The mortality benefit seen with the newer more potent oral P2Y12 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 P2Y12 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 P2Y12 inhibitors.

Klíčová slova:
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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 (Figure 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 R² = 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 P2Y₁₂ 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. The class effect demonstrated by our analysis might be considered surprising at first glance, when having in mind the full study results of TRITON and PLATO. However, our finding is not entirely new as the idea that the composition of the study population rather than the respective newer P2Y₁₂ inhibitor drives the mortality benefit when compared with clopidogrel was introduced in 2011 by De Servi [5]. Five years later, after more data from cohorts of TRITON and PLATO have been released, we could formally test this hypothesis by applying meta-regression techniques to the extended set of data now available.

Such a gradient of efficacy follows the broad experience of physicians that more potent treatments have greater benefits in patients at higher risk, as noted, for example, with anti-depression medication [23]. Applying such a concept to a mortality benefit from antithrombotic agents needs careful examination, as besides preventing ischaemic complications potentially resulting in death, more potent agents are associated with increased risk of bleeding, which is potentially fatal [24], thus there may be an underlying J-shaped kinetic with regards to antithrombotic power.

In that context, it is noteworthy that for both newer P2Y₁₂ inhibitors the largest proportional reduction in mortality was observed in the CABG cohorts; not a new finding either as this was reported in 2011/2012 [15,21]. Both CABG cohorts were at the higher end of mortality rates in the clopidogrel anchor arms in our analysis. Strikingly, a substantial benefit in terms of mortality was reported when CABG was performed after treatment with prasugrel or ticagrelor. This was independent of the...
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Table 1 – Patient cohorts for meta-regression analysis.

| Cohort            | N all | New P2Y12 inhibitor, N | Clopidogrel, N | CV death: new P2Y12 inhibitor, % (n) | CV death: clopidogrel, % (n) (baseline risk) | HR | In HR | Inverse of variance of ln HR (weight) | Source |
|-------------------|-------|------------------------|----------------|--------------------------------------|-----------------------------------------------|-----|-------|--------------------------------------|--------|
| Prasugrel         |       |                        |                |                                      |                                               |     |       |                                      |        |
| pPCI              | 2340  | 1152 1188              |                | 2.34% (27)                            | 3.54% (42)                                    | 0.66| –0.42| 17.2                                 | TRITON [13]|
| sPCI              | 1085  | 559 526                |                | 2.50% (14)                            | 2.85% (15)                                    | 0.88| –0.13| 7.2                                  | TRITON [13]|
| NSTE-ACS with PCI | 9728  | 4871 4857              |                | 1.79% (87)                            | 1.65% (80)                                    | 1.09| 0.08 | 41.7                                 | TRITON [14,15]|
| NSTE-ACS without RV | 3085 | 1524 1561              |                | 2.97% (45)                            | 2.88% (44)                                    | 1.03| 0.03 | 22.2                                 | TRILOGY [16]|
| CABG              | 346   | 173 173                |                | 1.73% (3)                             | 6.94% (12)                                    | 0.24| –1.42| 3.8                                  | TRITON [15]|
| Asian population  | 1363  | 685 678                |                | 1.46% (10)                            | 1.18% (8)                                     | 1.24| 0.21 | 4.5                                  | PRASFIT [17]|
| Total             | 17947 |                        |                |                                      |                                               |     |       |                                      |        |
| Ticagrel          |       |                        |                |                                      |                                               |     |       |                                      |        |
| pPCI              | 4949  | 2463 2486              |                | 3.57% (88)                            | 3.82% (95)                                    | 0.93| –0.07| 45.7                                 | PLATO [18,19]|
| STEMI other than pPCI | 2595 | 1289 1306              |                | 5.51% (71)                            | 7.66% (100)                                   | 0.71| –0.34| 42.7                                 | PLATO [20,21]|
| NSTE-ACS with PCI | 4456  | 2244 2212              |                | 0.98% (22)                            | 0.86% (19)                                    | 1.14| 0.13 | 10.2                                 | PLATO [20,21]|
| NSTE-ACS without RV | 5366 | 2708 2658              |                | 4.07% (110)                           | 5.44% (147)                                   | 0.74| –0.30| 64.2                                 | PLATO [20]|
| CABG              | 1258  | 629 629                |                | 3.97% (25)                            | 7.47% (47)                                    | 0.52| –0.65| 18.0                                 | PLATO [21]|
| Asian population  | 801   | 401 400                |                | 2.24% (9)                             | 1.75% (7)                                     | 1.28| 0.25 | 4.0                                  | PHILO [22]|
| Total             | 19,425|                        |                |                                      |                                               |     |       |                                      |        |

