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How did you learn about the YODA Project?: Colleague

Conflict of Interest

http://yoda.yale.edu/system/files/agj.pdf
http://yoda.yale.edu/system/files/ewan.pdf
http://yoda.yale.edu/system/files/ath.pdf
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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training
Associated Trial(s):

1. NCT01106625 - A Randomized, Double-Blind, Placebo-Controlled, 3-Arm, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemi
2. NCT01081834 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin as Monotherapy in the Treatment of Subjects With Type 2 Diabetes Mellitus Inadequately Co
3. NCT01106677 - A Randomized, Double-Blind, Placebo and Active-Controlled, 4-Arm, Parallel Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequ
4. NCT00968812 - A Randomized, Double-Blind, 3-Arm Parallel-Group, 2-Year (104-Week), Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of JNJ-28431754 Compared With Glimepiride in the Treatment of Subjects With Type 2 Diabetes Mellitus
5. NCT01106651 - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Compared With Placebo in the Treatment of Older Subjects With Type 2 Diabetes Mellitus In
6. NCT01137812 - A Randomized, Double-Blind, Active-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Canagliflozin Versus Sitagliptin in the Treatment of Subjects With Type 2 Diabetes Mellitus With Inadequate Glycemic Con

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

MASTERMIND: Stratification of response to SGLT2 inhibitor glucose lowering therapy

Narrative Summary:

The purpose of this research is to identify characteristics (such as weight or blood results) that predict treatment response and side effects for glucose lowering treatments, and ultimately help doctors treat patients with Type 2 diabetes with the drug most likely to work well for them. We will examine whether differences between people in studies of glucose lowering treatment studies (for example their age, weight, or common blood test results) can be used to identify those who are likely to have a large reduction in blood glucose and/or few side effects. We will compare results across many different studies and medications to ensure our results are true and accurate.

Scientific Abstract:

Background
Current guidelines for treating patients with Type 2 diabetes list a large number of drugs without giving clear guidance on which patients should have which drug. This makes it difficult for patients and their health care professionals to know which drugs are likely to suit them best. We know that patients with Type 2 diabetes vary greatly in how well they respond to different diabetes drugs, and whether they develop side effects.

Objective
To identify clinical characteristics associated with treatment response and side effects for SGLT2 inhibitor (SGLT2I) glucose lowering therapy.

Study design
A cohort study assessing the relationship between participant baseline characteristics and treatment response/side effects in those randomised to and receiving Canagliflozin therapy verses placebo, DPP4 inhibitor or sulfonylurea comparator. Where possible we will pool data from these studies at an individual level.

Participants
Individual patient level data from participants receiving SGLTI or comparator therapy (n>5400).

Main Outcome Measure
Change in HbA1c at 26 weeks.

Statistical analysis
We will examine clinical predictors of response to SGLT2I (HbA1c change). We will assess whether factors associated with glycaemic response to SGLT2I are also associated with response to comparator treatments, and with pre-specified side effects. Findings will be cross validated in additional trial and electronic healthcare record data sets available to the MASTERMIND consortium.

Brief Project Background and Statement of Project Significance:

This research forms part of a larger project funded by the UK Medical Research Council (MASTERMIND) studying stratification of glucose lowering treatment in Type 2 diabetes. Our vision is that a stratified medicine approach based on routinely available clinical characteristics and biomarkers will result in more effective use of glucose-lowering therapy for patients with Type 2 diabetes

There are a large and increasing number of glucose lowering therapies available for Type 2 diabetes with no clear rationale given for choice of one over another in current clinical guidelines beyond side effect profile and cost(1,2). The mechanism of action of glucose lowering therapies varies widely, with SGLT2 inhibitors (SGLT2I), a commonly used second and third line treatment class, acting through potentiate of renal glucose loss, in contrast to other common non-insulin therapies whose mechanisms of action include potentiation of insulin secretion, increasing insulin sensitivity, suppression of glucagon or effects on glucose absorption (3).

