Cardiovascular Research Unit

Information Sheet for the Study:

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.

Low **B**lood glucose & the **E**ffects of **S**ystemic Anti**T**hrombotics **IN** **T**ype **2** **D**iabetes
(BEST-IN-T2D)

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Summary

We would like to invite you to take part in this research study. Before you decide whether or not to take part, we would like you to understand fully the nature and purpose of this study and what it will involve. Discuss it with your friends and relatives if you wish. You are welcome to discuss any concerns you may have with us before, during or after your involvement in the study. Please read the following information carefully. Take as much time as you like to decide if you are interested, and ask us any questions you may have.

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 which anti-clotting medications we should investigate further in larger studies in T2D patients at risk of hypos and heart disease.

The study will involve health screening and then a period of either taking aspirin, prasugrel or no medication for 12 to 16 days. With regards to screening, we will review your medical records to obtain your medical history, laboratory results and imaging test results to ensure eligibility for the study is met. Specifically, we will confirm a diabetes diagnosis and assess if there is a history of medical conditions that could exclude you from the study because of increased risk from hypos and/or from use of anti-clotting medications. These include previous heart disease, stroke, peripheral vascular disease, kidney problems, cancer and significant eye damage from diabetes. We will also review your medication records to ensure eligibility for the study is met. You will also be asked to wear a continuous glucose monitoring (CGM) device to monitor your 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 your veins to control your blood sugar and bring it into the hypo range for a brief period of time. You will also have blood tests. You should feel sufficiently back to normal at the end of the day in order to go home. We will then see you the following day to do more blood tests and you will 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 your full day visit to hospital when your 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.

This study will be a research studentship for Dr Fahad Arshad who is undertaking an MD degree. Dr Arshad is a medically qualified doctor training to be a Diabetes Consultant.

This study is led by Professor Rob Storey (Cardiology Consultant and expert in anti-clotting medicines) and Dr Ahmed Iqbal (Diabetes Consultant and expert in hypos).

What is the purpose of the study?

People with T2D have more heart attacks and strokes than people without diabetes. The risk of heart disease and stroke is higher if blood sugar control is not right. In T2D, the level of sugar (glucose) in the blood tends to go very high, and is brought back to normal by tablets or injections of insulin. We already know that high glucose levels tend to cause

inflammation in the blood vessels, which results in furring up of these vessels, and causes strokes and heart attacks.

Because of this clear link between high sugar levels in T2D and heart attacks, we've been focusing treatment on getting ever better control of sugar levels in the blood in people with T2D. This can, however, lead to people with T2D experience low sugar levels (hypos). We've started to realise that hypos are harmful. Very quick drops in sugar levels are very unpleasant for people with diabetes, and are also associated with heart attacks and heart damage.

We have done research to show that hypos may cause inflammation and clotting in blood vessels in a similar way to high blood sugar levels and that this may lead to higher risk of heart attacks in those with T2D. We now want to see if we can prevent the harmful effects of hypos on the heart in those with T2D by using medications. We think that two anti-clotting medications, aspirin and prasugrel, which are commonly used after a heart attack by millions of people around the world may also help to reduce the harmful effects of hypos on the heart in those with T2D. This is because aspirin and prasugrel not only act on the immune system to reduce inflammation but are also good anti-clotting medications. In this study we will enrol eligible people with T2D and given them either aspirin, prasugrel or no anti-clotting medication for around 2 weeks before deliberately making their blood sugar go into the hypo range. This will allow us to study what effects anti-clotting medications have compared to no medication on the effects hypo has on the heart. If aspirin and prasugrel both help reduce the inflammation and clotting hypos cause in T2D, our results will also indicate which one of these two medications should be investigated further in this regard.

Why have I been invited?

We wish to enrol people with confirmed T2D who are aged between 18-65 years and are either taking tablets or insulin for their diabetes but have not had previous heart attacks or strokes. You have been invited because you fit into this group.

Do I have to take part?

No, you do not have to take part if do you do not wish to. If you choose to participate or not your usual care or access to NHS services will not be affected. If you do choose to take part, you will be asked to sign a consent form. We will, with your permission, inform your GP and your hospital Consultant (where applicable) if you do decide to take part in the study.

