Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial

David Preiss, Suzanne M Lloyd, Ian Ford, John J McMurray, Rury R Holman, Paul Welsh, Miles Fisher, Chris J Packard, Naveed Sattar

Lancet Diabetes Endocrinol 2014; 2: 116–24

Published Online November 7, 2013 http://dx.doi.org/10.1016/S2213-8587(13)70152-9

See Comment page 94

BHF Glasgow Cardiovascular Research Centre (D Preiss PhD, Prof J J McMurray MD, P Welsh PhD, Prof N Sattar PhD) **and Robertson Centre for Biostatistics** (S M Lloyd MSc, Prof I Ford PhD), **University of Glasgow, Glasgow, UK; Diabetes Trials Unit, University of Oxford, Oxford, UK** (Prof R R Holman FRCP); **Department of Diabetes, Glasgow Royal Infirmary, Glasgow, UK** (Prof M Fisher MD); **and Glasgow Clinical Research Facility, Tennent Building, Western Infirmary, Glasgow, UK** (Prof C J Packard DSc)

Correspondence to: Dr David Preiss, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, G12 8TA, UK **david.preiss@glasgow.ac.uk**

Summary

Background Metformin reduces cardiovascular risk in patients with type 2 diabetes seemingly independent of lowering blood glucose concentration. We assessed the cardiovascular effects of metformin in individuals without type 2 diabetes.

Methods We did a single-centre, double-blind, placebo-controlled trial at the Glasgow Clinical Research Facility (Glasgow, UK). We enrolled patients taking statins who did not have type 2 diabetes but who did have coronary heart disease and large waist circumferences. Participants were randomly assigned (1:1) by computer to either metformin (850 mg twice daily) or matching placebo in block sizes of four. Patients, investigators, trial staff, and statisticians were masked to treatment allocation. The primary endpoint was progression of mean distal carotid intima-media thickness (cIMT) over 18 months in the modified intention-to-treat population. Secondary endpoints were changes in carotid plaque score (in six regions), measures of glycaemia (HbA_{1c}, fasting glucose, and insulin concentrations, and Homeostasis Model Assessment of Insulin Resistance [HOMA-IR]), and concentrations of lipids, high sensitivity C-reactive protein, and tissue plasminogen activator. The trial was registered at ClinicalTrials.gov, number NCT00723307.

Findings We screened 356 patients, of whom we enrolled 173 (86 in the metformin group, 87 in the placebo group). Average age was 63 years. At baseline, mean cIMT was 0·717 mm (SD 0·129) and mean carotid plaque score was 2·43 (SD 1·55). cIMT progression did not differ significantly between groups (slope difference 0·007 mm per year, 95% CI –0·006 to 0·020; p=0·29). Change of carotid plaque score did not differ significantly between groups (0·01 per year, 95% CI –0·23 to 0·26; p=0·92). Patients taking metformin had lower HbA_{1c}, insulin, HOMA-IR, and tissue plasminogen activator compared with those taking placebo, but there were no significant differences for total cholesterol, HDL-cholesterol, non-HDL-cholesterol, triglycerides, high sensitivity C-reactive protein, or fasting glucose. 138 adverse events occurred in 64 patients in the metformin group versus 120 in 60 patients in the placebo group. Diarrhoea and nausea or vomiting were more common in the metformin group than in the placebo group (28 *vs* 5).

Interpretation Metformin had no effect on cIMT and little or no effect on several surrogate markers of cardiovascular disease in non-diabetic patients with high cardiovascular risk, taking statins. Further evidence is needed before metformin can be recommended for cardiovascular benefit in this population.

Funding Chief Scientist Office (Scotland).

Introduction

Cardiovascular disease is a leading cause of morbidity and mortality. Although type 2 diabetes increases cardiovascular risk, people with non-diabetic dysglycaemia also have increased risk[1] and some researchers regard insulin resistance as the most important cardiovascular risk factor.[2] The proatherogenic phenotype characterising dysglycaemia includes dyslipidaemia, vascular dysfunction, inflammation, and abnormal haemostasis, each of which are associated with cardiovascular events.[3,4]

Metformin—a safe and inexpensive glucose-lowering drug—is sometimes used to treat non-diabetic people with polycystic ovarian syndrome, for aiding weight loss, and for some people with impaired glucose tolerance, partly on the basis of its purported cardiovascular benefits.[5–7] Metformin improves dyslipidaemia and reduces concentrations of inflammatory and haemostatic biomarkers in non-diabetic individuals,[8,9] suggesting possible cardiovascular benefit. The effect of metformin on cardiovascular outcomes of patients with type 2 diabetes has been studied in two randomised controlled trials. In the UKPDS, overweight patients taking metformin had a 39% lower risk of myocardial infarction over 10 years than did patients on conventional dietary therapy, and post-trial observational data showed continuing benefit.[10,11] In the HOME trial,[12] which included 390 patients with type 2 diabetes on insulin, metformin reduced the composite cardiovascular endpoint by 40%. Metformin treatment also reduces the risk of developing type 2 diabetes.[13] However, its effects on cardiovascular endpoints in non-diabetic people remain unknown.

We designed the Carotid Atherosclerosis: MEtformin for insulin ResistAnce (CAMERA) study to assess the effect of metformin on progression of mean carotid intima-media thickness (cIMT) in non-diabetic individuals with coronary heart disease.

Methods

Study design and participants

CAMERA was a randomised, placebo-controlled, double-blind trial done at the Glasgow Clinical Research Centre (Glasgow, UK). Inclusion criteria were: age 35–75 years, proven coronary heart disease (previous acute coronary syndrome, coronary artery bypass surgery, or angiographically proven coronary heart disease), large waist circumference as per International Diabetes Foundation criteria (≥94 cm in men, ≥80 cm in women),[14] and prescribed a statin (dose and type were not adjusted[15]). Exclusion criteria were: pregnancy or lactation at screening; premenopausal woman not taking adequate contraception (daily oral hormonal contraception or regular injectable hormonal contraception); type 2 diabetes or people with either HbA_{1c} of 7·0% (53 mmol/mol) or more, or fasting plasma glucose of 7·0 mmol/L or more at screening; acute coronary syndrome within the previous 3 months; New York Heart Association functional class 3 or 4 heart failure; uncontrolled angina; hepatic impairment (based on assessment of available liver function tests and liver imaging by the study physician but not on biochemical thresholds); renal impairment (estimated glomerular filtration rate <45 mL/min per 1·73 m² at screening); hypersensitivity to metformin; acute illness (dehydration, severe infection, shock, acute cardiac failure); and suspected tissue hypoxia. People with HbA_{1c} 6·0–6·9% (42–52 mmol/mol) and fasting plasma glucose less than 7·0 mmol/L at screening had an oral glucose tolerance test; those with post-challenge glucose of 11·1 mmol/L or more were excluded. The trial was designed before the adoption of HbA_{1c} as a diagnostic test for type 2 diabetes.[16]

All participants provided written informed consent and were followed up for 18 months. This study was approved by the Medicines and Healthcare Products Regulatory Agency and West Glasgow Research Ethics Committee, and done in accordance with the principles of the Declaration of Helsinki and good clinical practice guidelines.