Patients with Type 2 diabetes show considerable inter-individual variation in both their underlying pathophysiology, and in their response to treatment (4, 5). There is increasing evidence that this variation in the response to therapy is, in part, robustly explained by differences in patients' underlying pathophysiology (5-7). Identifying robust

predictors of response to glucose lowering therapy, or to important side effects, may allow a stratified (or precision medicine) approach to therapy, where likely effectiveness or side effect risk is used to inform treatment choice.

Type 2 diabetes is common (>4% of the population) and most prescribing of relatively inexpensive therapy is in primary care. Therefore, for a stratified approach to be widely implemented it should ideally be based on clinical characteristics and readily available biomarkers; sophisticated and expensive testing, as used in conditions like cancer, is unlikely to be feasible (5).

The information gained from this work will be combined with results from large electronic healthcare record, cohort study and intervention trial data sets and an ongoing intervention crossover trial (see analysis plan), to produce robust evidence to inform guidelines for the most appropriate use of glucose lowering medication for specific subgroups of patients with Type 2 diabetes.

Specific Aims of the Project:

The aim of this research is to identify clinical characteristics and routinely measured biomarkers that predict treatment response and side effects for SGLT2 inhibitors (SGLT2I) relative to alternative therapies. The ultimate aim is to help doctors treat patients with Type 2 diabetes with the drug most likely to work well for them.

Objectives
Our objectives are to:
1.Identify if kidney function is associated with glucose lowering response to SGLT2I treatment
2.Identify whether clinical characteristics and blood tests associated with insulin secretion and insulin resistance are associated with glucose lowering response
3.Determine whether patients with higher glucose, and better glucose lowering response, have more side effects
4.Explore what other characteristics might help predict glucose lowering and side effects with SGLT2I

We will test two specific hypotheses:
A. That participants with high baseline glycaemia will have a higher incidence of glycosuria related side effects and treatment discontinuation with SGLT2 in comparison to placebo and comparator therapies at the same level of baseline glycaemia.
B. That glycosuria related side effects will be more common in those with increased glucose lowering response at a given level of baseline glycaemia

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populationsResearch that confirms or validates previously conducted research on treatment effectivenessOther

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Studies that have been selected are randomised controlled trials of SGLT2 inhibitor therapy in adult participants with non-insulin treated Type 2 diabetes and baseline HbA1c >7% (53mmol/mol). All selected studies have assessed HbA1c change over >=26 weeks, have an active (DPP4 inhibitor, sulfonylurea) or placebo comparator and cohort size >=400.

Data analysis will be of the per protocol population.

Main Outcome Measure and how it will be categorized/defined for your study:

The primary outcome measure will be baseline adjusted (least squares) change in HbA1c at 26 weeks after commencement of study medication.

Secondary outcome measures will include:
1. Time to glycaemic failure defined by HbA1c >baseline HbA1c on two consecutive measurements >8 weeks apart or a single measurement >baseline with addition of 'rescue' therapy
2. Baseline adjusted HbA1c change at 52 and 104 weeks
3. The development of short term side effects known to be associated with SGLT2 therapy using trial definitions:

Urinary tract infection, genital infection, hypoglycaemia, event consistent with volume depletion, polyuria, acute renal failure
4. Premature medication discontinuation due to an adverse event
5. Change in weight, blood pressure, eGFR (MDRD) and haematocrit at 24, 52 and 104 weeks

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

We will assess the relationships between glycaemic response and the following baseline characteristics, where available.
A. Estimated glomerular filtration rate (MDRD equation)
B. Glycaemia: baseline HbA1c, fasting glucose
C. Markers of beta cell failure: Diabetes duration, age of diagnosis, C-peptide (and/or insulin), insulogenic index, islet autoantibodies, proinsulin insulin ratio, HOMA2B
D. Markers of insulin resistance: BMI, fasting triglycerides, HDL, SHBG, HOMA2IR
Model fit will be assessed, and variables transformed or categorised where necessary, if model assumptions are not met.
Potential predictors may be grouped to create composite variables (e.g. does response differ in individuals exhibiting multiple characteristics associated with insulin resistance?).

