootstrap samples.[23] Calibration of the risk model for total stroke was assessed by comparing observed and expected numbers of events in each decile of risk.[24]

P values less than 0.05 were considered statistically significant. All analyses were by intention to treat and used SAS (version 9.2) or ACCorD (Analysis of Censored and Correlated Data) (version 1.6.3).

Results

Baseline characteristics and progression of diabetes

All 9795 participants were included in the analysis (Figure 1, Table 1). Follow-up continued until the end of the trial at median 5.0 years (final visits from January to

May, 2005). Complete follow-up was achieved for 99.1% of participants; 65 were not evaluable for morbidity (including stroke) at study close. Over the course of the study, $HbA1_c$ levels remained stable from a median of 52 mmol/mol at baseline to 53 mmol/mol at 5 years.

Outcomes

A total of 333 patients experienced 366 strokes during follow-up; 303 had one stroke, 28 two, one three, and one four (Table 2). The first on-study stroke was ischaemic in 81.4% of patients (95% CI 76.9 to 85.2%), haemorrhagic in 9.9% (95% CI 7.1 to 13.6%), and unknown in 8.7% (95% CI 6.1 to 12.2%). The most common cause of ischaemic stroke was small artery disease (108 events in 101 patients, 36.1%; 95% CI, 30.9 to 41.7%), followed by large artery disease (52 events in 50 patients, 17.4%; 95% CI, 13.5 to 22.1%), and embolism from the heart (38 events in 36 patients, 12.7%; 95% CI, 9.4 to 17.0%). The other 101 events in 99 patients (33.8%; 95% CI, 28.7 to 39.3 %) were ischaemic strokes of unknown or uncertain cause.

The cumulative risks of first stroke, first ischaemic or unknown stroke, first small artery ischaemic stroke, first large artery ischaemic stroke, and first haemorrhagic stroke were linear over the 5 years of follow-up (Figure 2). The average annual rate of first stroke was 0.67% (95% CI, 0.60 to 0.75%).

Predictors of risk of pathological subtypes of stroke

The baseline prognostic variables that were significantly and independently associated with stroke of ischaemic or unknown pathological type were age, male sex, history of stroke or TIA, history of hypertension, history of ischaemic heart disease, history of nephropathy (or albumin-creatinine ratio), current smoking, higher

systolic blood pressure, higher LDL cholesterol, HbA_{1c}, and fibrinogen concentration (Table 3). The discriminatory ability and calibration of the model were satisfactory (optimism adjusted *c* statistic of 0.72 with no statistically significant differences between observed and expected event counts within deciles of predicted risk (all $P>0.10$)).

Figure 3 shows diagrammatically the effect of selected risk profiles on the predicted 5-year absolute risk of ischaemic or unknown stroke.

Variables independently associated with haemorrhagic stroke were age, systolic blood pressure, plasma total homocysteine, and history of stroke or TIA.

Predictors of risk of aetiological subtypes of ischaemic stroke

Variables associated with large artery ischaemic stroke were age, history of hypertension, history of peripheral vascular disease, and HDL concentration. Variables associated with small artery ischaemic stroke were male sex, systolic blood pressure, current smoking, history of stroke or TIA, history of diabetic retinopathy, LDL cholesterol concentration, and diabetes duration.

Discussion

The principal findings from this observational study of nearly 10 000 patients with diabetes enrolled in a randomised trial were, first, that stroke occurred at a reasonably constant rate of about 6.7 per 1000 person–years over five years of follow-up; second, most stroke events were ischaemic; and third, the cause of ischaemic strokes was most commonly small artery disease, followed by large-artery disease, and embolism from the heart. Independent significant baseline predictors of a stroke of ischaemic or unknown pathological type were male sex, age, history of hypertension,