Randomisation and masking

Participants were randomly assigned to metformin or placebo (1:1) on the CAMERA website. The randomisation sequence was generated independently by computer (by the Robertson Centre for Biostatistics) with permuted blocks of four without stratification. Patients, investigators, trial staff, and statisticians were masked to treatment allocation.

Procedures

Participants were advised to take one study tablet (850 mg metformin or matching placebo) daily for 1 week before titrating up to 2 tablets daily (one with the morning meal, one with the evening meal). Participants unable or unwilling to take the medication twice daily could take one tablet daily from any point. Masked study medication was supplied in numbered bottles and compliance (defined as taking >80% of study medication during the trial) was assessed by tablet count. Study medication was reduced to one tablet daily if estimated glomerular filtration rate fell below 45 mL/min per 1·73 m², and stopped below 30 mL/min per 1·73 m².

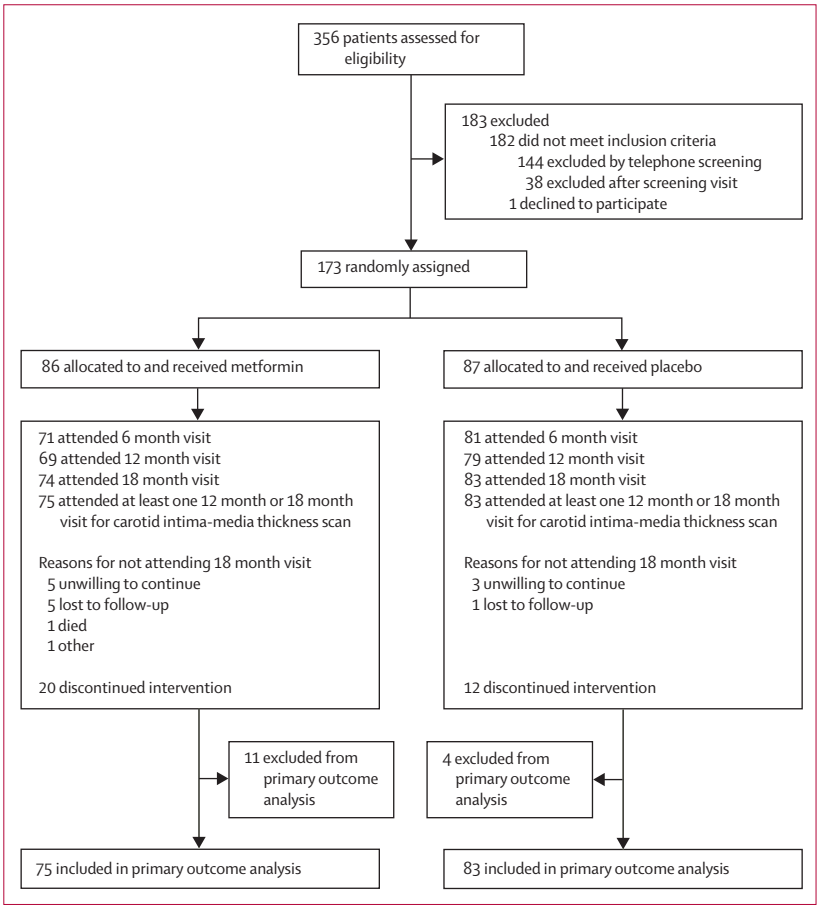

Figure 1: **Trial profile**

	Metformin group (n=86)	Placebo group (n=87)
Age (years)	63 (8)	64 (8)
Men	70 (81%)	63 (72%)
Smoking history		
Current	18 (21%)	17 (20%)
Former	42 (49%)	50 (57%)
Never	26 (30%)	20 (23%)
Blood pressure (mm Hg)	142/80 (21/11)	139/79 (21/12)
Heart rate (beats per min)	63 (11)	65 (10)
Bodyweight (kg)	87·8 (14·1)	86·8 (15·0)
Body-mass index (kg/m²)	30·2 (4·1)	30·5 (4·4)
Waist circumference (cm)	105 (10)	104 (10)
Hip circumference (cm)	108 (8)	108 (8)
Body fat (kg)	28·2 (7·5)	29·1 (7·5)

(Continues on next page)

	Metformin group (n=86)	Placebo group (n=87)
(Continued from previous page)		
Medical history		
Essential hypertension	35 (41%)	38 (44%)
Myocardial infarction	46 (53%)	38 (44%)
Coronary stent	29 (34%)	29 (33%)
Coronary artery bypass graft	23 (27%)	26 (30%)
Chronic heart failure (NYHA I or II)	9 (10%)	7 (8%)
Stroke	1 (1%)	3 (3%)
Biochemistry (fasting)		
Plasma glucose (mmol/L)	5·4 (0·6)	5·3 (0·5)
Insulin (pmol/L)*	60·6 (9·6)	62·4 (10·2)
HOMA-IR*	2·38 (1·67)	2·42 (1·73)
HbA_{1c} (%)	5·68 (0·32)	5·63 (0·31)
HbA_{1c} (mmol/mol)	38·7 (3·6)	38·2 (3·3)
High sensitivity C-reactive protein (mg/L)*	1·8 (2·9)	1·9 (3·1)
Total cholesterol (mmol/L)	4·2 (0·8)	4·3 (0·9)
HDL-cholesterol (mmol/L)	1·2 (0·3)	1·2 (0·3)
Non-HDL-cholesterol (mmol/L)	3·0 (0·8)	3·1 (0·9)
Triglycerides (mmol/L)*	1·5 (1·7)	1·5 (1·6)
Estimated glomerular filtration rate (mL/min per 1·73 m^2)	85 (16)	81 (17)
Alanine aminotransferase (U/L)	29·0 (17·5)	27·6 (12·4)
γ-glutamyltransferase (U/L)*	39·5 (2·0)	36·3 (2·1)
Vitamin B12 (pmol/L)	272 (115)	293 (132)
High sensitivity troponin T (pg/mL)	10·5 (4·6)	10·3 (5·7)
Tissue plasminogen activator (ng/mL)	9·4 (4·3)	9·6 (3·9)
Concomitant drugs		
Statin	86 (100%)	87 (100%)
Duration of statin treatment (years)	6·4 (3·7)	6·6 (4·2)
Duration of intensive statin treatment (years)†	4·4 (3·0)	4·5 (3·4)
Duration of moderate-dose statin treatment (years)‡	2·1 (3·8)	2·1 (3·7)
ACE inhibitor or angiotensin 2 receptor blocker	58 (67%)	45 (52%)
Calcium channel blockers	23 (27%)	26 (30%)
β blockers	56 (65%)	52 (60%)
Diuretics	13 (15%)	17 (20%)
Nitrates	50 (58%)	50 (57%)
Carotid measurements		
Carotid intima-media thickness (mm)	0·718 (0·128)	0·716 (0·131)
Carotid plaque score (out of six)§	2·38 (1·61)	2·47 (1·49)