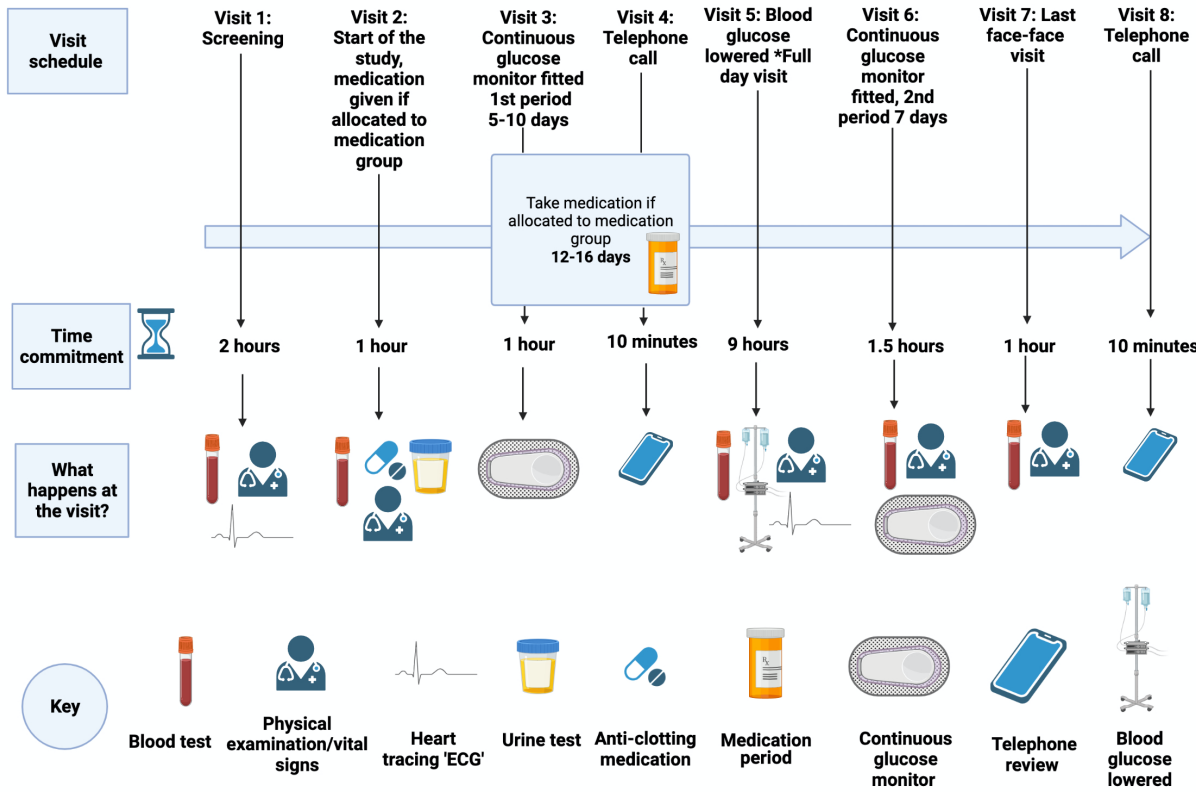
What if I want to stop taking part?

If at any point during the study you decide you no longer want to be involved, you can withdraw without giving a reason at anytime including the period during which we are lowering your blood sugar. You will continue to receive the same standard of care at the hospital or GP surgery whether you take part or not.

What will happen if I decide to take part?

You will be asked to attend the hospital for a total of 6 in person visits with 2 remote telephone visits (see Figure 1). The study is explained in more detail in the following paragraphs.

Figure 1: Summary of overall study design



Screening visit

This visit will take up to 2 hours. The study doctor will explain the research to you in detail and you will have the opportunity to ask further questions. If you are happy to participate, we will ask you to sign a consent form. If you need more time to decide, you can always come back at a later date. We will then find out about your medical history including any medicines you take, examine you including your height and weight and take blood tests. We will take just over 2 teaspoons (12.5 millilitres [ml]) of blood to check that your kidney and liver function are normal, your clotting is normal, check your recent blood glucose control (HbA1c) and check you are not anaemic. Thus, we may detect potential abnormalities on screening bloods in liver and kidney function in addition to detecting abnormalities in blood counts due to recent infection for example. We will also obtain an ECG or electric tracing of your heart and asses the function of the nerves supplying your heart. This will involve measuring your heart rate during simple breathing exercises and measuring changes in heart rate and blood pressure on standing. If this trial is right for you, we will then schedule a day for you to start taking part in the study. Your GP will be informed that you are taking part in this research. Your GP may also be informed of any abnormal results incidentally found on your study blood tests done at screening or at a later visit.