ischaemic heart disease, stroke or TIA, nephropathy, current smoking, higher systolic blood pressure, and concentrations of LDL cholesterol, HbA_{1c} and fibrinogen. Besides age, systolic blood pressure, and a history of stroke and TIA, there were notable differences in the baseline predictors of the pathological and aetiological subtypes of stroke. Male sex, a history of hypertension, ischaemic heart disease, nephropathy, current smoking, and concentrations of LDL cholesterol, HbA_{1c}, and fibrinogen increased the hazard of ischaemic stroke, whereas plasma total homocysteine increased the hazard of haemorrhagic stroke. Among the subtypes of ischaemic stroke, a history of peripheral vascular disease and the inverse of HDL cholesterol concentration (as well as age and a history of hypertension) increased the hazard of a large artery ischaemic stroke, whereas a history of diabetic retinopathy and LDL cholesterol concentration (as well as male sex, higher systolic blood pressure, current smoking, diabetes duration and a history of stroke or TIA) increased the hazard of small artery ischaemic stroke.

The strengths of this study, supporting the validity of the results, are that many diabetes patients, diagnosed by standardised diagnostic criteria and meeting predefined inclusion criteria, were prospectively assessed at baseline for relevant demographic, clinical and comorbidity features and followed up prospectively, regularly, and almost completely, for the occurrence of stroke (17,19,20). At the same time, patients' diabetes was managed in the real world setting of usual clinical care. Stroke was diagnosed and adjudicated, blinded to treatment allocation, by a panel of stroke experts (GJH, NA, MR) according to standard diagnostic criteria.

The limitations of the study are that the patients were recruited at varying times in relation to onset of their disease, the diagnosis of the aetiological subtype of ischaemic stroke relied on clinical and imaging criteria that could not be fulfilled in all cases (e.g. not all participants with a stroke underwent an MRI brain scan) and are not always accurate, and that the results are not necessarily generalisable to diabetes patients younger than 50 or older than 75 years or with plasma total cholesterol concentrations outside the eligibility range of 3.0 to 6.5 mmol/L. Further, 22 (0.2%) were lost to follow-up and 65 were not evaluable for morbidity at study close.

Our results are generally consistent with those of other studies,[1–6] but there are differences. First, unlike population based studies,[10–14] in this study intracranial small vessel disease was the major cause of stroke, as has been reported in hospital based studies.[7–9] The intracranial small vessel disease may be caused, to some extent at least, by the diabetes but could also reflect the higher prevalence of hypertension, or other unmeasured risk factors, among the participants with stroke. Second, the average annual rate of stroke of about 6.7 per 1000 person–years was higher than that observed among individuals with childhood-onset Type 1 DM (about 3.0 per 1000 person-years over a mean follow-up of 15 years) [25] but lower than in other cohorts of individuals with type 2 diabetes[2,3]. The prevalence of concurrent cardiovascular disease was similar among our cohort and other cohorts of type 2 diabetics, but our lower stroke rate may be explained by more vigilant follow-up by specialist diabetes physicians inherent in a clinical trial, and the more widespread availability and use of evidence-based treatments to lower stroke risk, such as lowering blood pressure and lowering cholesterol. Third, we did not find that the risk

of stroke was lower beyond the age of 54 years, as suggested in some studies.[1,2] Rather, in accordance with other studies,[3–6] we found that increasing age was an independent and significant prognostic factor for each subtype of stroke, except for small artery ischaemic stroke. Fourth, atrial fibrillation, reported as prognostic in other studies[2,5] and which might be expected to be related to stroke, was significant in our univariable model but not in multivariable analysis, presumably because it was highly correlated with age, history of hypertension, prior myocardial ischaemia, nephropathy, HbA_{1c} and age. Another reason for the failure of atrial fibrillation to be a significant independent predictor may be that cardioembolic stroke (for which atrial fibrillation is a risk factor) accounted for only a minority of ischaemic strokes (38/299; 13%); that is, cardioembolic stroke may not be as common in diabetes patients as other patient populations. Diabetes duration was similarly correlated with other factors and predicted only small artery ischaemic strokes.

In the Emerging Risk Factors Collaboration study, the adjusted HRs for ischaemic stroke with diabetes were higher for women, whereas our adjusted HRs were higher for men.[1] Our finding may reflect the younger age of our cohort (50–75 years) and failure to include older diabetic patients, among whom women may be at higher risk. In the Emerging Risk Factors Collaboration study, these adjusted HRs did not change significantly after additional adjustment for lipids,[1] concurring with our results for all ischaemic stroke, but we found that the adjusted HRs for the aetiological subtypes of ischaemic stroke did change after additional adjustment for lipids; the HRs for large artery ischaemic stroke were significantly higher with lower HDL cholesterol

concentrations and the HRs for small artery ischaemic stroke were significantly higher with higher LDL cholesterol concentrations.

