Clinical outcomes with extended duration dual antiplatelet therapy in patients with chronic kidney disease: a meta-analysis of randomized clinical trials

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Study protocol

The protocol was prepared based on the PRISMA 2009 checklist [1].

Rationale The optimum duration of dual antiplatelet therapy (DAPT) in patients with drug eluting stents has been studied in several randomized control trials [2-12]. Three recent meta-analyses showed that shorter DAPT is associated with a lower mortality rate compared with longer DAPT [13-15]. Patients on longer DAPT had more major bleeding events and higher non-cardiac mortality rates. Patients on shorter DAPT had a higher incidence of stent thrombosis and more myocardial infarctions [13-15].

It has been established that patients with chronic kidney disease (CKD) present a higher risk for major adverse cardiovascular events compared with non-CKD patients [16]. This observation has been attributed to a prothrombotic risk associated with CKD that has not been thoroughly explained. At the same time, CKD patients have higher tendency to bleed and an increased risk for major or minor bleeding events has been reported in patients with CKD who are prescribed antiplatelet agents [17].

It is unknown whether dual antiplatelet therapy is more protective in CKD patients compared with aspirin monotherapy due to the higher prothrombotic risk of these patients or whether it increases bleeding complications in a susceptible population and should be avoided. This meta-analysis tries to answer this question.

Objectives The purpose of this meta-analysis is to examine whether shorter DAPT in patients with drug eluting stents and CKD is associated with lower mortality or major adverse cardiovascular event rates compared with longer DAPT. We will also examine whether shorter vs. longer DAPT in CKD patients affects the incidence of myocardial infarction, stent thrombosis, and major bleeding.

Protocol registration The protocol will be registered in the PROSPERO registry (http://www.crd.york.ac.uk/PROSPERO/)

Eligibility criteria All the following should apply:

Study population: patients with cardiovascular disease (coronary artery disease, cerebrovascular disease, or peripheral vascular disease), after implantation of a drug-eluting stent, on DAPT. The studies should also include patients with CKD. CKD will be defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min.1.73 m² or an elevated baseline creatinine.

- Intervention: duration of dual antiplatelet therapy (short vs. long). Short is the minimal duration of DAPT after which the second antiplatelet agent was discontinued and the patients were treated only with aspirin. Long is the period of prolonged DAPT in each clinical trial. The exact duration of DAPT in each study arm has to be reported.
- Study design: randomized-controlled trials, published in the form of an article or abstract. The known meta-analyses will be also reviewed. Given the recent publication of several randomized controlled trials exploring the effect of DAPT on clinical outcomes, we decided not to include non-randomized observational cohort trials.
- At least one of the relevant outcomes should be reported: i) all-cause mortality, cardiovascular mortality, or non-cardiac mortality; ii) major bleeding or any bleeding events rate; iii) incidence of myocardial infarction, stroke, or definite or probable stent thrombosis.
Information source  A MEDLINE literature research will be conducted in PubMed from January 1960 through December 2016. The reference list of all selected studies and the available meta-analyses will also be reviewed.

Study selection Two authors will independently review the literature and select the studies to be included in the meta-analysis based on the aforementioned eligibility criteria. Any discrepancies will be resolved in a conference with the participation of the third author. For feasibility purposes, the corresponding authors of the main trials in the field [2-12] have already been contacted.

Data collection process Two authors will independently extract data from the reports using digital spreadsheets. The investigators will be contacted if more information is needed on the study design and population, especially if the results of the subgroup of patients with CKD have not been published. In case the participating investigators want to share the original data, only de-identified datasets will be requested. This seems to be the case for at least one of the trials, the ITALIC study (after having contacted the corresponding authors of the main trials in the field for feasibility purposes).

Data items The following variables will be extracted: year of publication, study size and location, exclusion criteria respective to the patients renal function, time of randomization to shorter or longer DAPT (in months post percutaneous coronary intervention), duration of DAPT in both study arms, number of patients in each study arm, number of patients with CKD in each study arm, definition of major bleeding events and of stent thrombosis (definite or probable), number of patients with CKD in each study arm, relevant patients characteristics in each arm (age, sex, race, diabetes, hypertension, dyslipidemia, liver disease, smoking status, prior myocardial infarction or stroke, prior PCI or CABG, history of major bleeding, percentage of patients presenting with an acute coronary syndrome (ACS), total lesions stented), number of deaths (cardiac, non-cardiac), major bleeding events, any bleeding events, myocardial infarction, stroke, repeat revascularization, and stent thrombosis (definite or probable, late, very late) in patients with and without CKD. The hazard ratios (with 95% confidence intervals, unadjusted and age- and gender-adjusted, where available) will be also extracted for these outcomes.

Study outcomes The primary outcome will be a composite of all cause mortality, myocardial infarction, stroke, and stent thrombosis (definite or probable). The principle secondary outcome is major bleeding.

Tertiary outcomes are the components of the primary outcome, repeat revascularization, late stent thrombosis (between 30 days and 1 year post-percutaneous coronary intervention (PCI)), very late stent thrombosis (>1 year post-PCI), any bleeding events, intracranial hemorrhage and a net clinical benefit outcome including all the components of the primary and secondary outcome. The endpoint definitions will be applied as defined in each of the included studies. Outcomes will be reported at the maximum available follow-up.
Risk of bias The Jadad score will be used to assess the quality of each study [18]. A separate analysis for all outcomes will be performed excluding studies with a Jadad score of 3 or less.

Summary measures The principal summary measures will be the hazards ratio and the odds ratio.

Synthesis of results The pooled hazard ratio or odds ratio for each outcome will be estimated using a random-effects model. Results will be presented in a forest plot. The $I^2$ index will be used to quantify heterogeneity and assess inconsistency. Heterogeneity will be considered mild, moderate, or severe, based on the following $I^2$ ranges: <25%, 25-50%, >50%. A funnel plot will be drawn to assess for publication bias. The main analysis will be done in the intention-to-treat population. A separate analysis in the per-protocol population will be considered.

Additional analyses The following additional sensitivity analyses have been pre-specified:
- Duration of the DAPT long arm post-randomization (<12 months vs. ≥12 months).
- Patients presenting with an ACS vs. those with elective stenting
- Randomization at PCI vs. randomization at DAPT allocation
- CKD stage 3, CKD stage 4
- Patients with CKD and patients without CKD (eGFR ≥ 60 ml/min.1.73 m² or below the respective creatinine cutoff)

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References