Metformin in non-diabetic hyperglycaemia: the GLINT feasibility RCT

Simon J Griffin,[1,2]* M Angelyn Bethel,[3] Rury R Holman,[3] Kamlesh Khunti,[4] Nicholas Wareham,[1] Gwen Brierley,[1] Melanie Davies,[4] Andrew Dymond,[1] Rose Eichenberger,[1] Philip Evans,[5] Alastair Gray,[6] Colin Greaves,[5] Kyla Harrington,[4] Graham Hitman,[7] Greg Irving,[2] Sarah Lessels,[3] Ann Millward,[5] John R Petrie,[8] Martin Rutter,[9] Mike Sampson,[10,11] Naveed Sattar[8] and Stephen Sharp[1]

[1]Medical Research Council Epidemiology Unit, University of Cambridge, Cambridge, UK
[2]Institute of Public Health, University of Cambridge, Cambridge, UK
[3]Diabetes Trials Unit, University of Oxford, Oxford, UK
[4]Diabetes Research Centre, University of Leicester, Leicester, UK
[5]University of Exeter Medical School, Exeter, UK
[6]Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford, UK
[7]Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, London, UK
[8]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK
[9]Faculty of Medical and Human Sciences, University of Manchester, Manchester, UK
[10]Norwich Medical School, University of East Anglia, Norwich, UK
[11]Department of Diabetes, Endocrinology and General Medicine, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, UK

*Corresponding author ProfGP@medschl.cam.ac.uk

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Scientific summary

The GLINT feasibility RCT

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Scientific summary

Background

Cardiovascular disease (CVD) is a growing major public health problem in the UK. Elevated glucose levels are considered a risk factor for CVD, even when they are below the threshold for type 2 diabetes (T2D). Metformin treatment reduces the risk of CVD and premature death among people with T2D and may even reduce the risk of cancer. However, the effects of glucose-lowering treatment, such as metformin, on the risk of CVD in people with non-diabetic hyperglycaemia (NDH) are unknown. This study aimed to explore the feasibility of carrying out the Glucose Lowering In Non-diabetic hyperglycaemia Trial (GLINT).

Glucose Lowering In Non-diabetic hyperglycaemia Trial is a multicentre, individually randomised, double-blind, parallel-group, pragmatic, primary prevention trial to examine the impact of prolonged-release metformin (Glucophage® SR, Merck KGaA, Bedfont Cross, Middlesex, UK) compared with placebo on a composite CVD outcome of non-fatal myocardial infarction, non-fatal stroke and CVD death.

Objectives

The overall objective of the study was to assess the feasibility of the study design and to estimate key parameters to inform the design of the full trial. These parameters include the recruitment strategy, randomisation, electronic data capture, drug distribution by post, adherence to study medication, questionnaire return and remote collection of outcomes and safety information. A full list of the study objectives is provided below.

- Assess the feasibility of the recruitment of general practices and practice consortia to GLINT during a period of reorganisation of health services and during the establishment of a vascular risk assessment programme (the NHS Health Check programme).
- Assess the feasibility of the recruitment of participants, including those from multiethnic populations, to GLINT at a time when uncertainties about the optimal mode of assessing diabetes risk and glycaemia within the NHS Health Check programme are being resolved.
- Examine the feasibility and relative efficiency of three proposed recruitment strategies:
    - recruitment via the NHS Health Check programme
    - recruitment directly from participating general practices
    - recruitment from existing research registers of people with NDH.
- Assess the efficiency of different search strategies, and the availability and accessibility of information, in computerised medical records concerning inclusion and exclusion criteria, such as records of NDH [glycated haemoglobin (HbA_{1c})] and estimates of modelled 10-year CVD risk.
- Assess if recorded estimates of modelled CVD risk and its constituent variables are accurate compared with those estimated based on data collected at the baseline visit in the feasibility study and hence whether or not CVD risk estimates in medical records could be utilised in recruitment in the main trial.
- Examine the feasibility and acceptability of the randomisation procedure to patients and practitioners.
- Describe the characteristics of recruited participants, including ethnic diversity, and estimate modelled 10-year CVD risk as an input to the revised sample size calculations for the main trial.
- Examine the feasibility of the delivery mechanism of the investigational medicinal product (IMP).
- Examine the acceptability of the IMP to patients and practitioners.
- Estimate adherence to the IMP in both randomised groups.
- Consider strategies to optimise adherence.

