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Efficacy and safety of $P2Y_{12}$ inhibitors according to diabetes, age, gender, body mass index and body weight: Systematic review and meta-analyses of randomized clinical trials

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ABSTRACT

Objective: The efficacy of antiplatelet drugs may differ in specific patient subgroups. We aimed to assess the efficacy and safety of the $P2Y_{12}$ inhibitors clopidogrel, ticlopidine, prasugrel, ticagrelor, and cangrelor according to diabetes status, age, gender, body mass index, and body weight.
Methods: Randomized clinical trials (RCTs) of $P2Y_{12}$ inhibitors reporting information on cardiovascular disease (defined as myocardial infarction, stroke, or cardiovascular death) and bleeding (defined as any bleeding) events among the subgroups diabetes and non-diabetes, age ≥65 and <65 year-old, men and women, body mass index ≥30 and <30 kg/m^2, and body weight ≥60 and <60 kg, were identified in Medline, Embase, Web of Science, and Cochrane Library on August 31st, 2014. For each inhibitor, random-effects meta-analyses were used to estimate the ratio of relative risks (rRR) for cardiovascular and bleeding events among patient subgroups.
Results: Twenty distinct RCTs (233 285 participants, 21 323 cardiovascular and 5183 bleeding events) were identified. Cardiovascular risk reduction with clopidogrel did not significantly differ according to diabetes (rRR: 1.04; 95% CI: 0.95 to 1.13; p = 0.395), age (0.98; 0.88 to 1.09; p = 0.347), gender (0.97; 0.90 to 1.04; p = 0.382), or body mass index (1.11, 0.95 to 1.31; p = 0.191). Results for other inhibitors were comparable, although available data were sparse. Limited data on bleeding events were available.
Conclusion: Data from RCTs did not show a different cardiovascular efficacy of clopidogrel in diabetes mellitus and other clinically relevant subgroups. Limited information was available on the efficacy and safety of other $P2Y_{12}$ inhibitors in specific subgroups.

1. Introduction

Firstly described for acetylsalicylic acid (ASA) treatment, a lower-than-expected efficacy of antiplatelet drugs in the prevention of cardiovascular events has been popularised as drug "resistance", and has generated a widespread interest in its definition, assessment, and clinical implication [1]. A diminished responsiveness to ASA has been reported in different clinical settings, including in patients with type 2 diabetes mellitus (T2DM) [2,3], potentially explaining the apparent failure of ASA in individual trials [4,5] and meta-analyses to reduce the risk of atherothrombotic events in diabetic subjects [6,7]. More recently, the concept of "resistance" has been suggested also for clopidogrel, a pharmacologically different antiplatelet drug ($P2Y_{12}$ inhibitor), and it has been associated with both modifiable and non-modifiable factors, including T2DM, body mass index (BMI), age, gender, smoking, and genetic polymorphisms [8–11].

The vast majority of studies reporting the occurrence of "resistance" to antiplatelet medication have relied on *ex vivo* measurement of platelet function, mainly light transmission or impedance aggregometry, platelet function analyzer PFA-100®, or the VerifyNow® Assay, all evaluating the capacity of platelets to respond to

Abbreviations: ASA, acetylsalicylic acid; BMI, body mass index; RCTs, randomized clinical trials; RR, relative risk; rRR, ratio of relative risk; T2DM, type 2 diabetes mellitus.

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an aggregating stimulus [1,10]. However, the high within-subject variability of such tests, and the unclear relation between *ex vivo* and *in vivo* platelet activation, could explain the varying associations across studies between baseline *ex vivo* "resistance" and cardiovascular outcomes [10], along with the so-far discouraging results of "personalized" antiplatelet therapy [12].

As previously reported [13], a possible method to estimate the presence of drug "resistance" in a specific condition is to compare within a randomized clinical trial (RCT) the relative risk (RR) in subjects who have vs those who do not have the condition of interest (ie, subgroup and interaction analysis). In this context, our aim was to investigate the efficacy and harm of the $P2Y_{12}$ inhibitors clopidogrel, ticlopidine, prasugrel, ticagrelor, and cangrelor according to diabetes mellitus, age, gender, BMI, and body weight.

2. Methods

2.1. Data sources and searches

The systematic review and meta-analysis was conducted according to a pre-specified protocol and followed the PRISMA guidelines for the conduct and reporting of systematic reviews [14]. We searched Medline, Embase, Web of Science, and the Cochrane Library for RCTs of clopidogrel, ticlopidine, prasugrel, ticagrelor, or cangrelor, published before August 31st, 2014 (Supplementary Fig. 1). No language restrictions were applied. Detailed information on the search strategy is provided in the Supplementary Material.