ACS – acute coronary syndrome; CABG – coronary artery bypass graft; CV – cardiovascular; HR – hazard ratio; KM – Kaplan–Meier; In HR – natural logarithm of the hazard ratio; NSTE – non-ST-segment elevation; PCI – percutaneous coronary intervention; pPCI – primary PCI; RV – revascularization; sPCI – secondary PCI; STEMI – ST-segment elevation myocardial infarction.

a KM estimate (and n derived from KM estimate); b calculated by subtracting CABG events with n derived from KM estimate [16]; c calculated subtracting CABG events from events with n derived from KM estimate [20].

Table 2 – Parameters and measures of goodness of fit for the meta-regression lines.

| Regression line | p-Value (model) | R² |
|-----------------|-----------------|----|
| Prasugrel       | 0.0066          | 0.871 |
| Ticagrel        | 0.0212          | 0.772 |
| Combined        | 0.0025          | 0.616 |

R² – coefficient of determination.

observed that in patients undergoing CABG after treatment with prasugrel there was an increase in bleeding and platelet transfusions (but not transfusions of red blood cells) when compared with the clopidogrel group, which was not seen with ticagrelor [15,21]. As in both studies about two-thirds of the CABG patients resumed their assigned study drug after the procedure, this probably accounts for a part of the mortality benefit. To what extent more residual P2Y12 inhibition with prasugrel or ticagrelor when CABG took place closer to the last drug intake contributed to this finding, potentially by preventing platelet activation and consumption by the procedural techniques, would warrant further investigation.

When considering antiplatelet agents besides P2Y12 inhibitors, a gradient of efficacy has been reported previously for the glycoprotein (GPIIb/IIIa)-inhibitor abciximab when given as adjunct to primary PCI [25].

To explain the striking reduction in mortality, as well as specific side-effects seen with ticagrelor in PLATO, a mode of action besides platelet inhibition has been suggested that directly affects adenosine metabolism by inhibiting the type 1 equilibrative nucleoside transporter (ENT1) [26,27]. Recent functional data, however, question if the plasma concentration of ticagrelor after normal dosing in humans is sufficient to result in a significant increase in extracellular adenosine and adenosine receptor stimulation via this mechanism [28]. The result of our analysis does not require an additional “pleiotropic” effect of ticagrelor to explain its effect (and that of prasugrel) on mortality. As we account for the differing compositions of the trial populations, our data suggest a class effect. If any, the steeper slope of the meta-regression line we obtained for prasugrel might suggest slightly more potential for benefit with prasugrel than with ticagrelor, provided there is substantial risk, such as that for primary PCI patients [13,29], or in patients with PCI of the unprotected left main coronary artery [30].

Further insight regarding the outcome with the two new agents will be derived from the currently ongoing ISAR-REACT 5 study, which compares prasugrel with ticagrelor in ACS [31]. This study is projected to report the primary endpoint towards the end of 2016 (clinicaltrials.gov). However, the planned sample size of 4000 patients may limit the potential to provide a definitive answer regarding mortality. This has also been a limitation of the recently reported Czech head-to-head comparison of the two agents in 1230 patients with acute MI treated with primary or immediate PCI. Neither the primary endpoint nor the components of it, including mortality, differed between groups receiving prasugrel or ticagrelor. Death from cardiovascular causes was reported at similar 30-day rates of 1.3% for both agents (HR 0.94, 95% CI 0.35–2.52,
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