At the start of the study

This visit will last 1 hour. You will be at the start of the study randomly allocated to one of three groups to take either aspirin, prasugrel or no anti-clotting medication for 12-16 days. The odds of being allocated to each group are 1 in 3 and the study is an open label trial so that you as the participant, the research team and your GP will know which group you

are allocated to and which study medication you are taking if allocated to a medication group. You will not have any interaction with other people in your group. The groups are part of how the study is designed so that we can get scientific results that are as accurate as possible and answer the questions we are asking in an unbiased way.

The specific medications and doses that you may be asked to take are as follows:

1. No medication
2. Aspirin 75 milligrams (mg) once daily – this is the standard dose of aspirin (equivalent to a 'baby' aspirin) given after heart attack
3. Prasugrel 10 mg – this is the standard dose of prasugrel given after heart attack (prasugrel 5 mg – this is the reduced dose of prasugrel given to people with a body weight of less than 60 kg)

Aspirin will be issued as standard or dissolvable tablets and prasugrel will be issued as standard tablets. Before you take the medications, we will take 27 ml (equivalent to about $5^1/_2$ teaspoons) of blood for baseline measurements. At this visit we will also measure the time it takes for your blood to clot, this is known as measuring the 'bleeding time'. To do this, we will make a very small cut on your lower arm just deep enough to cause a tiny amount of bleeding and use blotting paper to touch the cut every 30 seconds until bleeding stops. We will also measure your vital signs (blood pressure and temperature), examine you and give you a participant information card detailing treatment allocation, restrictions during the study and contact details of the research team.

Fitting the continuous glucose monitor

The next visit to hospital will be 6 to 8 days later and this will last for 1.5 hours. Here, we will take your vital signs again and fit you with a continuous glucose monitoring device (CGM)- see Figure 2 below. A CGM uses a small device (sensor) to measure your glucose levels continuously throughout the day and night. The sensor filament sits just beneath your skin usually in the lower abdomen and it is inserted using an applicator – the insertion is no more painful than having a blood test. CGM measurements are sent wirelessly to a hand held monitor or mobile phone which allows you to see trends in your glucose levels and alerts you to highs and lows. We will train you to use the CGM device and a member of the study team will also be available for troubleshooting during the study. If you own a smart phone, we will ask you to download a mobile application or 'app' to use the CGM system. If you do not own a smart phone, we will provide you with a hand-held monitor for the duration of the study to feedback CGM results. A CGM system measures your glucose level every few minutes, so you see a graph of your glucose levels over time. The sensor doesn't actually measure your *blood* glucose level; it measures the amount of glucose in the fluid that surrounds the cells in your body (called 'interstitial fluid'). Glucose levels in the interstitial fluid lag behind glucose levels in your blood by up to 15 minutes, and the lag time is longest if your blood glucose level is changing rapidly, for example after eating or if you are exercising. For this reason CGM does not replace finger prick blood glucose checks and you will be asked to continue this during the study if you do this ordinarily and also make a note of any episodes of hypo in a diary. The CGM sensor we will be using in the study is water-resistant but not water proof. The sensor is fine for bathing and showers that last less than 30 minutes and also for use in a hot tub for up to 15 minutes. The sensor will work less well with swimming, but swimming at a shallow depth is possible provided the sensor is covered with a clear plastic waterproof patch. We can provide clear, plastic, waterproof patches if are a regular swimmer.

You will wear the CGM device twice during this study. For the first period you will be asked to wear the CGM for between 5-10 days. We will telephone you in the evening before your full day visit when your blood glucose will be lowered (see below) to go over your sugar readings from the CGM and any sugar readings you may have recorded from finger prick tests. If you have had a hypo within 24 hours before your sugar was due to be lowered in hospital, we will need to postpone this visit by 24 hours.