Statistical Analysis Plan:

1. Clinical predictors of glycaemic response:
i. Models of glycaemic response to SGLT2 therapy: We will examine clinical predictors of response (HbA1c change) within the first 24 weeks of therapy as a continuous measure using linear regression analysis, with baseline adjusted change in HbA1c as the outcome and clinical characteristics as the independent variables. Analysis will be adjusted for potential confounders including dose, study & co-therapy. This work will be extended further using more complex analysis taking into account placebo response (Royston Stat Med 2004 PMID 15287081, Wang Stat Med 2015 PMID 25736915). Analysis will be per protocol and restricted to participants with >80% adherence and no change in glucose lowering co-therapy at the time point of interest.
ii. Are characteristics associated with response specific to SGLT2I? To explore whether a characteristic is specifically associated with response to SGLT2I (rather than being associated with response to any treatment) we will assess the relationship between characteristics associated with SGLT2I response and response to DPP4i and Sulfonylurea therapy, using the same methods described in i. above.
iii. Exploration of confounding: The distribution of baseline characteristics will depend on the study of origin, which could confound results if variation in characteristics potentially predictive of response are not sufficiently represented in those treated with a particular agent. To ensure this is not confounding results we will explore the relationship between characteristics associated with response against placebo in the whole group (pooled results) and response within the individual studies.
iv. Validation of findings: It will be important to validate findings in other data sets. We have current access to trial data of >15000 response episodes through data requests managed by clinicalstudydatarequest.com (GSK, Boehringer Ingelheim and Takeda) and observational primary care response data for >2500000 patients with type 2 diabetes from the UK clinical practice research datalink (CPRD) and GoDARTS, which will provide data for replication. In addition we are undertaking a randomised double blind crossover study directly comparing SGLT2i, DPPIV and Pioglitazone therapy to test stratification hypotheses derived from other trial data (n=600), this will allow us to replicate findings in the setting of comparative within individual response against other treatments.
2. Side effects
i. Analysis: We will assess the relationship between any baseline characteristics associated with SGLT2 inhibitor response as a continuous variable and incidence of specific side effects above using survival based methods, such as cox regression, with adjustment for (depending on outcome of interest) age, gender, duration of diabetes, renal function, baseline glycaemia or liver function, study allocation, dose and co-therapy. We will explore the use of more complex modelling based on fractional polynomials taking into account occurrence of these events in the comparison groups (Roystan, Stat Med 2004, PMID 15287081).
ii. Confounding: the covariates of interest above may simply be prognostic factors of occurrence in the population, and unrelated to treatment allocation, rather than predictors of occurrence with SGLT2 treatment. The analysis in i above is therefore exploratory and methods adjusting for occurrence of these in a comparison group (such as that described above) will therefore be required to validate any findings from logistic regression.
iii. Validation of findings: as outlined above findings will be validated in the additional datasets available to the MASTERMIND consortium.
3. Precision estimate

Based on data from the GoDarts study and 3000 participants allocated to SGLT2I being eligible for analysis inclusion conventional regression analyses will have 90% power to detect a co-variate that explains <1% of variance in HbA1c reduction with an alpha <0.05.

Project Timeline:

Analysts for this research are already in post and working with data made available through other requests and therefore analysis can commence rapidly on data availability. Assuming 3 months to data availability we anticipate the following timeline:
October 2017 - commence analysis
April 2018 - complete analysis
August 2018 - submit manuscript and report results to the YODA project.

Dissemination Plan:

Central to the communication of the research will be the dissemination to academic and scientific users of research both in
academia, charities and industry. We will do this via presentations at national (Diabetes UK) and international (EASD, ADA) conferences and open access publications in leading peer review journals (e.g. Lancet).

We will also directly engage with the industrial partners involved in MASTERMIND via our already established Industry Advisory Committee. We will also work with the UK Precision Medicine Catapult as it begins to be implemented in order to communicate our outputs to the broader industry community that do not have direct involvement with the project.

Communication to physicians and non academic clinicians is also crucial to maximise the reach and impact of the work. To ensure our findings are communicated to the wider medical community we will present our findings at locally and nationally at meetings attended by non academic clinicians, in the professional press and educational events (such as the training courses run by the Oxford and Exeter teams) . We will submit any validated stratification criteria to guideline providers to inform future treatment guidance, which will ensure wider take-up into clinical practice.

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