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The mortality benefit seen with the newer more potent oral $P2Y_{12}$ inhibitors prasugrel and ticagrelor over clopidogrel is dependent on the underlying risk: A class effect as suggested by a meta-regression analysis

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ABSTRACT

Background: The two newer oral $P2Y_{12}$ inhibitors prasugrel and ticagrelor have proven superior to clopidogrel in the treatment of acute coronary syndrome (ACS). The extent to which the reduction in mortality seen with ticagrelor is confined to this particular agent is hard to judge by simply looking at the overall study results as the study populations were composed of different cohorts at substantially different risk of death.

Methods: A meta-regression technique was applied to 12 distinctive patient cohorts, six for each of prasugrel and ticagrelor, to investigate differential effects on mortality of $P2Y_{12}$ inhibitors.

Results: Data for the analysis cohorts, totalling 37,372 patients, were extracted from publications and cover a widely comparable spectrum of patient types, defined by the type of ACS and treatment strategy. The meta-regression lines for cardiovascular mortality with prasugrel or ticagrelor (each versus clopidogrel), as well as for both agents pooled, indicate a linear relationship with increasing benefit seen with higher underlying risk ($p = 0.007$, 0.021 and 0.003, and $R^2 = 0.87$, 0.77 and 0.62, respectively).

Conclusions: In the ACS patients studied, we found a mortality benefit with the two newer oral $P2Y_{12}$ inhibitors prasugrel and ticagrelor when compared with clopidogrel, which increases progressively as the underlying risk of death increases. This appears to be a class effect for these two newer agents.

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Introduction

Inhibition of $P2Y_{12}$-mediated platelet aggregation is a cornerstone in the treatment of acute coronary syndrome (ACS). As there are limitations in the metabolic generation of the active metabolite of clopidogrel [1], prasugrel and ticagrelor were developed to provide stronger and more consistent inhibition of platelet aggregation. Prasugrel still is a pro-drug, however, the production of the active metabolite occurs more quickly and with less inter-individual variability than clopidogrel [1], while ticagrelor is an active molecule with an active metabolite that also contributes to its pharmacodynamic activity [2]. In the initial phase 3 studies TRITON-TIMI 38 and PLATO, both agents have proven superior to clopidogrel in preventing ischaemic complications, accompanied with some increase in the risk of bleeding [3,4]. However, their effect on mortality is less clear. The extent to which the overall reduction in mortality seen with ticagrelor versus clopidogrel [4] is confined to this particular agent is hard to judge by simply looking at the overall results, as the study populations in the prasugrel and ticagrelor phase 3 studies were composed of different patient cohorts at substantially different risk of death [5]. As the available body of evidence mainly consists of the aforementioned phase 3 studies, meta-analyses do not provide much additional understanding of the question of mortality [6–12]. To obtain further insight to the question of a potential differential effect between the two newer oral $P2Y_{12}$ inhibitors with regards to mortality in ACS patients, less confounded by the composition of the study populations, we conducted an analysis using meta-regression techniques applied to data from patient cohorts at different risk of mortality, defined by type of ACS and treatment strategy.

Methods

A literature search was carried out for peer-reviewed publications up to March 2016 reporting randomized controlled trials (RCTs) of prasugrel or ticagrelor versus clopidogrel in patients with ACS, preferably verified by angiography, with the dosage of the agents reflecting the standard adult dose. Reports were selected if they provided mortality data, preferably cardiovascular (CV) death, at follow-up centred around 1 year (>6 month and <18 month) from start of therapy. CV death was chosen as the endpoint as it most closely captures events of deaths related to the direct antiplatelet activity of these agents, including the potential impact of a suggested ''pleiotropic'' effect specific to ticagrelor, and being least confounded by events potentially related to co-morbidities frequently seen in ACS populations. We included distinctive study cohorts for the phase 3 studies TRITON TIMI-38, PLATO and TRILOGY, defined by ACS type and/or treatment strategy. Our analysis included recently reported data for more specific cohorts (e.g. for patients with primary percutaneous coronary intervention [PCI] only, or those who have undergone coronary artery bypass graft [CABG]). In some older reports, the cohorts were composed of more than one patient type, e.g. groups comprised all non-ST-segment elevation ACS (NSTE-ACS) patients or all ST-segment elevation myocardial infarction (STEMI) patients. In order to minimize the overlap between cohorts, we split larger samples where possible, e.g. we singled out CABG cases or primary PCI cases from larger samples where they were nested. In order to this we worked with raw event rates (n/N). In the few cases where only Kaplan–Meier estimates were provided, we used these to calculate n/N. Summary statistics are provided as hazard ratios (HRs) and 95% confidence intervals (CIs). The HRs were calculated based on raw event rates under the assumption of an exponential distribution. A fixed-effects meta-regression analysis for the natural logarithm of the hazard ratio (ln HR) for CV mortality versus clopidogrel, depending on the hazard in the respective clopidogrel anchor arm, was carried out using SAS 9.3. The weight of each study was defined as the reciprocal of the variance of the ln HR. Results are reported as the coefficient of determination (R^2) and the corresponding p-value for the model; we also report the parameters defining the meta-regression lines. These are reported for prasugrel and ticagrelor separately and for the two agents pooled.

Results

Data from 10 publications, five each for prasugrel and ticagrelor, reporting long-term mortality for patient cohorts from TRITON-TIMI 38, TRILOGY and PLATO, as well as from two dedicated Asian-population studies, were eligible for our analysis (Table 1) [13–22]. Six distinctive cohorts were extracted for each agent, covering a widely comparable spectrum of patient types. For prasugrel these were: primary PCI, secondary PCI, NSTE-ACS with PCI, NSTE-ACS without revascularization (RV), CABG cases and an Asian population; 17,947 cases in total. For ticagrelor the cohorts were: primary PCI, STEMI other than primary PCI, NSTE-ACS with PCI, NSTE-ACS without RV, CABG cases and an Asian population; 19,425 cases in total. The NSTE-ACS with PCI cohorts for both agents were created by removing the CABG cases [15,21] from a wider sample comprised of NSTE-ACS with interventions [14,20]. For ticagrelor, the cohort STEMI other than primary PCI was created by removing the primary PCI cases [18] from a wider STEMI sample [19].

Fig. 1 shows the relationship between the patient's risk profile in the clopidogrel anchor arm and the benefit in terms of long-term cardiovascular mortality seen with prasugrel and ticagrelor when compared with clopidogrel. The meta-regression lines for prasugrel and ticagrelor, as well as for both agents pooled (Fig. 1 and Table 2), indicate a linear relationship with increasing benefit seen with higher underlying risk ($p = 0.007$, 0.021 and 0.003, and $R^2 = 0.87$, 0.77 and 0.62, for prasugrel, ticagrelor and pooled data, respectively).

Discussion

The main finding of our analysis is that in patients with ACS we saw an incremental mortality benefit with both newer and more potent oral $P2Y_{12}$ inhibitors prasugrel and ticagrelor when compared with clopidogrel, which was dependent on the patient's underlying risk of death as defined by type of ACS and treatment strategy, presenting as a gradient of efficacy.

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