Data are mean (SD) or n (%) unless stated otherwise. NYHA=New York Heart Association. HOMA-IR=homoeostatic model assessment insulin resistance. *Geometric mean (SD). †Lovastatin ≥80 mg, atorvastatin ≥20 mg, simvastatin ≥40 mg, or any dose of rosuvastatin daily. ‡All doses lower than intense doses of lovastatin, atorvastatin, simvastatin, or any dose of pravastatin or fluvastatin daily. §In the carotid bulb, distal 10 mm of the common carotid artery, and proximal 10 mm of the internal carotid artery.

Table 1: **Baseline characteristics**

For assessment of mean cIMT, carotid artery scans were done at baseline, 12 months, and 18 months. The imaging protocol consisted of B-mode ultrasound image acquisition of the right and left far walls of the distal 10 mm of the common carotid arteries, using an Acuson Sequoia C512 (Siemens Medical Solutions; Erlangen, Germany) with an L8 5–12 MHz linear array broadband transducer, and electrocardiogram gating.[17] All images were obtained from a single ultrasound machine by one doctor (DP). Participants were positioned recumbent with the head tilted 10° to the contralateral side. On each side of the neck, three digital clips were recorded from lateral, posterolateral, and anterolateral angles, each clip including roughly three QRS complexes. Depending on image quality, up to 18 cIMT images (in end-diastolic frame) were available from each visit for analysis of mean cIMT. Mean left-side and right-side cIMT were calculated separately and averaged to give the overall mean cIMT. Participants in whom only one side could be assessed at baseline had the same side analysed throughout. Images were analysed when all study visits had been completed by a single researcher using semiautomated artery measurement software[18] or a combination of semiautomated and manual approaches depending on image quality. Pretrial intra-individual cIMT reproducibility was 7%.

Carotid plaque score—a value of 0–6 depending on plaque presence in six regions—was assessed by transverse and longitudinal transducer positioning. Presence of plaque was assessed in three regions for both left and right carotid arteries (ie, six regions): distal 10 mm of the common carotid artery, carotid bulb (from the widening of the common carotid artery to the flow divider), and proximal 10 mm of the internal carotid artery (distal from the flow divider). Plaque was defined as cIMT of 1·5 mm or more, or 0·5 mm or more focal encroachment into the arterial lumen. Plaques in the entire common carotid artery and internal carotid artery were also recorded for a sensitivity analysis to avoid any effect of variations in the selection of the 10 mm boundaries. Other plaque surrogate markers (carotid plaque area and carotid plaque volume) have been proposed;[19] however, we did not use them because of concern about potential subjectivity of carotid plaque area and the requirement for experience in operating specialised equipment to assess carotid plaque volume.

Laboratory assessments measured at every visit included renal and liver function tests and—at every 6 month visit—fasting plasma glucose, HbA_{1c}, fasting lipid profile, high sensitivity C-reactive protein, fasting insulin, vitamin B12, tissue plasminogen activator, and high sensitivity troponin T. With the exception of insulin, vitamin B12, tissue plasminogen activator, and high sensitivity troponin T, all biochemical and haematology analyses were done at Gartnavel General Hospital, Glasgow, UK, with strict quality control procedures and where all assays (Abbott Diagnostics, North Chicago, IL) performed acceptably according to UK National External Quality Assessment Service, our external quality assurance scheme. Vitamin B12 and high sensitivity troponin T were analysed from stored plasma samples with an automated clinically validated analyser (Roche Diagnostics; Burgess Hill, UK) and manufacturer standards and quality control material; the low control coefficient of variation was 8·1% for vitamin B12 and

8·3% for high sensitivity troponin T and high control coefficient of variation was 10·4% for vitamin B12 and 5·7% for high sensitivity troponin T. Concentrations for insulin and tissue plasminogen activator were also measured from stored samples with commercial ELISAs (Mercodia, Diagenics Bletchley, UK; and Stago, Theale, UK). Intra-assay coefficient of variation was 5·5% for insulin and 8·4% for tissue plasminogen activator, and interassay coefficient of variation was 9·7% for insulin and 6·2% for tissue plasminogen activator. We calculated homoeostasis model assessment of insulin resistance (HOMA-IR; fasting plasma glucose [mmol/L]×fasting insulin [mU/L])/22·5) and estimated glomerular filtration rate (with abbreviated Modification of Diet in Renal Disease equation[20]).

Vital signs (blood pressure, pulse, bodyweight, body fat by bio-impedance with a Tanita BIA body fat analyser [Tanita Corporation, Tokyo, Japan]), waist circumference (measured midway between lowest rib and iliac crest), and hip circumference (measured around widest part of the buttocks) were measured at each visit. Participants were asked about adverse events and serious adverse events at each visit. Serious adverse events were recorded from paper and electronic hospital records but were not independently reviewed.

The primary endpoint was progression of mean distal common carotid artery cIMT at 18 months. Secondary endpoints were progression of carotid plaque score and change in HOMA-IR, HbA_{1C}, total cholesterol, HDL-cholesterol, non-HDL-cholesterol, triglycerides, tissue plasminogen activator, and high sensitivity C-reactive protein. Additional (not prespecified) endpoints were changes of adiposity (bodyweight, body fat, body-mass index (BMI), and waist circumference), vitamin B12 concentrations, high sensitivity troponin T concentrations, and surrogate markers of liver fat—ie, γ glutamyltransferase and alanine aminotransferase concentrations.

