APPENDIX 5

Systematic Review/Meta-analysis Protocol:

Optimal Dual Antiplatelet Therapy in Diabetic Patients with Acute Coronary Syndrome

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Background

Acute coronary syndromes (ACS) are a spectrum of cardiovascular conditions characterised by the presence of an unstable atherosclerotic plaque with overlying thrombus.[1] Globally, the prevalence of diabetes mellitus (DM) is increasing[2,3], and given that this population is well described to have increased platelet reactivity [4–6] it is unsurprising that in large landmark antiplatelet trials as many as 15-39% of all patients presenting with ACS have a background of DM [7,8]; this figure correlates well with registry data percentages (GRACE registry 26%, Swedeheart registry 24%, PACIFIC registry 35%).[9–11] Furthermore this population is known to have worse mortality and morbidity outcomes compared to their non-diabetic counterparts; independent of other co-morbidities.[12]

This increased aggregation of platelets in diabetes mellitus is driven primarily by hyperglycaemia affecting a multitude of pathways including increasing p-selectin expression via activation of protein kinase C, impaired function of endogenous antiplatelet agents such as nitric oxide and prostacyclin [13], amplified platelet adhesion [14], a proinflammatory environment [2]and increased platelet turnover. [15]Importantly up regulation of $P2Y_{12}$ signalling and GPIIb/IIIa surface receptors are also implicated.[3,14] Therefore with the focus of pharmacological management of ACS being the reduction of thrombus burden and platelet reactivity[16,17] targeting $P2Y_{12}$ receptors is of great importance particularly in this population, who may stand to receive the most benefit.

Until recently clopidogrel was the most widely used $P2Y_{12}$ receptor inhibitor in addition to aspirin, following randomised control trial data showing a reduction in cardiovascular death, myocardial infarction and stroke. [8,18,19] However in the diabetic patient there has been a suggestion of a muted response to clopidogrel, which has been cited as multifactorial, including genetic, metabolic, cellular and clinical.[20,21] This has increased the interest in more novel $P2Y_{12}$ receptor antagonists, such as prasugrel and ticagrelor. Published data has led to preferential use of these agents in the general population[7,22,23] and possible better outcomes with prasugrel in the diabetic cohort, [2,15] but no specific data has been systematically reviewed with both direct and indirect comparison for the management of the diabetic patient.

Review question and inclusion criteria

This review seeks to establish, through the available literature, what is optimum practice for management of diabetic patients who present with acute coronary syndrome in regards to their antiplatelet therapy.

The specific review questions to be addressed are:

(1) In combination with aspirin which is the superior agent for P2Y12 blockade to improve clinical outcomes?

(2) Is this benefit outweighed by increased risk of adverse events?

Participants

This review will consider all studies that involve diabetic human adult subjects with acute coronary syndrome.

Intervention

Intervention of focus is the pharmacological agent used to block the P2Y12 receptor as antiplatelet therapy for acute coronary syndrome.

Outcome measure

The primary outcome of interest is clinical outcomes including (but not restricted to) cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. Secondary outcomes are safety outcomes include adverse bleeding events and any other clinically relevant outcomes.

Study design

The review will consider all randomised control trials with no language or date restriction. Case series and case reports are excluded from the review owing to the high potential for bias in these study designs. Case–control studies, cohort studies and economic evaluations are also excluded.

Population

The review population will have a diagnosis of diabetes with no differentiation made between type. All articles relevant to acute coronary syndrome and P2Y12 blockade will be careful reviewed for eligibility to ensure no important data excluded. If the publication is not restricted to diabetic patients, only the sub group data relevant to the review will be incorporated. If no isolated results for diabetic patients present the study will be excluded.

Interventions and comparators

Intervention explored in the review is P2Y12 blockade in the management of acute coronary syndrome in diabetic patients, including oral and intravenous administration. The studies may compare P2Y12 blockade against placebo or two differing agents.

Outcomes

Primary outcomes measured will include, but not restricted to, mortality, MACE or revascularisation. Secondary outcomes will include safety profile focusing on bleeding rates. Studies are not required to report all outcomes of interest to meet inclusion criterion.

Study design

Due to the number of large studies focused on the pharmacological management of acute coronary syndrome, to reduce the risk of bias while still maintaining adequate data, we will restrict the paper to reviewing randomised control trials. This will ensure the highest quality review.

