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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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SOUHRN

Kontext: Je prokázáno, že prasugrel a ticagrelor, dva nové perorální inhibitory $P2Y_{12}$, jsou v léčbě akutních koronárních syndromů (AKS) obecně výhodnější než clopidogrel. Míru snížení mortality pozorovanou konkrétně v případě ticagreloru lze těžko posoudit pouhým pohledem na celkové výsledky studií, protože hodnocené populace zahrnovaly různé kohorty s podstatně odlišným rizikem úmrtí.
Metody: Byla provedena regresní metaanalýza údajů 12 různých kohort pacientů, přičemž šest kohort užívalo prasugrel a dalších šest ticagrelor; cílem metaanalýzy bylo zkoumat účinky uvedených inhibitorů $P2Y_{12}$ na mortalitu.
Výsledky: Údaje pro analýzu kohort (celkem 37 372 pacientů) byly získány z publikací a zahrnují z mnoha hledisek srovnatelné spektrum různých typů pacientů, definované typem AKS a strategií léčby. Linky mortality z kardiovaskulárních příčin vynesené pomocí údajů z regresní metaanalýzy výsledků léčby prasugrelem nebo ticagrelorem samostatně, případně souhrnných výsledků léčby těmito látkami (vždy ve srovnání s clopidogrelem), ukazují na lineární vztah mezi zvyšujícím se přínosem a zvyšujícím se základním rizikem (p = 0,007; 0,021 a 0,003 a R^2 = 0,87; resp. 0,77 a 0,62).
Závěry: U hodnocených pacientů s AKS jsme zaznamenali přínos podání dvou nových perorálních inhibitorů $P2Y_{12}$ ve srovnání s clopidogrelem; přínos se postupně zvětšuje se zvyšujícím se základním rizikem úmrtí. Zdá se, že se jedná o účinek inhibitorů $P2Y_{12}$ jako lékové skupiny.

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.

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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.