Statistical analysis

Metformin reduced cIMT by 0·032 mm at 12 months in a single-centre randomised trial of non-diabetic participants (n=60).[21] In the single-centre ARBITER trial (n=161),[22] cIMT decreased by 0·059 mm in 12 months in patients taking atorvastatin 80 mg compared with those taking pravastatin 40 mg. Our sample size calculations suggested that 180 participants completing the trial would be needed to detect a difference of 0·021 mm (SD 0·050 mm) between groups for cIMT progression with 80% power at 18 months. This estimate was based on two cIMT readings per participant whereas our study included three. We initially intended to follow up participants for 24 months but this was reduced to 18 months to enable completion within the time available. This change occurred in June 2010, when 115 participants had been randomly assigned to treatment but none had yet completed 18 months of follow-up.

Non-normally distributed variables were log-transformed with data presented as geometric means. We used repeated measures regression models to assess progression of mean cIMT and progression of carotid plaque score. These models allowed for participant-specific random intercepts and random slopes. We estimated the rate of change (slope) for each treatment group and the difference in these slopes. We also adjusted the models for pre-defined baseline cardiovascular risk factors (age, sex, smoking status, systolic blood pressure, diastolic blood pressure, HDL-cholesterol, LDL-cholesterol, and estimated glomerular filtration rate). We did sensitivity analyses for progression of mean cIMT for right and left cIMT separately; an analysis based on a minimum number of cIMT values per participant per visit (when a participant had 5–9 measurements per side and when average values could be calculated for both sides); an analysis of only those participants who completed the study, did not reduce the dose, and took more than 80% of study medication; and a carotid plaque score analysis of the carotid bulb and entire internal carotid artery and common carotid artery.

All analyses were done for the modified intention-to-treat population (had baseline and at least one later cIMT or plaque measurement) apart from a pre-planned per-protocol analysis, which was done for the primary outcome including only patients with no major or minor protocol deviations. Major protocol deviations included errors in the recording of informed consent, failure to comply with inclusion or exclusion criteria, and failure to amend study drug prescription based on biochemical data. Minor protocol deviations included compliance less than 50%, failure to attend all visits, failure to record study measurements, and stopping study drug before the end of the study. We did analyses for the primary outcome at 18 months comparing subgroups of tertiles for cIMT, fasting insulin, HbA_{1c}, BMI, and non-HDL-cholesterol at baseline plus sex.

	Metformin group	Placebo group
Baseline	0·712 (0·126)	0·715 (0·131)
12 months	0·725 (0·127)	0·734 (0·135)
18 months	0·747 (0·142)	0·739 (0·131)
Unadjusted analysis		
Slope (95% CI; mm per year)	0·023 (0·014 to 0·032)	0·016 (0·007 to 0·025)
Difference in slope (95% CI; mm per year)	0·007 (–0·006 to 0·020); p=0·29	..
Adjusted analysis*		
Slope (95% CI; mm per year)	0·024 (0·014 to 0·033)	0·017 (0·008 to 0·026)
Difference in slope (95% CI; mm per year)	0·007 (–0·006 to 0·020); p=0·29	..

Data are mean (SD) unless otherwise stated. Analyses are for modified intention-to-treat analyses of participants with at least one measurement after baseline. Figure 1 shows number of patients attending the relevant visits. *Adjusted for age, sex, smoking status, systolic and diastolic blood pressure, HDL-cholesterol, LDL-cholesterol, and estimated glomerular filtration rate.

Table 2: **Repeated measures analysis of mean carotid intima-media thickness**

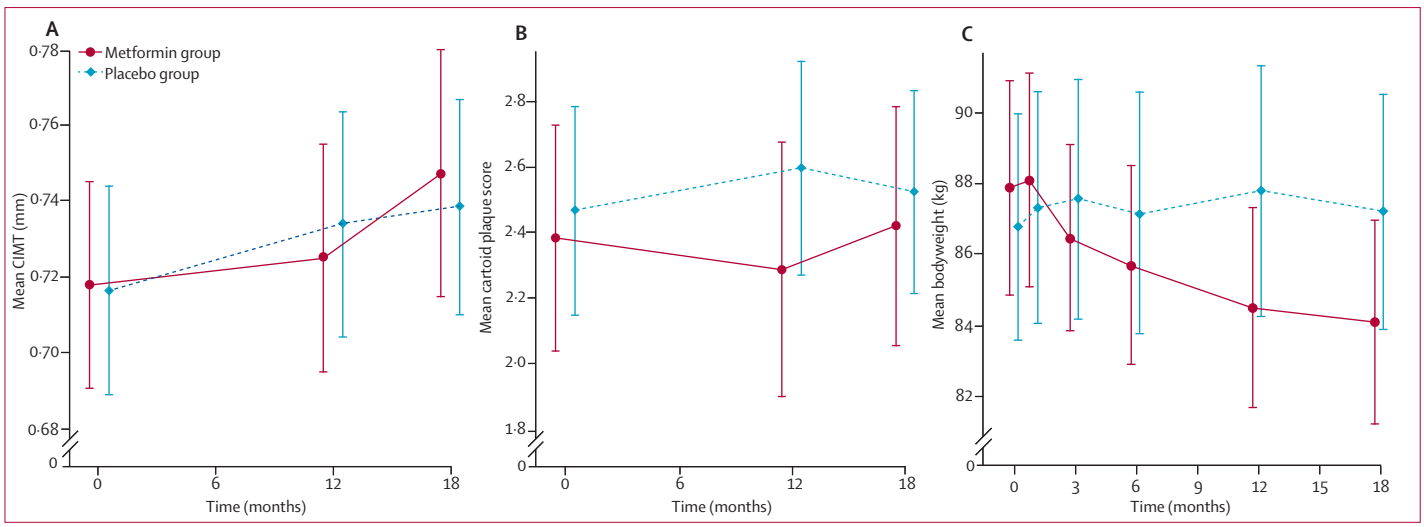

Figure 2: **Progression in mean cIMT (A), carotid plaque score (B), and bodyweight (C)**
Error bars are 95% CIs. cIMT=carotid intima-media thickness.