Inclusion criteria

- Human
- Adult (≥18 year old)
- Randomised Control Trial
- Acute Coronary Syndrome
    - Unstable Angina
    - Non ST Elevation MI
    - ST Elevation MI
- Diabetic Patients – analysed independently of total population
    - Type 1
    - Type 2
- Comparing P2Y12 blockade vs Placebo or two differing P2Y12 blocking agents
    - Clopidogrel
    - Prasugrel
    - Ticagrelor
    - Cangrelor

    - Elinogrel
- Outcomes to be clinical
    - Death
    - Myocardial Infarction
    - Revascularistation
    - Bleeding
    - Any other clinical outcome
- NO outcome data on platelet function (eg VerifyNow)
- NO data on ticlopidine due to limited clinical use of medication in UK
- NO language restriction
- NO date restriction

Methodological quality

The methodology of all papers meeting inclusion criteria will be reviewed and carefully scrutinised for possible bias. This will be discussed in the review but the article not excluded. We will use the Cochrane risk of bias assessment tool for this. (24)

Language

No language restriction is being placed on the systematic review. We will attempt to retrieve all relevant data.

Publication type/status

To reduce the possibility of publication bias, we searched through conference abstracts to identify any more studies eligible for inclusion.

Identifying research evidence

By using a defined search strategy, we will systematically search electronic databases (MEDLINE and Embase) for paper published between 1946 to the current date with no language restrictions. Our search strategy will have the following threads: i) Clopidogrel, Cangrelor, Ticagrelor, Prasugrel, Elinogrel, P2Y12 receptor antagonist, P2Y12 receptor inhibitor, ADP receptor antagonist or ADP receptor inhibitor. These will all be combined with the Boolean operator “OR”. The search terms will be linked to Medical Subject Headings (MESH). Our results will then be limited to human, adult (≥18 years of age) and randomised controlled trials.

After excluding for duplicates, the retrieved titles and abstracts will then be independently reviewed by two investigators (JAR and OIB) for relevant studies which are focused on coronary artery disease. We will then obtain full text articles for all remaining studies.

The investigators will then screened these remaining articles by electronically searching the studies for the word stem “diab”, “mellitus” or “DM”. They will exclude studies if they do not contain this term, or only included it in baseline patient characteristics. Finally the investigators again independently assess for the presence of clinical outcome data. Following this, the remaining studies will then be reviewed to confirm they meet the inclusion/exclusion criteria.

Any discrepancies in results will be resolved by group consensus.

Data extraction

Two investigators (JAR and OIB) will then extract data from the studies which are relevant, as laid out in the protocol.

The following data will be extracted: title, author(s), country, publication year, study period, patient population, treatment arms, outcome definition (see below), follow up duration, overall incidence, diabetic subgroups, number of patients and relative risks/hazard ratios with 95% confidence interval.

The outcome measures will include both primary and secondary outcome measures. Primary outcome measures will include: cardiovascular mortality; myocardial infarction and stroke. Secondary outcomes will include, but not limited to, bleeding and any other adverse events or relevant clinical endpoint. Any discrepancies will be resolved by group meeting and discussion with a third investigator (AH).

If there is missing data, the study will be excluded from the analysis. Foreign language papers will be included and will be translated by medically trained peers fluent in that language (reference peers in acknowledgements).

Quality assessment

We will assess methodological quality by using the "The Cochrane Collaboration's tool for assessing risk of bias". (24) Methodological quality will be taken into account when discussing the results of the meta-analysis.

Data synthesis

The eligible studies will be entered into RevMan5 software package, and the statistical methods will then be programmed into RevMan 5.1 analysis software.

The number in each group and the number of events in each group will be extracted. For the dichotomous data the hazard ratios and risk ratios along with their 95% confidence intervals will be calculated. The results from the trials will then be pooled using the fixed effects and random effects models. We will test for heterogeneity with the Cochran Q statistic, which will be considered to be significant if $p<0.10$. If significant, a random effect model will be used to allow generalisation of the results and sources of heterogeneity will be investigated. Z tests will be used to test for the overall effect.

Dissemination

Hopefully our findings will be presented in the form of journal publications and presentation at medical conferences.

How to deal with protocol amendments during the review

Any modifications to the protocol required during the review will be clearly documented and defined. No alterations will be made that would risk introducing bias.

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