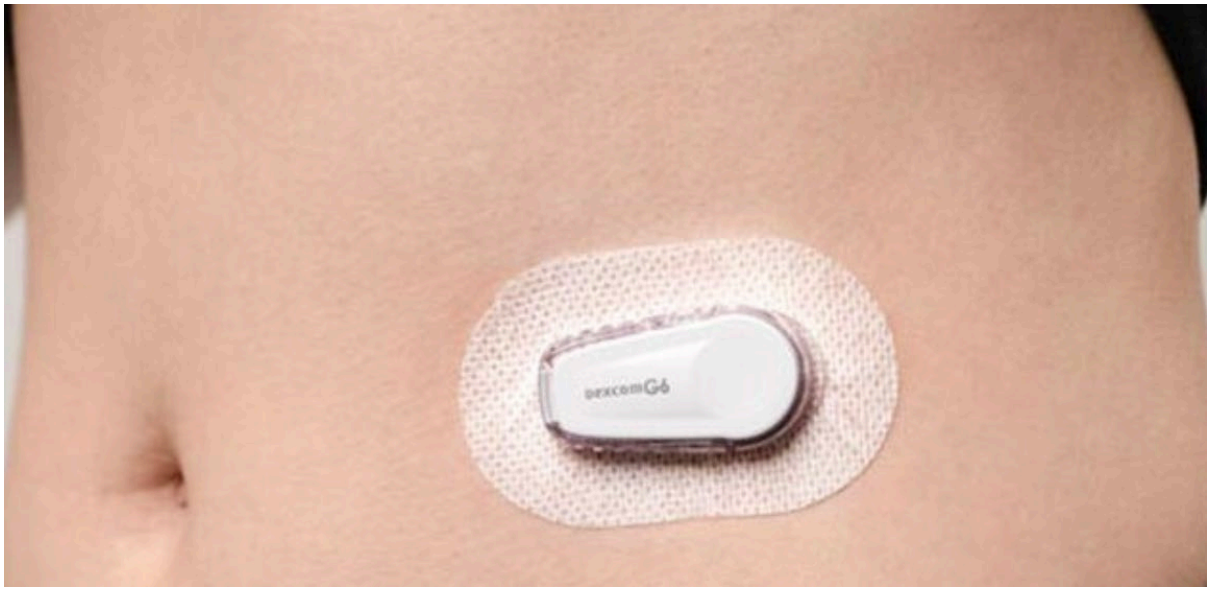


Figure 2: Continuous glucose monitoring device participants will be asked to wear during the study.

Full day visit to have your blood sugar lowered

This will be a full day visit from 08 AM to 5 PM. After you have had aspirin, prasugrel or no medication for 12-16 days, we will ask you to attend the Clinical Research Facility in the morning for a full day visit, you will access to WiFi and a television. We will ask you to fast from midnight and advise you to avoid smoking, caffeine intake on the day and vigorous exertion in the previous 24 hours as well omitting your normal anti-diabetes medications 12 hours before the visit. You will also be asked to limit your alcohol intake to 2-3 units the night before the visit. We will examine you, obtain a heart tracing, ask about side effects of anti-clotting medications and download glucose data from the CGM device. We will then carefully maintain your blood sugar at the desired level using a drip of insulin and glucose given via a small plastic tube (cannula) in your arm. In order to do this we will place your non-dominant hand (left hand for a right handed person) in a warm box for glucose sampling for the duration of the study. The hand will feel warm but set at a temperature no greater than 55˚C (for reference, a moderately warm shower or bath is usually set at 43˚C). Some people can find this uncomfortably warm but it does not cause damage to the skin and you can always periodically remove your hand from the hand warmer to allow it to cool. We will lower your blood glucose to 2.5 mmol/L (hypo) for 60 minutes. This experiment itself will be for a total 360-minute period. Throughout the day, we will be checking your blood pressure, heart rate and monitoring your heart rhythm. We will measure your blood sugar every 5 minutes before and during the hypo part of the experiment. Blood samples for sugar levels will be taken from a cannula in the back of your hand, inserted with a local anaesthetic cream. Once the cannula is inserted, blood samples can be taken without any further needles. A separate

cannula will be inserted into the opposite arm for other blood tests that cannot be taken from the hand cannula. These will include blood tests for hormones, inflammation and clotting markers that will be measured when your blood sugar reaches a steady state. We will also measure the 'bleeding time' on three occasions during this visit, this will involve three small cuts on the lower arm over the day. The cuts will be just enough to cause tiny amount of bleeding and we will use blotting paper to touch the cut every 30 seconds until bleeding stops. At the end of the study, we will provide you with a meal and you will be able to go home as soon as ready. For the whole day, we will approximately take a total of approximately 8-10 tablespoons of blood. This is less than a quarter of what is normally taken during a blood donation.

The days after your blood sugar is lowered

The day after your blood sugar is lowered we will ask you to attend the Clinical Research Facility again for another 1.5 hour visit. We will examine you, draw 20 ml (equivalent to 4 teaspoons) of blood for inflammation and clotting markers and fit a CGM sensor again for the second time in the study. For this second period you will be asked to wear the CGM for 1 week.

We will then see you in person to remove the CGM, examine you and draw a final 20 ml of blood, with this visit lasting 1 hour. After this we will telephone you around 12-16 days after your blood sugar was lowered to check you remain well and to formally draw your participation in the study to a close. If you withdraw from the study, provided you have received one dose of the study medication or have had your blood sugar lowered, we will telephone you around 12-16 days from withdrawal to make sure you continue to be well.