	Metformin group	Placebo group
Carotid bulb, distal 10 mm of common carotid artery, and proximal 10 mm of internal carotid artery		
Baseline	2·33 (1·60)	2·50 (1·52)
12 months	2·29 (1·61)	2·63 (1·44)
18 months	2·42 (1·57)	2·55 (1·41)
Unadjusted analysis		
Slope (95% CI; points per year)	0·05 (–0·12 to 0·23)	0·04 (–0·13 to 0·21)
Difference in slope (95% CI; points per year)	0·01 (–0·23 to 0·26); p=0·92	..
Adjusted analysis*		
Slope (95% CI; points per year)	0·03 (–0·14 to 0·21)	0·05 (–0·12 to 0·22)
Difference in slope (95% CI; points per year)	–0·02 (–0·26 to 0·23); p=0·89	
Carotid bulb, entire common carotid artery, and entire internal carotid artery†		
Baseline	2·51 (1·72)	2·61 (1·63)
12 months	2·49 (1·72)	2·79 (1·55)
18 months	2·66 (1·68)	2·82 (1·59)
Unadjusted analysis		
Slope (95% CI; points per year)	0·09 (–0·05 to 0·24)	0·14 (0·00 to 0·27)
Difference in slope (95% CI; points per year)	–0·04 (–0·24 to 0·16); p=0·68	..
Adjusted analysis*		
Slope (95% CI; points per year)	0·08 (–0·07 to 0·22)	0·15 (0·01 to 0·29)
Difference in slope (95% CI; points per year)	–0·07 (–0·28 to 0·13); p=0·48	..

Data are mean (SD) unless otherwise stated. Analyses are for modified intention-to-treat analyses of participants with at least one measurement after baseline; baseline data missing for one patient in placebo group, therefore not analysed. Figure 1 shows number of patients attending the relevant visits. *Adjusted for age, sex, smoking status, systolic and diastolic blood pressure, HDL-cholesterol, LDL-cholesterol, and estimated glomerular filtration rate. †Sensitivity analysis.

Table 3: **Repeated measures analysis of carotid plaque score**

Other secondary endpoints and additional endpoints were analysed with repeated measures models that allowed for random intercepts only and assumed a general covariance structure; the visit was fitted as a fixed categorical variable. Treatment-by-visit interactions were evaluated to assess whether overall treatment effects or treatment effect by visit were appropriate analyses. Analyses were done with SAS (version 9.3). p values were two-sided and 0·05 was the threshold for statistical significance.

This trial is registered with ClinicalTrials.gov, number NCT00723307.

Role of the funding source

The sponsors had no role in study design, data collection, analysis, or interpretation, or writing of the report. DP, SML, IF, and NS had access to the raw data. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Results

We identified roughly 3000 potential participants from electronic searches of Glasgow general practice databases, supplemented by patients from hospital cardiology clinics. Of those invited, 805 replied and 356 were screened. 173 were enrolled and randomly assigned (86 to metformin, 87 to placebo; figure 1). Trial visits were done between 2009 and 2012. Baseline characteristics did not differ substantially between treatment groups (table 1). Average age was 63 years, mean cIMT was 0·717mm (SD 0·129), and mean carotid plaque score was 2·43 (SD 1·55). Of the patients for whom complete data were available based on drug return, 64 of 82 (78%) assigned to metformin and 68 of 85 (80%) assigned to placebo were compliant. More participants taking metformin (n=19) than placebo (n=10) reduced to one tablet daily. 12 participants assigned to metformin and four assigned to placebo did not attend the final visit. Those participants lost to follow-up (n=6) could not be reached by post or telephone. However, according to electronic hospital records, none had a serious adverse event during follow-up. During follow-up, four participants stopped statin treatment

(three taking metformin, one taking placebo), while estimated glomerular filtration rate fell to 30–44 mL/min per 1·73m² in five participants (two taking metformin, three taking placebo) but did not fall lower than 30 mL/min/ per 1·73m² in any participants.

Over 18 months, mean cIMT increased significantly in both groups (0·024 mm per year [95% CI 0·014 to 0·033] for metformin, 0·017mm per year [95% CI 0·008 to 0·026] for placebo). Rates of cIMT progression in the metformin and placebo groups did not differ significantly (difference in slope 0·007 mm per year, 95% CI –0·006 to 0·020; p=0·29; table 2, figure 2A). This null cIMT finding was consistent in all sensitivity analyses (data not shown), in the per-protocol population (n=140; difference in slope 0·008 mm per year, 95% CI –0·005 to 0·022; p=0·23), and when restricted to participants five or more images analysed from each side (data not shown). For 101 participants who completed the trial without reducing dose and who were compliant with study drug (45 in the metformin group and 56 in the placebo group), results were also much the same (difference in slope 0·014 mm per year, 95% CI –0·003 to 0·031; p=0·11). Analyses using thirds of baseline cIMT and thirds of selected baseline variables did not identify benefit in any subgroups (appendix). Similarly, there was no difference according to sex. Scan reproducibility, assessed as SD for change in cIMT in the placebo group, was 0·046 mm at 12 months and 0·059 mm at 18 months.

Change in carotid plaque score in the carotid bulb, distal 10 mm of the common carotid artery, and proximal 10 mm of the internal carotid artery combined did not differ between groups (0·01 per year, 95% CI –0·23 to 0·26; p=0·92; table 3, figure 2B). In the sensitivity analysis of carotid plaque score in the carotid bulb, entire common carotid artery, and internal carotid artery, treatment groups did not differ significantly (table 3).

HbA_{1c}, log fasting insulin concentration, log HOMA-IR, and tissue plasminogen activator were reduced in the metformin group compared with placebo, whereas we detected no significant difference for total cholesterol, HDL-cholesterol, non-HDL-cholesterol, fasting plasma glucose, triglycerides, and high sensitivity C-reactive protein (table 4).

Metformin significantly reduced all measures of adiposity (bodyweight, body fat, BMI, waist circumference compared with placebo at 18 months (p<0·0001 for all). Mean weight loss in the metformin group was 3·2 kg (SD 4·2) versus 0·0 kg (SD 3·8) in the placebo group at 18 months (figure 2C, appendix). Metformin also led to a progressive fall of vitamin B12 concentration (–62 pmol/L, 95% CI –89 to –35; p<0·0001) by 18 months. γ glutamyltransferase concentration fell in patients taking metformin compared with those taking placebo (p=0·0002) but high sensitivity troponin T and alanine aminotransferase concentrations did not change significantly (appendix).