- Assess change in predefined safety parameters, including renal function and plasma vitamin B_{12} levels, to inform decisions about the level of safety monitoring required in the full trial.
- Examine the feasibility of the system of adverse event (AE) reporting.
- Assess the acceptability and feasibility of collecting end-point data from participants, their general practitioners (GPs) and routine data sources [Office for National Statistics Health and Social Care Information Centre (now NHS Digital), cancer registries and Hospital Episode Statistics].
- Examine patient experiences of taking part in the trial via a questionnaire and/or interview.
- Establish systems for collecting resource use and quality of life data for future cost-effectiveness analyses.
- Finalise the costing for the full trial and negotiate with other funders.

Design

The study recruited from three UK regions: Cambridgeshire, Norfolk and Leicestershire. Participants were identified through three pathways: (1) referral following a NHS Health Check, (2) searches of existing research registries held by GLINT investigators, and (3) searches of general practice electronic records using the key eligibility criteria and diabetes risk scores.

We invited potentially eligible individuals to attend a screening visit at one of the local practices or research sites. Informed consent and baseline measures were collected by the National Institute for Health Research (NIHR) Comprehensive Local Research Network nurses at primary care sites and by local research staff at specialised clinical research facilities.

Randomisation took place after informed consent was obtained and eligibility was confirmed, and it was carried out by an independent statistician within the Oxford Diabetes Trials Unit. Participants were individually randomised on a 1 : 1 basis, blocked within each site.

Participants

Males and females aged $\geq$ 40 years with NDH who had a high risk of CVD and met the eligibility criteria were invited to participate in the study.

The main inclusion criteria were:

- age $\geq$ 40 years
- HbA_{1c} level of $\geq$ 36.6 mmol/mol but $<$ 47.5 mmol/mol
- estimated 10-year CVD risk of $\geq$ 20% (Framingham Risk Score or QRISK2 score).

The main exclusion criteria were:

- unable to provide written consent
- prior history of physician-diagnosed T2D
- prior history of CVD
- planned or anticipated coronary revascularisation procedure
- history of cirrhosis of the liver or other significant hepatic impairment
- end-stage renal disease [chronic kidney disease stage 3b or worse and estimated glomerular filtration rate (eGFR) of $<$ 45 ml/minute/1.73 m^2].

Interventions

We allocated participants to up to three tablets per day of 500 mg of prolonged-release metformin (Glucophage SR) or the matched placebo, administered orally. Study medication was added to the participants' usual care. We standardised one aspect of usual care by providing all participants with a theory-based brochure containing advice about reducing the risk of heart attacks and diabetes. The study drug was distributed by post in 16-weekly batches. Participants were followed up for a minimum of 6 months.

This was a double-blind trial, with participants, their GPs and researchers unaware of which participants were on active treatment. The IMP had the same visual appearance as the placebo.

Main outcome measures

Participant follow-up was carried out using questionnaires posted to participants and their GPs at 4 months, 1 year (when applicable) and the end of the study. Questionnaires assessed medication adherence, treatment satisfaction, quality of life and health-service use and collected information about safety and outcome events. The completed questionnaires were returned by Freepost. Non-serious AEs were reported only if they were assessed by a clinician to be possibly or probably related to the study drug and if they led to cessation of the study drug. Participants also attended clinic visits at 3 and 6 months, during which blood samples were collected to assess biochemical outcomes (e.g. HbA_{1c} and cholesterol levels) and safety parameters (eGFR, vitamin B_{12} and alanine aminotransferase levels).

We assessed the feasibility and efficiency of recruitment. This included assessment of the number of general practices that were recruited, the proportions of participants who were identified using the three recruitment strategies, whether or not historical laboratory values were available in medical records and were suitable for assessment of eligibility and the proportion of consenting participants who were randomised. We also assessed the reliability and acceptability of the delivery of the IMP to participants' homes, the proportions of GP and participant questionnaires that were returned, the proportion of study participants who were taking the IMP during the follow-up phase and the feasibility of the remote collection of study data and safety information using questionnaires.

Results

Ten general practices and 21 participant identification centres (PICs) recruited participants. This recruitment strategy was the main source of potentially eligible people, followed by searches of existing research databases, identifying 4129 and 1122 people, respectively.

We sent a total of 5251 invitations and 511 people consented to take part in the study (9.7% of those invited). Following screening during a face-to-face visit, 262 people (51.3%) were found to be ineligible; 215 of these people (82.1%) had an ineligible modelled CVD risk and 86 (32.8%) had an ineligible HbA_{1c} level, with 46 (17.6%) ineligible on both criteria. Seven people (2.7%) were ineligible for other reasons.