What are the risks of taking part?

Previous experience from work carried out by us and other researchers has shown that the risks to participants of being involved in the studies we describe are minimal. Specifically, 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. There are, however, risks that you should be aware of before considering taking part in this study. The risks depend on which one of the three study groups you are randomly allocated to. All participants will undergo a full day visit to have their blood sugar lowered and risks associated with this as well as separate risks for each study group are discussed below. When referring to the risks in these sections, we have used the terms, very common, common, uncommon, rare and very rare. The likelihood or odds of risks for these terms are as follows:

- Very common means 1 in 10 people (or more) are affected
- Common means between 1 in 10 and 1 in 100 people affected
- Uncommon means between 1 in 100 and 1 in 1,000 people affected
- Rare means between 1 in 1,000 and 1 in 10,000 people affected
- Very rare means fewer than 1 in 10,000 people are affected

Risks in the no anti-clotting medication group

Participants in this group will receive no medication and there are therefore no study medication risks but please see the section below on risks associated with having your blood sugar lowered.

Risks in the aspirin group

Taking aspirin commonly increases the risk of bleeding and you may notice that you bleed longer if you cut yourself. The risk of serious internal bleeding including from heavier than normal periods is, however, rare. In addition, aspirin can commonly cause a mild stomach upset. Aspirin can also cause a rash but this is uncommon and serious rashes occur rarely. These side effects all resolve soon after stopping the drug.

Rarely, taking aspirin may cause an allergic reaction, which might include rash, swelling and difficulty breathing. If the reaction was bad enough to make you feel unwell in yourself you should seek emergency medical care, but in all cases, you should stop taking the aspirin and discuss with the study team as soon as possible.

Risks in the prasugrel group

Taking prasugrel commonly increase the risk of bleeding including a nose bleed and you may notice you bleed longer if you cut yourself. Serious internal bleeding is, however, uncommon and a low platelet count which can make bleeding worse is rare with prasugrel. Prasugrel can also commonly cause anaemia from long-term (>6 months) use. Bruising and a mass of clotted blood (haematoma) can commonly form under the skin if you have a blood test but this usually resolves in a few days. These side effects all resolve soon after stopping the drug.

Prasugrel can uncommonly cause an allergic reaction which might include rash, swelling and difficulty breathing. If the reaction was bad enough to make you feel unwell in yourself you should seek emergency medical care, but in all cases, you should stop taking the aspirin and discuss with the study team as soon as possible.

Risks of having your blood sugar lowered (all participants)

General risks

On the day we lower your blood glucose (hypo) you might experience side effects from the low blood sugar. The lowest level (2.5 mmol/L) we are bringing your blood sugar to is that of a hypo that would have been experienced by people with diabetes who are on insulin or on oral medication at some stage in the past. During this study, we will have much more precise control of your blood sugars compared with what happens to people with diabetes day-to-day. Extremely low blood sugars (2.0 mmol/L) will be avoided. The duration of hypo you will experience is 60 minutes which may be longer than what you may have experienced in the past, however. Also, the magnitude of symptoms you get with a hypo will depend on your overall glucose control and the symptoms any individual experiences with a hypo can vary from person to person. It is, however, common to feel shaky, hungry, sweaty and be aware of your heart beat more strongly during the hypo but this subsides when your 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.

Effects of hypo on the heart

Abnormal heart rhythms have very rarely between reported at 2.5 mmol/L during similar hypo research studies. Your heart rhythm will be continuously monitored during the study. The abnormal rhythm if it occurs is correctible with drugs and/or electrical treatment and is generally reversed when blood sugars are returned to normal. We will at all times be able to rapidly bring up your blood sugar to normal. We do not expect any long-lasting

harmful effects of inflammation this episode of hypo will cause on your heart. This is because inflammation caused by the hypo we will induce is short-lived (up to 7 days) and weak compared to inflammation most participants would have experienced in the past for example from a cold.

Effects of hypo on the brain

The brain uses sugar as a fuel and low blood sugar levels below 3 mmol/L can commonly cause people to have a mild headache which resolves when blood sugars are brought to normal. At a blood sugar of 2.5 mmol/L, people commonly have a temporarily reduced ability to perform complex tasks that require the brain such as solving a puzzle, solving a tricky mathematical problem and memorising large amounts of information. This resolves completely when blood sugars are brought back to normal. It is important to highlight that at the level of hypo we will induce, participants will remain fully conscious and able to communicate freely throughout the hypo period. This means that if you feel unwell and would like to stop the study you will be able to instruct us to stop at all times and we can bring your sugar levels up to normal levels rapidly. We do not expect any long-lasting harmful effects of this episode of hypo on your brain.