We recorded 258 adverse events: 138 in 64 participants assigned to metformin and 120 in 60 participants assigned to placebo (table 5, appendix). More patients

See Online for appendix

	Metformin group (mean change; SD)	Placebo group (mean change; SD)	Treatment effect (metformin–placebo)		$p_{interaction}$
			Effect (95% CI)*	p value	
HbA_{1c} (%)					
6 months	–0·12 (0·23)	0·04 (0·16)	–0·13 (–0·18 to –0·07)	<0·0001	0·45
12 months	–0·11 (0·19)	0·03 (0·17)	..		
18 months	–0·14 (0·25)	0·00 (0·26)	..		
HbA_{1c} (mmol/mol)					
6 months	–1·3 (2·6)	0·4 (1·8)	–1·4 (–2·0 to –0·8)	<0·0001	0·62
12 months	–1·2 (2·1)	0·3 (1·8)	..		
18 months	–1·3 (2·6)	0·1 (2·7)	..		
Insulin (log; pmol/L)					
6 months	–0·16 (0·37)	0·01 (0·51)	–0·19 (–0·33 to –0·06)	0·0047	0·89
12 months	–0·11 (0·48)	0·09 (0·52)	..		
18 months	–0·06 (0·59)	0·10 (0·55)	..		
HOMA-IR (log)					
6 months	–0·19 (0·42)	–0·01 (0·54)	–0·23 (–0·37 to –0·08)	0·0025	0·78
12 months	–0·15 (0·50)	0·10 (0·56)	..		
18 months	–0·08 (0·64)	0·12 (0·61)	..		
Glucose (mmol/L)					
6 months	–0·14 (0·60)	–0·01 (0·46)	–0·14 (–0·29 to 0·01)	0·064	0·11
12 months	–0·08 (0·52)	0·04 (0·52)	..		
18 months	–0·11 (0·66)	0·17 (0·74)	..		
Total cholesterol (mmol/L)					
6 months	–0·07 (0·81)	–0·01 (0·7)	–0·03 (–0·25 to 0·18)	0·78	0·81
12 months	–0·09 (0·80)	–0·08 (0·90)	..		
18 months	0·08 (0·85)	0·03 (0·92)	..		
HDL-cholesterol (mmol/L)					
6 months	0·04 (0·16)	0·02 (0·13)	0·04 (–0·01 to 0·08)	0·095	0·73
12 months	0·05 (0·19)	0·01 (0·13)	..		
18 months	0·06 (0·18)	0·02 (0·19)	..		
Non-HDL-cholesterol (mmol/L)					
6 months	–0·12 (0·76)	–0·03 (0·69)	–0·07 (–0·28 to 0·14)	0·53	0·86
12 months	–0·14 (0·76)	–0·08 (0·89)	..		
18 months	0·02 (0·81)	0·01 (0·93)	..		
Triglycerides (log; mmol/L)					
6 months	–0·10 (0·37)	0·00 (0·31)	–0·08 (–0·16 to 0·00)	0·054	0·68
12 months	–0·11 (0·40)	–0·02 (0·34)	..		
18 months	–0·07 (0·37)	–0·03 (0·40)	..		
High-sensitivity C-reactive protein (log; mg/L)					
6 months	–0·14 (1·00)	0·05 (0·79)	–0·19 (–0·39 to 0·00)	0·054	0·84
12 months	–0·20 (1·00)	–0·02 (0·81)	..		
18 months	–0·23 (0·73)	0·01 (0·97)	..		
Tissue plasminogen activator (ng/mL)					
6 months	–0·93 (2·91)	–0·38 (2·29)	–0·77 (–1·46 to –0·08)	0·029	0·21
12 months	–1·00 (2·92)	0·21 (2·72)	..		
18 months	–0·90 (3·60)	–0·57 (2·91)	..		

*Overall treatment effects given that treatment effect by time was not significant; modified intention-to-treat analysis for participants with at least one measurement after baseline. Figure 1 shows number of patients attending the relevant visits.

Table 4: **Effect of metformin treatment on secondary endpoints**

assigned to metformin developed diarrhoea and nausea or vomiting than those assigned to placebo (28 *vs* 5). 41 serious adverse events occurred, 14 in 11 participants assigned to metformin and 27 in 18 participants assigned to placebo. Few participants had cardiovascular events (n=10), were diagnosed with cancer (n=5), or developed type 2 diabetes (n=8). One participant had an out-of-hospital cardiac arrest and died from presumed cardiovascular causes in the first few months of follow-up and therefore no data were available for analyses of the primary and secondary endpoints.

	Metformin group (n=86)	Placebo group (n=87)
Diarrhoea	18 (21%)	4 (5%)
Nausea or vomiting	10 (12%)	1 (1%)
Newly diagnosed neoplasm	1 (1%)	4 (5%)
New-onset diabetes*	2 (2%)	6 (7%)
Non-fatal myocardial infarction	0 (0%)	4 (5%)
Unstable angina	0 (0%)	1 (1%)
Coronary stent	2 (2%)	5 (6%)
Non-fatal stroke	1 (1%)	0 (0%)
Cardiovascular death	1 (1%)	0 (0%)
Composite cardiovascular disease event†	4 (5%)	6 (7%)

Data are number of patients (%). The appendix shows a full list of adverse and serious adverse events. *HbA_{1c} ≥6·5% (≥48 mmol/mol) at any post-baseline visit or fasting plasma glucose ≥7·0 mmol/L from at least two post-baseline visits (three patients had baseline HbA_{1c} ≥6·5% and all subsequent values were <6·5% in these patients). †Non-fatal myocardial infarction, non-fatal stroke, coronary revascularisation, unstable angina, or cardiovascular death.

Table 5: **Important adverse and serious adverse events**

Panel: **Research in context**

Systematic review

Treatment with metformin was shown to reduce cardiovascular events in patients with type 2 diabetes by the initial 10 year follow-up of UKPDS,[10] with continued benefit shown in a subsequent analysis of long-term follow-up over 25 years.[11] Systematic reviews and meta-analyses of the cardiovascular effects of metformin have produced mixed results depending on the inclusion criteria used. For example, a systematic review[23] published in 2008 found that metformin treatment reduced cardiovascular mortality by 26% in an analysis of 11 385 patients with type 2 diabetes from six trials. By contrast, a meta-analysis[24] published in 2012 with 13 110 participants with type 2 diabetes from ten trials found no change in cardiovascular mortality. Given that a generic form of metformin is available and has also been shown to reduce the risk of developing type 2 diabetes,[13] there is interest in its cardiovascular effects for individuals at high cardiovascular risk but without type 2 diabetes.

Interpretation

In the placebo-controlled CAMERA study, we evaluated the effect of metformin treatment on the progression of carotid intima-media thickness, carotid plaque score, and other surrogate markers of cardiovascular disease and type 2 diabetes in 173 participants without diabetes but with established coronary heart disease already taking statins. Over 18 months, neither carotid intima-media thickness nor carotid plaque score improved for patients taking metformin. However, metformin did lead to a significant reduction of weight together with improvements in other risk factors for development of type 2 diabetes. Major cardiovascular outcome trials are needed to conclusively assess metformin's cardiovascular effects in people without type 2 diabetes—such trials are underway at present.