In conclusion, patients with diabetes in this large clinical trial cohort had a 0.7% annual risk of stroke. Those at highest risk of stroke were older and had a history of a previous stroke. Most strokes were ischaemic and most ischaemic strokes were due to small vessel disease. However, ischaemic large artery disease and embolism from the heart also accounted for a significant proportion of ischaemic strokes. This highlights the importance of individualised assessment and management of diabetics who experience a stroke. Our results will help clinicians quantify the absolute risk and independent significant predictors of stroke and its subtypes for typical patients with diabetes aged 50 to 75 years.

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Figure legends

Figure 1

Enrolment and progress of FIELD patients

CVD, cardiovascular disease, TIA, transient ischaemic attack.

Figure 2

Time to first stroke

Stroke of any type (black line), first ischaemic or unknown stroke (blue), first small-artery ischaemic stroke (red), first large-artery ischaemic stroke (yellow), and first haemorrhagic stroke (green). Average annual rates of stroke (%, 95% CI): any, 0.67 (0.60–0.75); ischaemic or unknown, 0.61 (0.55—0.69); small-artery ischaemic, 0.21 (0.17–0.25); large-artery ischaemic, 0.10 (0.08–0.13); haemorrhagic, 0.07 (0.05– 0.10).

Figure 3

Typical profiles of risk

Effect of selected risk profiles on the predicted 5-year absolute risk of ischaemic or unknown stroke (keeping constant: placebo, no history of hypertension; no prior angina or coronary artery procedure; no nephropathy; LDL cholesterol=3.0 mmol/L, fibrinogen=3.6 g/L).

Acknowledgments

Rhana Pike, from the NHMRC Clinical Trials Centre, undertook substantive and technical editing and coordinated manuscript development. We thank all the doctors, nurses and patients who participated in this trial.

Sources of funding

The FIELD trial was funded by a grant from Laboratoires Fournier SA, Dijon, France (now part of Abbott), and also supported by the National Health and Medical Research Council, Australia. This study had no specific funding.

Table 1: Baseline characteristics of patients in relation to on-study strokes over a median of 5 years of follow-up*†

	Stroke (*n*=333)	Other CVD event (*n*=962)	No CVD event (*n*=8500)
General characteristics			
Fenofibrate treatment group	158 (47.4%)	454 (47.2%)	4283 (50.4%)
Male sex	245 (73.6%)	735 (76.4%)	5158 (60.7%)
Age at visit 1 (years, mean(SD))	65.2 (6.2)	64.0 (6.7)	61.9 (6.9)
Diabetes duration (years, median(IQR))	7 (3–12)	7 (3–12)	5 (2–9)
Body-mass index (kg/m^2, median(IQR))	30.0 (27.2–33.5)	29.6 (26.8–33.0)	29.8 (26.8–33.6)
Waist-to-hip ratio (mean(SD))	0.95 (0.07)	0.95 (0.08)	0.93 (0.08)
Smoking			
Non smoker	115 (34.5%)	309 (32.1%)	3505 (41.2%)
Ex-smoker	180 (54.1%)	532 (55.3%)	4232 (49.8%)
Current smoker	38 (11.4%)	121 (12.6%)	763 (9.0%)
Systolic blood pressure (mmHg, mean(SD))	148.1 (16.3)	142.8 (15.4)	139.9 (15.2)
Diastolic blood pressure (mmHg, mean(SD))	84.2 (9.0)	82.0 (8.8)	81.9 (8.5)
Clinical history			
History of hypertension	246 (73.9%)	593 (61.6%)	4707 (55.4%)
Heart rate (bpm, mean(SD))	72.2 (9.7)	72.6 (9.6)	72.4 (8.8)
Atrial fibrillation	17 (5.1%)	37 (3.8%)	145 (1.7%)
Prior myocardial infarction	32 (9.6%)	146 (15.2%)	307 (3.6%)
Prior angina, PTCA or CABG	92 (27.6%)	270 (28.1%)	923 (10.9%)
Prior stroke	34 (10.2%)	49 (5.1%)	264 (3.1%)
Prior TIA	33 (9.9%)	44 (4.6%)	230 (2.7%)
History of diabetic retinopathy	50 (15.0%)	128 (13.3%)	636 (7.5%)