Our hospital has a lot of experience in running these studies and we have performed over 500 of these studies, including both healthy volunteers and people with T2D, with no untoward events. Worldwide over 5,000 similar procedures have been performed. The study doctor(s) and research nurses will be present constantly and our first priority will be to maintain your personal safety. We are not expecting this study to cause any harm but, if it did, we would seek to adjust the study to make it even safer. If necessary we would stop it. If we were to have any problems, we would report them to the hospital, the national medicines authority and an independent committee, known as an Ethics Committee.

Women who may fall pregnant

Pregnancy excludes participants from this trial because of potential harm to the unborn child from exposure to study medications and low blood sugar. If you are a woman of childbearing potential, we will ask you to have a pregnancy test and to use contraception during your participation in the trial. Examples of suitable contraception would be the pill or an intrauterine device such as the Mirena Coil.

Men with partners of childbearing potential

Men are not affected.

What are the benefits of taking part?

There are no guaranteed benefits to you from taking part in this trial.

What happens at the end of the study?

If you were randomised to receive either study medication, you will not continue to receive this at the end of the study. This is because we are exploring potential benefits of the study medication and there is currently no clinical evidence to support use of study medications in reducing harmful effects of hypos on the heart in T2D. It will take us some months to analyse the results. We can update you to let you know what we find, if you would like us to inform you of the results we will ask your permission to do so on the study consent form. In this case, we will provide a brief written summary of our findings. None of the data we generate will be directly useful to you, however. The results may be published in medical

journals and presented in national and international conferences. The information will be kept completely anonymous and you will not be identified.

Are there any restrictions during the study I should be aware of?

During the study medication periods we ask you to avoid taking any medications that might interact with the study drugs. This includes over-the-counter preparations such as:

- Non-steroidal anti-inflammatory drugs such as aspirin, ibuprofen, naproxen or diclofenac by-mouth or in skin creams; and mouthwashes such as benzydamine. If you do need to take any painkilling medication, paracetamol or co-codamol (which are safe with the study medication but we ask you to contact the study team as soon as possible after taking it in order to determine if you need to stop or restart your participation in all or part of the study, or postpone the next visit.
- Anti-histamine tablets (such as cetirizine, loratadine or chlorphenamine) or creams/ointments (such as mepyramine or diphenhydramine). Anti-histamines are broadly safe with the study medication but may invalidate the results of the tests we perform so we ask you to avoid them if possible.
- Steroid preparations such as hydrocortisone cream and some nasal or eye treatments. Illicit steroids (anabolic steroids or other prescription only hormone preparations that are misused without prescription to increase muscle mass and improve athletic performance) also fall into this category. Steroids are broadly safe with study medication but may invalidate the results of the tests we perform so we ask you to avoid them if possible.

We ask to check carefully that any over-the-counter preparations you wish to take do not contain these types of substances. If in doubt please try to discuss it with the study team first using the contact details provided later in this document.

We will also provide you with a study participation card. This includes a list of prescription-only medications that should be avoided whilst taking part in the study. In the event of requiring medical treatment during the time you are involved in the study, you should show the card to any healthcare professional who assesses or treats you to provide information.

There are no specific restrictions on diet, lifestyle or exercise during the study except on the day before your blood glucose is lowered as already outlined. We will ask you to inform us if you have any symptoms of COVID-19 and/or have a positive test so that any study visits can be appropriately re-arranged. Also, as we will be measuring markers of inflammation and thrombosis, study visits cannot take place within 2 weeks of having either the first of second COVID-19 vaccine jab as this may interfere with study results.

What we will do with the samples we take

We will use the samples to find out whether the medications we are studying affect the normal immune response. We plan to look at the effects hypo has on your white blood cells, platelets and clotting factors amongst other things. We will then look to see if aspirin and prasugrel change this response. Samples will be transferred to the Cardiovascular Research Unit laboratory, University of Sheffield, located within the Clinical Research Facility, Northern General Hospital on the day the samples are obtained. The blood will be stored by the University of Sheffield for the duration of the study. We ask for your permission to perform any tests we wish to on these samples relevant to assessing the drugs' effects. We will label the samples with a unique study code rather any identifiable data to ensure confidentiality.