2.2. Study selection

To be included in the present analysis, RCTs were required to report on fatal or non-fatal cardiovascular events and/or any bleeding events within at least one of the subgroups of interest, ie diabetes mellitus, age, gender, BMI, or body weight. Reference lists of eligible studies, as well as systematic reviews and meta-analyses of antiplatelet agents, were manually scanned for additional relevant studies.

2.3. Data extraction and quality assessment

Two authors independently performed the literature search and extracted study information using standardised pre-defined forms. The extracted data included first author name, trial name, publication year, study location, type of study population, type of intervention, definitions of the cardiovascular and bleeding endpoint, duration of follow-up, and the number of participants and events overall and within subgroups. For each study, we extracted information on the overall and subgroup RR estimates with corresponding 95% confidence intervals using the following approaches, in this order: 1) RR as reported by the authors; 2) RR estimated from number of cases and non-cases in each trial arm; 3) correspondence with study authors; 4) use of digital graphic software (Engauge Digitizer; http://digitizer.sourceforge.net/). Studies were combined, according to trial arm interventions, in five treatment groups: clopidogrel vs control (placebo or ASA or clopidogrel lower dose); ticlopidine vs control (placebo or ASA); prasugrel vs control (placebo or clopidogrel); ticagrelor vs control (clopidogrel); cangrelor vs control (clopidogrel). In case the two independent reviewers disagreed on the eligibility of an article or any pieces of the extracted information, consensus was reached by re-evaluation of the article and consultation with a third reviewer. Study quality was assessed using the Cochrane risk of bias tool [15].

2.4. Data synthesis and analysis

Our analysis explored differences according to diabetic status (present vs absent), age ($\geq$75 vs < 75 years and $\geq$65 vs < 65 years), gender (men vs women), BMI ($\geq$30 vs < 30 kg/m^2), and body weight ($\geq$60 vs < 60 kg). When studies reported RRs according to multiple subgroup categories (ie, three age subgroups, <65 year-old, 65-75 year-old and $\geq$75 year-old), the subgroups were combined using a fixed-effect meta-analysis (ie, RR of <75 was estimated combining RRs of <65 and 65–75 age subgroups). In case studies reported RRs for different time-points, we used the RRs for longest follow-up time.

For each study, we firstly compared treatment versus control group (ie, clopidogrel vs. control) separately within each subgroup (ie, in males and in females). Then, we divided these ratios between the subgroups (ie, the clopidogrel vs. control ratio in males was divided by the clopidogrel vs. control ratio in females) [16]. Lastly, we combined these ratios of ratios across studies using the DerSimonian and Laird method for random-effects meta-analysis. Presence of heterogeneity was estimated using the I^2 statistics, and publication bias was assessed through graphical (funnel plot) and formal (regression symmetry) tests [17]. Random-effects meta-regressions were used to assess associations between rRRs and study-level characteristics (duration of follow-up and number of subgroup participants).

Two-sided statistical tests were performed with Stata 12 (Stata Corp, College Station, TX, USA), and results are reported with 95% confidence intervals.

3. Results

3.1. Study characteristics

We identified 27 articles [18–44] published between 1989 and 2013, and reporting data from 20 distinct RCTs (11 clopidogrel vs control; 2 ticlopidine vs control; 3 prasugrel vs control; 1 ticagrelor vs control; and 3 cangrelor vs control).

Study features and quality assessments are reported in Table 1, Supplementary Table 1, and Supplementary Table 2. Fifteen studies (75.4% of the total subjects) were multinational trials, 3 North American (2.7%), and 2 Asian (21.9%). A total of 233 285 subjects participated in the RCTs, of which 21 323 experienced the primary endpoint of a cardiovascular event. Twelve studies (60%) reported on an aggregate of 5183 total bleeding events for one or more subgroup, although definitions of bleeding events differed across studies (Table 1 and Supplementary Table 1).

3.2. Cardiovascular events

3.2.1. Clopidogrel vs control

Eleven studies evaluated clopidogrel in comparison to ASA, placebo, or lower dose of clopidogrel, involving 160 321 participants and 15 076 events (three studies included also all-cause mortality). Information on subgroups was available for diabetes (nine studies and 27 096 participants), age $\geq$75 year-old (three studies; 6936), gender (ten studies; 97 038 men), age $\geq$65 year-old (six studies; 30 627), and BMI $\geq$30 kg/m^2 (two studies; 5207). No subgroup data were available for body weight $\geq$60 kg. Study-specific RRs for subgroups, along with number of participants, are reported in Supplementary Table 3.

The random-effect estimates of rRRs across studies did not show statistically significant difference according to presence of diabetes (rRR, 95% confidence interval: 1.04, 0.95 to 1.13; $p = 0.395$), age $\geq$75 year-old (1.11, 0.89 to 1.38; $p = 0.347$), male sex (0.97, 0.90 to 1.04; $p = 0.382$), age $\geq$65 year-old (0.98, 0.88 to 1.09; $p = 0.650$), or BMI