In total, 249 people (219 men and 30 women) were randomised (124 to the placebo group and 125 to the metformin group), 4.8% of all those invited. Participants were generally elderly {mean age 70 years [standard deviation (SD) 6.7 years]} and overweight [mean body mass index 30.1 kg/m^2 (SD 4.5 kg/m^2)], 98% were white, 14.5% were current smokers and the mean modelled 10-year CVD risk was 28.8% (SD 8.5%). Over half of participants were prescribed statins. The participants had normal liver and renal function tests at baseline. The mean HbA_{1c} level was 41 mmol/mol (5.9%).

Recruitment was successful, primarily achieved through general practice electronic records searches, but resource intensive. The efficiency of this strategy was improved following adjustments to the search strategy to optimise the CVD risk profiles of those invited to participate. Historical laboratory results to assess eligibility were available for fewer than half of the participants, but when available they were similar to the results of the baseline tests undertaken for the study.

The level of support that was required to recruit and manage the participating practices is not sustainable on a larger scale. Personal visits from the principal investigators to recruit practices and technical support from the study team to assist with searching of electronic medical records and sending out invitations to potential participants are not feasible for a UK-wide endeavour.

Randomisation and remote follow-up by questionnaire were efficient, successful and acceptable to participants. Questionnaire return rates from both GPs and participants remained reasonably high throughout the study (≈88% at 4 months and ≈84% at 1 year), demonstrating that this was an effective method of follow-up and event ascertainment. Only one participant withdrew permission for follow-up for the primary outcome using register data.

Delivery of the study drug by post was feasible and efficient, with < 2% of all drug packs requiring replacement. Adherence to the study treatment was lower than expected, with ≈30% of participants having stopped taking the study drug by 6 months, but there was no difference between treatment groups. However, among those reporting adherence data, 81.5% of the placebo group and 75.6% of the metformin group reported taking the maximum dose of three tablets per day. The mean duration of exposure to the study drug was 0.92 years (SD 0.46 years) and 0.90 years (SD 0.46 years) in the placebo and metformin groups, respectively. At 4 months, side effects associated with the study medication were reported by similar proportions of participants in the placebo and metformin groups (23.8% and 24.0%, respectively).

The biochemistry results showed no detrimental effects of the study interventions on participants. There were small declines in renal function over 6 months, as one might expect in this study population with a mean age of 70 years, with no significant difference between groups. Compared with placebo, metformin was associated with small improvements in HbA_{1c} level [–0.82 mmol/mol, 95% confidence interval (CI) –1.39 to –0.24 mmol/mol], eGFR (2.31 ml/minute/1.73 m^2, 95% CI –0.2 to 4.81 ml/minute/1.73 m^2) and low-density lipoprotein cholesterol level (–0.11 mmol/l, 95% CI –0.25 to 0.02 mmol/l) and a reduction in plasma vitamin B_{12} level (–16.4 ng/l, 95% CI –32.9 to –0.01 ng/l) that was not clinically significant. Health utility, measured using the EuroQol-5 Dimensions questionnaire, was unaffected by participation in the trial (measured by change from baseline) or by allocation to the metformin or placebo group. There was no difference between the groups in functional status (measured using the Short Form questionnaire-8 items) at 4 months.

There were 35 serious adverse events (SAEs) reported in the study, 13 in the placebo group and 22 in the metformin group, none of which was deemed to be treatment related. Two deaths and three cardiovascular events were reported and there were three diabetes events and two non-melanoma cancer events. Side effects were reported by 25 people in the placebo group and 22 people in the metformin group. A greater proportion of participants in the placebo group than in the metformin group experienced these as very bothersome.

Conclusions

We have demonstrated that a large, simple, pragmatic randomised trial comparing the effects of prolonged-release metformin and placebo on the risk of CVD events is potentially feasible. In particular, practice and participant recruitment was feasible but unlikely to be sufficiently scalable using the approaches undertaken in the feasibility study. Randomisation procedures efficiently generated well-balanced groups.

The characteristics of the recruited participants highlighted the need for a more efficient means of identifying individuals at higher CVD risk. Postal delivery of the study drug was feasible and acceptable and the drug appeared to be safe and was reasonably well tolerated; however, the proportion of participants discontinuing the study medication would threaten the validity of the study findings. Proposed methods of collecting data concerning outcomes, adverse effects and resource use were feasible and acceptable to participants and practitioners.

The study question remains important for the reasons outlined in *Background*. However, we have a number of recommendations concerning changes to the design and conduct of the study to make it possible for the trial to be scaled up efficiently. These recommendations include using large primary care databases to increase recruitment rates; changing the inclusion criteria to allow people with pre-existing CVD to be recruited from primary and secondary care databases to increase the recruitment and event rates; conducting follow-up remotely to reduce costs and improve efficiency; and including a run-in period prior to randomisation to optimise adherence to the study procedures and drug adherence.

Trial registration

This trial is registered as ISRCTN34875079.

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