Optional subheading

When the study is complete, we will destroy any cellular material but ask for your consent to store cell-depleted fluids (plasma and serum) for 2 years after study completion for any ethically approved future research relevant to this study. Similarly, we also ask for your permission to store and analyse DNA and related material (RNA) extracted from your blood for 2 years after study completion as part of as yet unplanned research related to this study and other future studies. Any DNA tests will be analysed anonymously and results will not be traceable back to individuals. If you wish, we could arrange instead that samples are destroyed at the end of the study or you can request that the samples are destroyed at any later date (contact Trial Coordinator Dr Hannah McMellon 0114 2266159, h.mcmellon@sheffield.ac.uk)

Expenses and payments

We appreciate that this study will involve you having to make 6 visits to the Clinical Research Facility, including the one full day when your blood sugar will be lowered. We also appreciate that we are asking you to take medication for 12 to 16 days before this experimental day and, for those who work, this involves time off work and the potential need to make childcare arrangements. Accordingly, we are able to offer you £150 to recompense your expenses, the time you spend with us, and any discomfort caused by the study if you participate in the study including the day where your blood sugar is lowered. Participants who attend the initial screening visit but are unable to complete the rest of the study for any reason will receive £10 as a reimbursement for their time. Transportation to and from the Clinical Research Facility will be provided for when your blood glucose is lowered and on additional visits if necessary.

How will I be protected from COVID-19?

All members of the study team are double vaccinated against COVID-19 which will also confer protection to participants. All COVID-19 precautions as recommended by Sheffield Teaching Hospitals will be adhered to during study visits. Sheffield Teaching Hospitals have an indoor face mask policy for all visitors. We anticipate that many, if not all, potentially eligible participants will already be double vaccinated by the time the study commences given that those with diabetes are a recognised high risk group.

What if there is a problem, or I suffer harm as a result?

The study has insurance from the University of Sheffield. In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Sheffield, but you may have to pay your legal costs. NHS indemnity is also in place. Further details are available on request.

What if I want to complain about anything?

If you have any cause to complain about any aspect of the way you have been approached or treated during the course of the study, you should contact the Chief Investigator (Professor Robert Storey, Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Beech Hill Road, Sheffield S10 2RX).

If you would prefer not to approach the research team directly with your complaint you can contact the Sheffield Teaching Hospitals Patient Services Team on 0114 271 2400 or email sth.pals@nhs.net and they can guide you through the process.

Alternatively, the normal National Health Service (via letter to The Chief Executive, Sheffield Teaching Hospitals NHS Foundation Trust, 8 Beech Hill Road, Sheffield S10 2SB) or the normal University complaints mechanisms are available (via Professor David Petley, Chair of the University's Research and Innovation Committee please see link for full details https://www.sheffield.ac.uk/polopoly_fs/1.759258!/file/policy.pdf).

Will my taking part in the study be kept confidential?

Sheffield Teaching Hospitals NHS Foundation Trust is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. All information that we collect during the course of this study will be kept strictly confidential; the only people who will have access to your identity, contact details and test results will be the staff running the study. Each participant will be given a unique study specific number that will be used to identify them on study documentation/records (this is known as pseudonymised data). The principal investigator, Dr Ahmed Iqbal, is based at the University of Sheffield, consequently pseudonymised study data may be analysed at the University of Sheffield (based on E Floor of the Royal Hallamshire Hospital). Your identifiable data will be stored within a University of Sheffield facility (the Cardiovascular Research Unit) which is situated on a Hospital site (within the Clinical Research Facility, Northern General Hospital). This information will be stored in these University premises as the research team including the lead investigator, key laboratory staff and trial coordinator are based in this facility and the University of Sheffield is a formal collaborator in this study. Personal information will be collected by the investigators, kept secure within a room in the Cardiovascular Research Unit that is kept locked and alarmed out-of-hours, and will be maintained by the staff of the Cardiovascular Research Unit. Specifically, in this study, Dexcom Inc (a medical device company based in the United States) is providing continuous glucose monitoring equipment for use in the study. Anonymised glucose recording data obtained during the course of the study will be shared with Dexcom Inc. No personal health data or other (non-glucose) data generated during the study will be shared. This information will not identify you and will not be combined with other information in a way that could identify you. The information will only be used for the purpose of health and care research, and cannot be used to contact you or to affect your care. It will not be used to make decisions about future services available to you, such as insurance.

We also ask for your consent to tell your GP and where applicable hospital Consultant about your involvement in the study. Study information will be kept for 15 years after the study, after this period all documentation will be destroyed according to Trust protocols.

How will we use information about you?

We will need to use information from you and from your medical records for this research project. This information will include your initials, NHS number, name and contact details. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a unique study specific code number instead.