	Stroke (*n*=333)	Other CVD event (*n*=962)	No CVD event (*n*=8500)
Neuropathy (self-reported or monofilament test)	83 (24.9%)	254 (26.4%)	1354 (15.9%)
Nephropathy (self-reported or ACR measurement)	140 (42.0%)	363 (37.7%)	2095 (24.6%)
Amputation (microvascular)	1 (0.3%)	1 (0.1%)	16 (0.2%)
Peripheral vascular disease	44 (13.2%)	148 (15.4%)	573 (6.7%)
Metabolic syndrome	289 (86.8%)	826 (85.9%)	6986 (82.2%)
Laboratory data			
Urine albumin-creatinine ratio ‡			
Normal	197 (59.2%)	608 (63.2%)	6482 (76.3%)
Microalbuminuria	106 (31.8%)	276 (28.7%)	1722 (20.3%)
Macroalbuminuria	30 (9.0%)	78 (8.1%)	296 (3.5%)
Total cholesterol (mmol/L, mean (SD))	5.06 (0.71)	5.08 (0.68)	5.03 (0.71)
LDL cholesterol (mmol/L, mean (SD))	3.10 (0.64)	3.13 (0.63)	3.06 (0.65)
HDL cholesterol (mmol/L, mean (SD))	1.05 (0.23)	1.03 (0.24)	1.11 (0.26)
Fibrinogen (g/L, mean (SD))	3.72 (0.81)	3.64 (0.76)	3.58 (0.74)
Triglycerides (mmol/L, median (IQR))	1.84 (1.40–2.38)	1.81 (1.38–2.45)	1.72 (1.34–2.30)
HbA_{1c} (mmol/mol, median (IQR))	54.1 (46.4-65.0)	54.6 (46.4-65.0)	50.8 (42.6-61.2)
Plasma creatinine (umol/L, mean (SD))	83.6 (18.3)	82.8 (16.6)	76.7 (15.4)
Estimated GFR (mL/min per 1.73 m^2, median (IQR))	80.5 (70.4–95.0)	83.1 (72.2–94.4)	86.6 (75.9–99.4)
Homocysteine (umol/L, median (IQR))	10.6 (8.7–13.0)	10.0 (8.4–12.3)	9.5 (7.9–11.3)
Baseline medication			
Any antithrombotic/anticoagulant	161 (48.3%)	430 (44.7%)	2475 (29.1%)
Any warfarin	14 (4.2%)	43 (4.5%)	185 (2.2%)
Aspirin or other antithrombotic (no warfarin)	147 (44.1%)	387 (40.2%)	2290 (26.9%)
Statin	0 (0.0%)	1 (0.1%)	2 (0.0%)

	Stroke (*n*=333)	Other CVD event (*n*=962)	No CVD event (*n*=8500)
Anti-hypertensive	211 (77.9%)	538 (74.1%)	4095 (75.4%)

Data are number (%) unless otherwise indicated.

* *P*<0.001 between the 3 event groups for all characteristics except metabolic syndrome, LDL cholesterol (both *P*=0.002), treatment group, heart rate, BMI, amputation, total cholesterol, statin and anti-hypertensive (all *P*>0.05).

† Missing values at baseline were imputed for homocysteine (273), urinary albumin (27), diabetes duration (17), BMI (7), waist–hip ratio (13), fibrinogen (1), urinary creatinine (27), albuminurea (27)

‡ Normal ACR, <3.5 mg/mmol (men), <2.5 (women); microalbuminuria, 3.5 -35 (men), 2.5 -25 (women); macroalbuminuria, > 35 (men), > 25 (women)

CVD=cardiovascular disease. SD=standard deviation. PTCA=percutaneous transluminal coronary angioplasty. CABG=coronary artery bypass grafting. IQR=interquartile range. GFR=glomerular filtration rate.