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

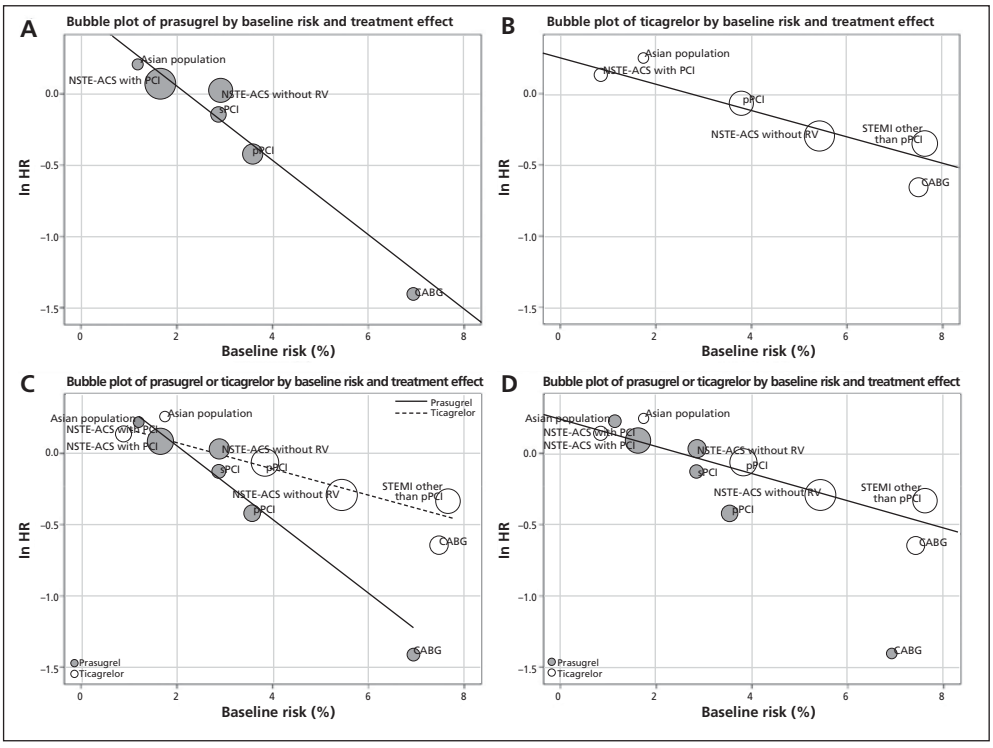

Fig. 1 – Effect on mortality (ln hazard ratio) by underlying risk in the clopidogrel anchor arm. (A) prasugrel, (B) ticagrelor, (C) prasugrel and ticagrelor with individual regression lines and (D) regression line for pooled prasugrel and ticagrelor.
Negative values of the ln HR (y-axis) mean greater benefit in mortality associated with prasugrel or ticagrelor compared with clopidogrel, whereas the risk in the clopidogrel anchor arm (x-axis) represents the risk profile of the respective cohort. The size of the circle corresponds to the inverse variance of the ln hazard ratio and indicates the statistical weight of the sample.
ACS – acute coronary syndrome; CABG – coronary artery bypass graft; ln 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.

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 $R^2 = 0.87$, 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. 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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

Table 1 – Patient cohorts for meta-regression analysis.

Cohort	*N* all	New $P2Y_{12}$ inhibitor, *N*	Clopidogrel, *N*	CV death: new $P2Y_{12}$ inhibitor,% *(n)*	CV death: clopidogrel, % (*n*) (baseline risk)	HR	ln 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)[b]	1.65% (80)[b]	1.09	0.08	41.7	TRITON [14,15]
NSTE-ACS without RV	3085	1524	1561	2.97% (45)[a]	2.88% (44)[a]	1.03	0.03	22.2	TRILOGY [16]
CABG	346	173	173	1.73% (3)[a]	6.94% (12)[a]	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								
Ticagrelor									
pPCI	4949	2463	2486	3.57% (88)	3.82% (95)	0.93	–0.07	45.7	PLATO [18]
STEMI other than pPCI	2595	1289	1306	5.51% (71)	7.66% (100)	0.71	–0.34	42.7	PLATO [18,19]
NSTE-ACS with PCI	4456	2244	2212	0.98% (22)[c]	0.86% (19)[c]	1.14	0.13	10.2	PLATO [20,21]
NSTE-ACS without RV	5366	2708	2658	4.07% (110)[a]	5.44% (147)[a]	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; ln 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)	R^2
Prasugrel	y = –0.260x + 0.575	0.0066	0.871
Ticagrelor	y = –0.092x + 0.248	0.0212	0.772
Combined	y = –0.095x + 0.227	0.0025	0.616

R^2 – coefficient of determination.

observation 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 $P2Y_{12}$ 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 $P2Y_{12}$ 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,

p = 0.901) [32]. These numbers from a first direct comparison of the two agents, with the limitation regarding power acknowledged, would fit with the conclusion of the meta-regression analysis reported here.

Limitations

Our analysis is based on aggregate data retrieved from publications, and for three cohorts raw event rates were not available so we used KM estimates (as indicated in the footnote of Table 1). For both agents, two cohorts were numerically created by removing CABG cases from larger NSTE-ACS cohorts, based on the fact that the majority of the CABG cases entered the trials under the diagnosis of NSTE-ACS. One additional cohort for ticagrelor was created by removing primary PCI cases from a larger STEMI cohort. Based on the follow-up schedules of the respective trials, the follow-up period for our endpoint was slightly different between treatments: 15 months for prasugrel (except for the Asian population with 48 weeks) compared with 12 months, generally, for ticagrelor.

Conclusion

When the confounding differences in composition of study populations were accounted for by means of meta-regression techniques, we found a mortality benefit with the two oral $P2Y_{12}$ inhibitors prasugrel and ticagrelor when compared with clopidogrel; this benefit increased progressively with the underlying risk of death. This appears to be a class effect for these two newer and more potent agents. Our data do not suggest that the mortality benefit is confined to ticagrelor only.

Conflicts of interest

J. Wouter Jukema/his department has received research grants from and/or was speaker (with or without lecture fees) on a.o. (CME accredited) meetings sponsored by AstraZeneca, Bayer, Daiichi Sankyo, Lilly, Medtronic, Merck-Schering-Plough, Pfizer, Sanofi Aventis, The Medicine Company, the Netherlands Heart Foundation, CardioVascular Research the Netherlands (CVON), the Interuniversity Cardiology Institute of the Netherlands and the European Community Framework KP7 Programme.
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Ethical statement

Authors state that the research was conducted according to ethical standards.

Informed consent

The authors declare that informed consent was obtained from the patient participating in this study.

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