Discussion

Metformin—a drug already used for patients without type 2 diabetes—did not reduce progression of mean cIMT or carotid plaque score at 18 months in statin-treated non-diabetic participants with established coronary heart disease and large waist circumferences. Metformin generated expected reductions in markers of diabetes risk together with notable reductions in measures of adiposity. Gastrointestinal adverse events were common in patients taking metformin.

The results of twwo previous randomised trials—UKPDS[10] and HOME[12]—suggest that metformin reduces cardiovascular risk for patients with type 2 diabetes (panel). In UKPDS, the cardiovascular benefit was greater than expected for the differences in glycaemic control achieved, suggesting that metformin might reduce cardiovascular risk for non-diabetic individuals by mechanisms independent of glucose-lowering. However, less than 2% of participants in UKPDS and 32% in HOME were treated with statins. All participants in CAMERA were taking statins, which might have limited the ability of metformin to show a reduction in cIMT. Similarly, although small randomised trials of metformin have shown reductions of total cholesterol and LDL-cholesterol[8] in people who did not have diabetes, participants in CAMERA had no improvement for these predictors. A meta-analysis has also cast doubt on metformin's purported cardiovascular benefits.[24]

Metformin can modestly reduce weight.[13] In CAMERA, participants who were selected partly on the basis of large waist circumference had sustained and progressive reductions for all measures of adiposity, similar to that achieved by weight loss drugs,[25] even in this non-diabetic group. Metformin can also reduce hepatic steatosis and biochemical markers of liver fat;[26] we recorded a reduction in γ glutamultransferase but not alanine aminotranferase concentrations. As in previous studies,[27] a moderate fall in vitamin B12 concentrations occurred in the metformin group. Tissue plasminogen activator was also lower with metformin than with placebo, consistent with previous studies,[8] suggesting that its purported cardiovascular benefit could partially be a result of a reduction in prothrombotic potential. Unexpectedly, high sensitivity troponin T concentrations were higher in the metformin group than in the placebo group (though not significantly) in the absence of change of renal function. This finding should be studied further.

CAMERA had several strengths, including its randomised placebo-controlled double-blind design; inclusion of patients with high cardiovascular risk, all taking statins as per best practice; ultrasound scans were analysed with semiautomated software and yearly cIMT progression rates were entirely consistent with large pooled studies,[28] suggesting that our method was robust;

and we used metformin doses commonly used to treat type 2 diabetes, although some participants did reduce their dose. Potential weaknesses include use of cIMT—a surrogate marker albeit approved by the US Food and Drug Administration—as the primary endpoint; some drugs have reduced cIMT progression but not improved cardiovascular outcomes in large trials[29,30] whereas others have shown improvements,[31,32] and the relationship between cIMT progression and cardiovascular events in epidemiological studies has been questioned.[33] In addition, fewer participants than needed completed the trial (158 completed *vs* 180 needed according to our sample size calculation), although this calculation was based on two carotid ultrasound scans per participant, rather than three. Participants were followed up for 18 months rather than 24 months, although previous cIMT studies[22,34,35] have shown treatment effects over even shorter periods. Substantially larger multicentre multinational cIMT trials have been done[36] but CAMERA is similar in size to other single-centre cIMT trials[22] and benefited from a single sonographer and a single scan reader throughout. The number of participants who discontinued or reduced treatment, together with the use of several statistical tests, might have reduced our ability to detect meaningful effects.

GLINT (ISRCTN34875079), with a feasibility phase commencing in 2013, is a double-blind randomised trail planned to assign roughly 12 000 people with non-diabetic hyperglycaemia and increased cardiovascular risk to metformin or placebo for 5 years with a cardiovascular primary outcome. Metformin's effect on cardiovascular surrogate markers is also being tested in other trials such as REMOVAL (assessing change of cIMT over 3 years in patients with type 1 diabetes; NCT01483560) and GIPS-III (assessing change in left ventricular ejection fraction for 4 months after acute myocardial infarction in non-diabetic patients; NCT01217307).[37]

Further evidence is needed from large trials of cardiovascular outcomes before metformin can be recommended for cardiovascular benefit for non-diabetic patients with high cardiovascular risk who are being treated with statins.

Contributors

DP had the idea for and designed the study, collected, analysed, and interpreted data, wrote the first draft and revised later drafts of the article, and obtained funding for the study. SML collected, analysed, and interpreted data, did the statistical analysis, and revised the article. IF analysed and interpreted data, did the statistical analysis, revised the article, and obtained funding. JJM analysed and interpreted data, revised the article, obtained funding, and supervised the study. RRH, MF, and CJP analysed and interpreted data, revised the article, and obtained funding. PW analysed and interpreted data, revised the article, and provided administrative, technical, and material support. NS had the idea for and designed the study, analysed and interpreted data, revised the article, obtained funding, and supervised the study.

Conflicts of interest

DP has acted as conational coordinator for a clinical trial funded by Roche (now discontinued). IF has received honoraria for serving on data safety monitoring boards for Novo Nordisk and Medtronic device trials. RRH has received research support from Amylin, Bayer, Merck, and Novartis; participated in advisory boards for Amylin, Lilly, Merck, Novartis, and Novo Nordisk; and received compensation for lectures from Bayer, Lilly, Merck, and Merck Serono. MF has received direct payment for advisory work from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Janssen, Merck Sharp & Dohme, Novartis, Novo Nordisk, Roche, Sanofi, and Takeda. NS has consulted for Eli Lilly, Bristol-Myers Squibb, Merck Sharp & Dohme, AstraZeneca, Sanofi, and Boehringer Ingelheim; and received research support from Merck. SML, JJM, PW, and CJP declare that they have no conflicts of interest.

Acknowledgments

CAMERA was funded by a project grant from the Chief Scientist Office, Scotland (CZB/4/613), which had no influence over the trial's conduct. Trial medication and matching placebo were provided for free by Merck Serono, who had no influence over the conduct of the trial or analysis of results. We thank all participants, all NHS Greater Glasgow and Clyde General Practice surgeries that assisted with recruitment and also key trial staff (Victoria Paterson, Lorraine McGregor, Anne Benson, Muire O'Connell, Jill Griffiths, Colin Rodden). Sharon Kean and colleagues at the Robertson Centre for Biostatistics generated the CAMERA website. Elaine Butler and Lynne Cherry did biochemistry analyses at the BHF Glasgow Cardiovascular Research Centre. We acknowledge the financial support of NHS Research Scotland—through the Scottish Primary Care Research Network—for assisting DP with recruitment. Thomas Gustavsson (University of Gothenberg, Sweden), provided AMS software for carotid scan analysis. Frank Dunn (Department of Cardiology, Stobhill Hospital, Glasgow, UK), helped to obtain funding for CAMERA. RRH is a National Institute for Health Research Senior Investigator.