Table 2: Number of strokes during follow-up

Type	First stroke events	Total stroke events	Number of patients*
Ischaemic stroke	271	299	276
Large-artery cerebral infarct	46	52	50
Small-artery cerebral infarct	96	108	101
Cardioembolic infarct	34	38	36
Other causes, or uncertain or unknown cause †	95	101	99
Haemorrhagic stroke	33	37	37
Intracerebral haemorrhage	26	29	29
Subarachnoid haemorrhage	7	8	8
Stroke of unknown pathological type	29	30	29
Ischaemic stroke or stroke of unknown pathological type	300	329	302
Any stroke	333	366	333

* Some patients had more than one stroke and more than one type of stroke.

† Included 1 retinal infarction.

Table 3: Results of multivariable analyses for stroke types*

	Ischaemic stroke or stroke of unknown pathological type (302 events)		Large-artery ischaemic stroke (50 events)		Small-artery ischaemic stroke (101 events)		Haemorrhagic stroke (37 events)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age								
<60	1		1				1	
60–65	1.98 (1.41–2.78)	<0.001	7.70 (2.26–26.28)	0.001			1.73 (0.56–5.34)	0.34
>65	2.35 (1.71–3.23)	<0.001	9.52 (2.89–31.31)	<0.001			3.33 (1.24–8.92)	0.02
Sex male	1.72 (1.33–2.24)	<0.001			1.64 (1.05–2.55)	0.03		
History of hypertension	1.60 (1.22–2.11)	<0.001	2.16 (1.13–4.15)	0.02				
Diabetes duration								
≤2					1			
2–10					1.52 (0.86–2.67)	0.15		
≥10					2.06 (1.15–3.71)	0.02		
Systolic blood pressure (per 15 mmHg)	1.34 (1.19–1.50)	<0.001			1.36 (1.13–1.63)	0.001	1.54 (1.15–2.07)	0.004
Current smoker	1.52 (1.07–2.18)	0.01			1.78 (1.01–3.14)	0.05		
Prior stroke or TIA	2.06 (1.51–2.80)	<0.001			2.51 (1.48–4.26)	<0.001	2.80 (1.27–6.20)	0.01
Prior peripheral vascular disease			2.77 (1.44–5.35)	0.002				
Prior angina, PTCA, or CABG	1.85 (1.43–2.41)	<0.001						
History of diabetic retinopathy					1.82 (1.08–3.07)	0.03		
Nephropathy (self-reported or ACR measurement)	1.33 (1.05–1.70)	0.02						

	Ischaemic stroke or stroke of unknown pathological type (302 events)		Large-artery ischaemic stroke (50 events)		Small-artery ischaemic stroke (101 events)		Haemorrhagic stroke (37 events)	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
HDL cholesterol (per 0.3 mmol/L)			0.64 (0.46–0.90)	0.01				
LDL cholesterol (per 0.7 mmol/L)	1.14 (1.02–1.27)	0.03			1.30 (1.06–1.58)	0.01		
HbA_{1c} (quartile) (mmol/mol)								
<43	1							
43–51	1.64 (1.14–2.36)	0.008						
>51–62	1.71 (1.18–2.47)	0.004						
>62	1.82 (1.26–2.63)	0.001						
Fibrinogen (per 0.74 g/L)	1.14 (1.02–1.27)	0.02						
Log homocysteine (per 0.3 (=1 SD on log scale)							1.44 (1.09–1.91)	0.01

* All models were stratified by treatment group.

