ISRCTN53525957 https://doi.org/10.1186/ISRCTN53525957

Low Blood glucose & the Effects of Systemic antiThrombotics IN Type 2 Diabetes (BEST-IN-T2D)

Submission date
28/06/2022

Recruitment status
No longer recruiting

Registration date
18/07/2022

Overall study status
Completed

Last Edited
14/10/2025

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Heart attacks and strokes cause more deaths in people with type 2 diabetes (T2D) than any other cause and mostly result from the formation of blood clots inside blood vessels supplying the heart and brain. A common side-effect of treating high blood sugar levels in T2D is episodes of low sugar levels, called hypoglycaemia ('hypos'). We have discovered that hypos cause inflammation and increased clotting tendency in T2D. In this study, we will study what effects two commonly-used anti-clotting drugs, aspirin and prasugrel, have on the harmful effects of hypos in T2D. This may indicate the most promising anti-clotting medication in T2D patients, especially in those at risk of hypos and heart disease.

Who can participate?
People with confirmed T2D who are aged between 18-65 years old and are either taking tablets or insulin for their diabetes but have not had previous heart attacks or strokes.

What does the study involve?
The study will involve health screening and then a period of either taking aspirin, prasugrel or no medication for 12 to 16 days. Medical records will be reviewed at the screening visit to obtain medical history, medication records, laboratory results and imaging test results to ensure eligibility for the study. Specifically, we will confirm a diabetes diagnosis and assess if there is a history of medical conditions that could exclude potential participants from the study because of increased risk from hypos and/or from the use of anti-clotting medications. These include previous heart disease, stroke, peripheral vascular disease, kidney problems, cancer, and significant eye damage from diabetes. Participants will be asked to wear a continuous glucose monitoring (CGM) device to monitor their blood sugars for up to 10 days in this period. This will be followed by a full day at the Clinical Research Facility at Northern General Hospital to have drips of insulin and glucose given into their veins to control their blood sugar and bring it into the hypo range for a brief period of time. Participants will also have blood tests during this visit. Participants will then be seen the following day to do more blood tests and to be fitted with a CGM device for another week before coming back for a final set of blood tests. We will also keep in contact by telephone until 2 weeks after the full-day visit to hospital when their blood sugar

was controlled. Overall, there will be 6 in-person visits which include one full-day visit and 2 telephone calls with the study team.

What are the possible benefits and risks of participating?
There are no guaranteed benefits to participants taking part in this trial.
The risks to participants of being involved in this study are minimal. The study medications, aspirin and prasugrel, are routinely used in the care of patients having, or have had, a heart attack and are usually well tolerated. However, both medications commonly increase the risk of bleeding and participants receiving these medications may notice they bleed longer if they cut themselves. All participants will have their blood sugar lowered (hypo) for 60 minutes (the lowest level is 2.5 mmol/l); the symptoms any individual experiences with a hypo can vary from person to person. It is, however, common to feel shaky, hungry, and sweaty and for them to be aware of their heartbeat more strongly during the hypo but this subsides when their blood sugars are brought up to the normal level. Putting the cannula in can sometimes cause a bruise or slight inflammation, which may be uncomfortable, but usually settles down in a few days.

Where is the study run from?
Northern General Hospital (United Kingdom)

When is the study starting and how long is it expected to run for?
October 2020 to November 2025

Who is funding the study?
Medical Research Council (MRC) (United Kingdom)

Who is the main contact?
Dr Ahmed Iqbal (Principal Investigator) (United Kingdom)
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-002906-28

Integrated Research Application System (IRAS)
1003876

Central Portfolio Management System (CPMS)
51549

Study information

Scientific Title
A proof-of-concept randomised intervention trial to establish the impact of prasugrel versus aspirin on the proinflammatory and prothrombotic effects of experimental hypoglycaemia in type 2 diabetes