References

1 The Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375:** 2215–22.

2 Eddy D, Schlessinger L, Kahn R, Peskin B, Schiebinger R. Relationship of insulin resistance and related metabolic variables to coronary artery disease: a mathematical analysis. *Diabetes Care* 2009; **32:** 361–66.

3 Despres JP, Lamarche B, Mauriege P, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *N Engl J Med* 1996; **334:** 952–57.

4 Grundy SM. Obesity, metabolic syndrome, and cardiovascular disease. *J Clin Endocrinol Metab* 2004; **89:** 2595–600.

5 Bird ST, Hartzema AG, Etminan M, Brophy JM, Delaney JA. Polycystic ovary syndrome and combined oral contraceptive use: a comparison of clinical practice in the United States to treatment guidelines. *Gynecol Endocrinol* 2013; **29:** 365–69.

6 Seifarth C, Schehler B, Schneider HJ. Effectiveness of metformin on weight loss in non-diabetic individuals with obesity. *Exp Clin Endocrinol Diabetes* 2013; **121:** 27–31.

7 Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 2007; **30:** 753–59.

8 Fontbonne A, Charles MA, Juhan-Vague I, et al. The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution. BIGPRO Study Group. *Diabetes Care* 1996; **19:** 920–26.

9 Charles MA, Morange P, Eschwege E, Andre P, Vague P, Juhan-Vague I. Effect of weight change and metformin on fibrinolysis and the von Willebrand factor in obese nondiabetic subjects: the BIGPRO1 Study. Biguanides and the Prevention of the Risk of Obesity. *Diabetes Care* 1998; **21:** 1967–72.

10 UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998; **352:** 854–65.

11 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359:** 1577–89.

12 Kooy A, de Jager J, Lehert P, et al. Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch Intern Med* 2009; **169:** 616–25.

13 Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; **346:** 393–403.

14 Alberti KG, Zimmet P, Shaw J. Metabolic syndrome—a new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet Med* 2006; **23:** 469–80.

15 Vergeer M, Zhou R, Bots ML, et al. Carotid atherosclerosis progression in familial hypercholesterolemia patients: a pooled analysis of the ASAP, ENHANCE, RADIANCE 1, and CAPTIVATE studies. *Circ Cardiovasc Imaging* 2010; **3:** 398–404.

16 American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care* 2010; **33** (suppl 1)**:** S11–61.

17 Touboul PJ, Hennerici MG, Meairs S, et al. Mannheim intima-media thickness consensus. *Cerebrovasc Dis* 2004; **18:** 346–49.

18 Liang Q, Wendelhag I, Wikstrand J, Gustavsson T. A multiscale dynamic programming procedure for boundary detection in ultrasonic artery images. *IEEE Trans Med Imaging* 2000; **19:** 127–42.

19 Spence JD. Measurement of intima-media thickness vs. carotid plaque: uses in patient care, genetic research and evaluation of new therapies. *Int J Stroke* 2006; **1:** 216–21.

20 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999; **130:** 461–70.

21 Meaney E, Vela A, Samaniego V, et al. Metformin, arterial function, intima-media thickness and nitroxidation in metabolic syndrome: the mefisto study. *Clin Exp Pharmacol Physiol* 2008; **35:** 895–903.

22 Taylor AJ, Kent SM, Flaherty PJ, Coyle LC, Markwood TT, Vernalis MN. ARBITER: Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol: a randomized trial comparing the effects of atorvastatin and pravastatin on carotid intima medial thickness. *Circulation* 2002; **106:** 2055–60.

23 Selvin E, Bolen S, Yeh HC, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. *Arch Intern Med* 2008; **168:** 2070–80.

24 Boussageon R, Supper I, Bejan-Angoulvant T, et al. Reappraisal of metformin efficacy in the treatment of type 2 diabetes: a meta-analysis of randomised controlled trials. *PLoS Med* 2012; **9:** e1001204.

25 Sjöström L, Rissanen A, Andersen T, et al, for the European Multicentre Orlistat Study Group. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. *Lancet* 1998; **352:** 167–72.

26 Shyangdan D, Clar C, Ghouri N, et al. Insulin sensitisers in the treatment of non-alcoholic fatty liver disease: a systematic review. *Health Technol Assess* 2011; **15:** 1–110.

27 de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. *BMJ* 2010; **340:** c2181.

28 Bots ML, Evans GW, Riley WA, Grobbee DE. Carotid intima-media thickness measurements in intervention studies: design options, progression rates, and sample size considerations: a point of view. *Stroke* 2003; **34:** 2985–94.

29 Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 2009; **361:** 2113–22.

30 Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med* 2011; **365:** 2255–67.

31 Huang Y, Li W, Dong L, Li R, Wu Y. Effect of statin therapy on the progression of common carotid artery intima-media thickness: an updated systematic review and meta-analysis of randomized controlled trials. *J Atheroscler Thromb* 2013; **20:** 108–21.

32 Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet* 2010; **376:** 1670–81.

33 Lorenz MW, Polak JF, Kavousi M, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): a meta-analysis of individual participant data. *Lancet* 2012; **379:** 2053–62.

34 Mazzone T, Meyer PM, Feinstein SB, et al. Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in type 2 diabetes: a randomized trial. *JAMA* 2006; **296:** 2572–81.

35 Taylor AJ, Villines TC, Stanek EJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 2009; **361:** 2113–22.

36 Lonn EM, Bosch J, Diaz R, et al; GRACE and ORIGIN Investigators. Effect of insulin glargine and n-3FA on carotid intima-media thickness in people with dysglycemia at high risk for cardiovascular events: the glucose reduction and atherosclerosis continuing evaluation study (ORIGIN-GRACE). *Diabetes Care* 2013; **36:** 2466–74.

37 Lexis CP, van der Horst IC, Lipsic E, et al. Metformin in non-diabetic patients presenting with ST elevation myocardial infarction: rationale and design of the glycometabolic intervention as adjunct to primary percutaneous intervention in ST elevation myocardial infarction (GIPS)-III trial. *Cardiovasc Drugs Ther* 2012; **26:** 417–26.