HR=hazard ratio. TIA= transient ischaemic attack. PTCA=percutaneous transluminal coronary angioplasty. CABG=coronary artery bypass grafting. LDL=low-density lipoprotein. HDL=high-density lipoprotein. Hb=hemoglobin. ACR=albumin-creatinine ratio.

figure 1

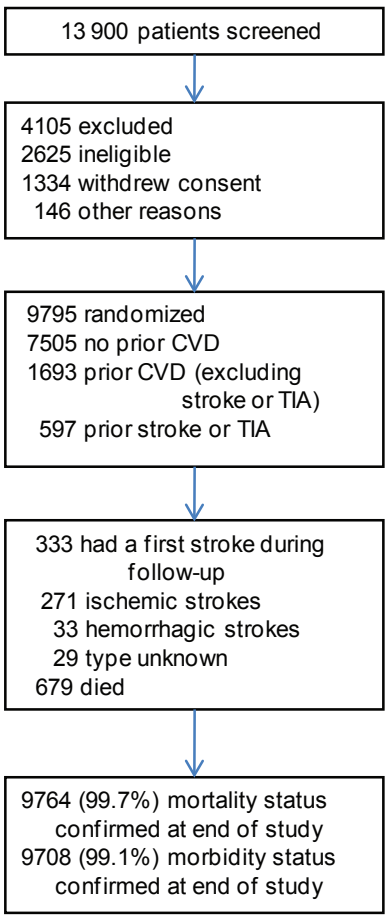

13 900 patients screened
4105 excluded
2625 ineligible
1334 withdrew consent
146 other reasons
9795 randomized
7505 no prior CVD
1693 prior CVD (excluding stroke or TIA)
597 prior stroke or TIA
333 had a first stroke during follow-up
271 ischemic strokes
33 hemorrhagic strokes
29 type unknown
679 died
9764 (99.7%) mortality status confirmed at end of study
9708 (99.1%) morbidity status confirmed at end of study

figure 2

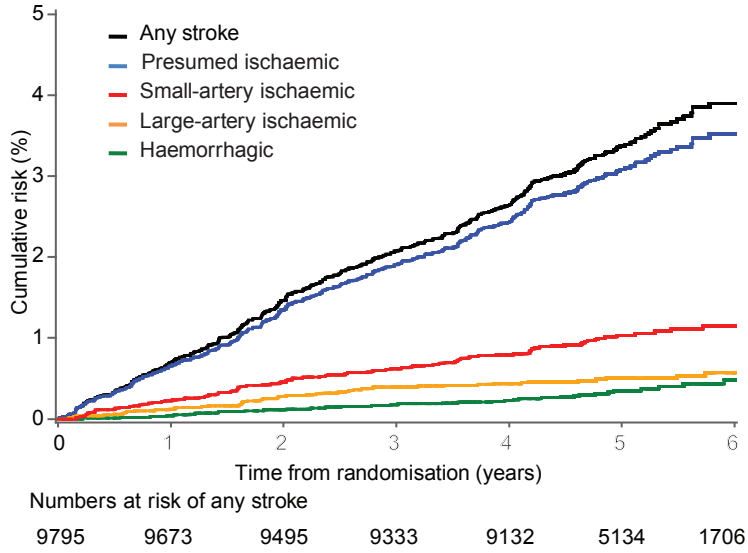
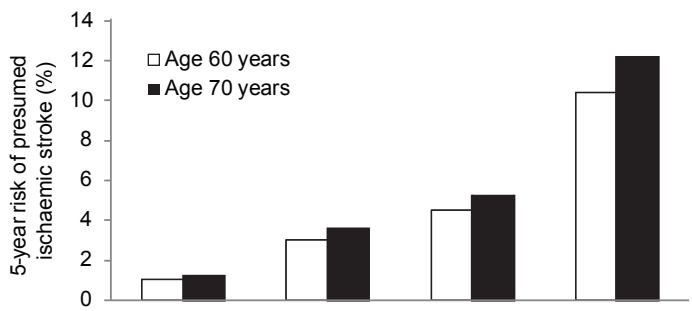

Any stroke
Presumed ischaemic
Small-artery ischaemic
Large-artery ischaemic
Haemorrhagic
Cumulative risk (%)
0
1
2
3
4
5
0
1
2
3
4
5
6
Time from randomisation (years)
Numbers at risk of any stroke
9795
9673
9495
9333
9132
5134
1706

figure 3



Risk factors				
Sex	F	F	M	M
Smoking	no	yes	no	yes
Systolic blood pressure (mmHg)	130	160	140	160
Prior stroke or TIA	no	no	yes	yes
HbA_{1c} (%)	6.5	8.5	7.5	8.5