Acronym
BEST-IN-T2D

Study objectives
P2Y12 inhibitors and aspirin will differentially modulate the deleterious proinflammatory and prothrombotic consequences of experimental hypoglycaemia in type 2 diabetes with prasugrel providing superior protection from these consequences compared with aspirin

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 31/01/2022, East Midlands – Leicester South Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, United Kingdom; +44 (0)207 104 8115; leicestersouth.rec@hra.nhs.uk), ref: 21/EM/0276

Primary study design
Interventional

Study design
Randomized interventional proof-of-concept open-label single-centre parallel-group-assignment study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Type 2 diabetes

Interventions
We hypothesise that P2Y12 inhibitors and aspirin will differentially modulate the deleterious proinflammatory and prothrombotic consequences of experimental hypoglycaemia in type 2 diabetes (T2D) with prasugrel providing superior protection from these consequences compared with aspirin. We aim to test this hypothesis in a proof-of-concept, open-label, single-centre, randomised clinical trial of three independent parallel groups of participants with T2D (n=45). Participants will be randomised to aspirin 75 mg orally per day for 14 ± 2 days (n=15) or prasugrel 10 mg orally per day for 14 ± 2 days (n=15), or to a no antiplatelet control group (n=15). All participants will then undergo hyperinsulinaemic-hypoglycaemia.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Prasugrel

Primary outcome(s)
The increase in pre-treatment baseline plasma IL-6 levels measured using enzyme-linked immunosorbent assay (ELISA) in participants with T2D receiving prasugrel (10 mg or 5 mg orally /day according to body weight) compared with aspirin (75 mg orally/day) at 60 minutes of recovery (180 minutes clamp time point) following 60 minutes of hyperinsulinaemic-hypoglycaemia at 2.5 mmol/l

Key secondary outcome(s)
Changes in the levels of:
1. Inflammatory cytokines measured using ELISA
2. White cell kinetics measured using a clinical grade haematology analyser
3. Platelets measured using impedance aggregometry
4. Thrombus formation measured using multi-colour flow cytometry
- in participants with T2D receiving prasugrel (10 mg or 5 mg orally/day according to body weight) or with aspirin (75 mg orally/day) compared with no antiplatelet drugs in the medication period from 0 to 180 minutes clamp time points

Completion date
30/11/2025

Eligibility

Key inclusion criteria
1. Provision of informed consent prior to any study-specific procedures
2. Male or female aged between 18 and 65 years old
3. Confirmed diagnosis of T2D taking oral hypoglycaemic agents and/or glucagon-like peptide 1 analogs/insulin: participants treated with insulin will be eligible if the duration of treatment with insulin is 2 years
4. Screening glycated haemoglobin A1c (HbA1c) 6.5-10.5% (48-91 mmol/mol), if the screening HbA1c is outside this range then participants will be ineligible

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
All

Total final enrolment
54

Key exclusion criteria
1. History of previous myocardial infarction or any other acute coronary syndrome event, ischaemic heart disease as a clinical diagnosis and/or proven through percutaneous coronary intervention (PCI) and/or cardiac imaging modalities
2. History of cardiac arrhythmia other than ectopic beats
3. History of heart failure (clinical diagnosis and/or based on echocardiographic findings)
4. History of peripheral vascular disease (clinical diagnosis and/or based on vascular imaging studies)
5. History of stroke (haemorrhagic or ischaemic)
6. History of transient ischaemic attack (TIA)
7. Significant visual impairment due to retinopathy in the opinion of the investigator, untreated stage 3 or above diabetic retinopathy, evidence of active retinal haemorrhage as determined by ongoing treatment and/or ophthalmology follow up
8. Diabetic nephropathy defined as an album-to-creatinine ratio > 30 mg/mmol on routine clinical tests performed within the last year or an estimated glomerular filtration rate <30 ml/min /1.73m2 on bloods performed at screening
9. Clinically significant abnormality on resting 12-lead ECG, including a resting heart rate outside