We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

What are your choices about how your information is used?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

Where can you find out more about how your information is used?

You can find out more about how we use your information:

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from https://www.sheffieldclinicalresearch.org/for-patients-public/how-is-your-information-handled-in-research/
- by asking one of the research team

Who has assessed and funded this study?

This study has been independent scientifically reviewed by the Medical Research Council, who are funding the study. All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and granted a favourable opinion by East Midlands- Leicester south Research Ethics Committee. The study was also be approved by the Healthcare Regulatory Authority and the NHS Health Research Authority prior to its commencement.

Dexcom Inc (a medical device company based in the United States) is providing continuous glucose monitoring equipment free of charge. No personal identifiable data from participants will be shared with Dexcom inc (please see section on management of confidential data).

Contact details

The contact details of Professor Robert Storey are given above. The contact details for Dr Ahmed Iqbal, the Diabetes doctor organising the study, are The Cardiovascular Research Unit, Centre for Biomedical Research, Northern General Hospital, Herries Road, Sheffield, S5 7AU, telephone 0114 3052003 (or via the hospital switchboard 0114 2434343). Please feel free to contact us at any time to discuss any queries that you may have.

Thank you for taking time to read this information and considering taking part in our study.

Study Number: STH12590
Patient Identification Number for this trial:
Short title: BEST-IN-T2D

CONSENT FORM

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.

Low **B**lood glucose & the **E**ffects of **S**ystemic Anti**T**hrombotics **IN** Type **2** **D**iabetes: ***BEST-IN-T2D***

Name of researcher (site principal investigator):
Dr Ahmed Iqbal
Clinical Lecturer in Diabetes
Department of Oncology & Metabolism
University of Sheffield
Beech Hill Road
Sheffield, S10 2RX

Instructions: please insert your initials in the boxes below

1. I confirm that I have received verbal information and read and understand the information sheet dated.....Version..... for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐
3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the Sheffield Teaching Hospitals NHS Trust and from regulatory authorities, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.	☐
4. I agree to my GP and where applicable hospital Consultant being informed of my participation in the study and for the details of the information I provide to be checked with my GPs and/or hospital records.	☐

5. I agree to my GP being informed of any abnormal results found on my study blood tests at screening or at a later visit.	☐
6. I agree to my identifiable data being stored within a University of Sheffield facility (the Cardiovascular Research Unit) which is situated on a Hospital site (within the Clinical Research Facility, Northern General Hospital).	☐
7. I agree that all the samples mentioned in the patient information sheet can be taken for the purposes of this study and transferred to the University of Sheffield for use in tests relevant to the effects of hypoglycaemia, aspirin and prasugrel during the course of the study.	☐
8. I agree to having a continuous glucose monitoring (CGM) device fitted for the purposes of this study. This will be over two separate periods during the study. I agree to wearing the CGM device for between 5-10 days for the first period and then again for 7 days for the second period.	☐
9. I agree to having my blood glucose lowered using drips of insulin and glucose given via small plastic tubes (cannulas) in my arm.	☐
10. I understand that pseudonymised data generated during the study and any unused plasma and serum may be kept stored within the University of Sheffield in order to carry out other ethically approved research in the future. I give permission for this storage and for future, as yet unplanned, research to be carried out on these data and samples by the study team and other organisations, which may be either in the UK or abroad. I understand stored samples will be labelled with a unique study code rather any identifiable data to ensure confidentiality.	☐
11. I give permission for samples (serum, plasma, DNA and RNA) to be extracted from the blood I donate for the study and for this to be stored for 2 years after study completion within the University of Sheffield in order to carry out tests including DNA analysis as part of as yet unplanned research related to this study and other ethically approved future studies. I understand stored samples will be labelled with a unique study code rather any identifiable data to ensure confidentiality.	☐
12. I understand that I may withdraw my consent to the use of my blood samples at any time. If I withdraw my consent when a sample has been taken but **before** my blood sample is sent for research, the study doctor will arrange to have it destroyed. If I withdraw my consent **after** my blood sample has been sent for research the study doctor will ensure that my blood sample is destroyed. However, if research has already been performed, the research team is not obliged to destroy results of this research. In this case only my blood will be destroyed.	☐
13. I do/do not (delete as appropriate) wish to receiving a brief written summary of the study findings.	☐
14.I agree to take part.	☐

_____	_____	_____
Name of Participant (BLOCK CAPITALS)	Date	Signature
_____	_____	_____
Investigator	Date	Signature

When completed: 1 for participant; 1 for researcher site file; 1 (original) to be kept in medical notes.