the range of 50-100 beats per minute but excluding atrial or ventricular ectopic beats on an ECG performed at screening
10. Significant symptoms suggestive of CV disease
11. Known untreated hyperthyroidism
12. Epilepsy or previous seizures
13. Participants on blockers or QT interval prolonging drugs
14. Cardiac autonomic neuropathy as measured at screening
15. Serious intercurrent illness within the last 6 weeks
16. Previous history of deep vein thrombosis or pulmonary embolism
17. Any active malignant disease (under active treatment and/or oncology follow-up) or a history of any malignant disease in the last 5 years
18. Family history of sudden death
19. Inability to communicate in English
20. Treatment or planned treatment with antiplatelet (including aspirin, prasugrel, clopidogrel, ticagrelor, dipyridamole, cilostazol, or glycoprotein IIb/IIIa antagonists), anti-inflammatory /immunomodulatory (oral, topical or inhaled corticosteroids; disease-modifying anti-rheumatic drugs; immunosuppressants; chemotherapy drugs; oral or topical antihistamines) anticoagulant medications (warfarin, dabigatran, rivaroxaban, edoxaban, apixaban, parenteral anticoagulants) or fibrinolytic agents within 2 months of randomisation
21. Any planned surgery or other procedure that may require suspension or discontinuation of trial medication expected to occur within 2 months of randomisation
22. Current or planned use of a non-steroidal anti-inflammatory drug
23. Known hypersensitivity to aspirin, salicylic acid (including certain asthma patients who may suffer an asthma attack or faint), prasugrel or excipients
24. Clinically significant liver disease, defined as known or suspected diagnosis of hepatic cirrhosis with current Child-Pugh class B or C; or elevation of serum alanine transferase or aspartate transferase greater than 3 times the upper limit of the normal range for the processing laboratory on bloods performed at screening
25. Abnormal clotting profile on screening that in the opinion of the investigator, would preclude safe involvement in the study or compromise its scientific credibility
26. Abnormal full blood count on screening that in the opinion of the investigator, would preclude safe involvement in the study or compromise its scientific credibility
27. Evidence of active pathological bleeding or peptic ulceration, or history of peptic ulceration or gastrointestinal haemorrhage
28. History of alcohol or drug abuse, defined as regular use of an illicit substance for recreational purposes or regular consumption of greater than 50 units (males) or 35 units (females) of alcohol per week, in the last year
29. Participants with a clinically significant CV, respiratory, metabolic, renal, hepatic, gastrointestinal, haematological, dermatological, neurological, psychiatric,or other major disorder that, in the opinion of the investigator, would preclude safe involvement in the study or compromise its scientific credibility
30. Any clinically significant abnormal laboratory test results at screening that, in the opinion of the investigator, would preclude safe involvement in the study
31. Pregnant or breast-feeding women
32. Methotrexate used at doses >15 mg/week
33. Active gout
34. Haemorrhagic diathesis; coagulation disorders such as haemophilia and thrombocytopenia
35. Any contraindication for prasugrel or aspirin treatment as detailed in the respective SmPCs
36. Women of child-bearing potential (WOCBP)A unless negative pregnancy test at screening and willing to use highly-effective contraception for the duration of treatment with study medication

Date of first enrolment
01/09/2022

Date of final enrolment
31/10/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Northern General Hospital
Northern General Hospital NHS Trust
C Floor, Huntsmnan Building
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Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Research council

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request. Dr Ahmed Iqbal (Principal Investigator) (United Kingdom), ahmed.iqbal@sheffield.ac.uk, will act as the point of contact for data set enquiries for 2 years from the end of the trial period (indicative date Mar 25). This can only be summary data supplementary to the publication of the main results and will be anonymised.

IPD sharing plan summary
Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No
Participant information sheet	version 1.4	14/01/2022	15/07/2022	No	Yes