Network meta-analysis of prasugrel, ticagrelor, high- and standard-dose clopidogrel in patients scheduled for percutaneous coronary interventions

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Summary
Since novel antiplatelet treatments (prasugrel, ticagrelor, high-dose clopidogrel) have been predominantly tested against standard-dose clopidogrel, data on direct comparisons between these therapies are scarce. We therefore indirectly compared their efficacy and safety in patients undergoing percutaneous coronary intervention. Electronic databases were searched systematically to identify head-to-head randomised controlled trials (RCTs). Network meta-analysis was performed using generalised linear mixed models with adjustment for length of follow-up. Findings were corroborated by mixed treatment comparison through Bayesian methods. Fourteen RCTs were identified and included in the analysis (high- vs. standard-dose clopidogrel: 9 trials, prasugrel vs. high-dose clopidogrel: 2 trials, prasugrel vs. standard-dose clopidogrel: 2 trials, ticagrelor vs. standard-dose clopidogrel: 1 trial). No significant differences were found for efficacy outcomes except for stent thrombosis favouring prasugrel (vs. ticagrelor: odds ratio [OR] 0.63, 95% confidence interval [CI]: 0.42, 0.94; vs. high-dose clopidogrel: OR 0.70, 95%CI: 0.48, 1.01). Prasugrel exhibited a similar bleeding risk as high-dose clopidogrel, but more major (OR 1.43, 95%CI 1.07, 1.90) and minor or minor bleeding (OR 1.36, 95%CI 1.09, 1.69) compared to ticagrelor. Ticagrelor was also associated with less major or minor bleeding compared to high-dose clopidogrel (OR 0.81, 95%CI 0.69, 0.96). No differences were seen for non CABG-related major bleeding between the three strategies. Results were corroborated in a subgroup analysis comprising only patients with acute coronary syndromes. In the absence of head-to-head clinical trials, network meta-analysis suggests potentially relevant differences in efficacy and bleeding risk among novel antiplatelet treatments and may thereby advance understanding of their differential therapeutic properties.

Keywords
Antiplatelet agents, meta-analysis, percutaneous coronary intervention

Introduction
Dual antiplatelet therapy (DAPT) consisting of aspirin and clopidogrel has become a cornerstone in the treatment of patients undergoing percutaneous coronary intervention (PCI) to prevent ischaemic events and stent thrombosis (1, 2). However, over the past years, several drawbacks of clopidogrel therapy have been identified, such as slow onset of action, irreversibility of platelet inhibition, potential drug-drug interactions, and a wide variability of platelet response including both increased and decreased responsiveness (3–5). A growing number of studies have linked high platelet reactivity despite clopidogrel treatment to an increased risk of major cardiovascular (CV) events, in particular stent thrombosis (6–9). Pharmacogenetic studies have further identified genetic polymorphisms, mainly in the hepatic cytochrome P450 (CYP) 2C19 system, leading to an alteration in the metabolite levels of clopidogrel and, subsequently, its antiplatelet effects (4, 10). The reduced-function CYP2C19 genotype was also shown to be associated with adverse clinical outcome in some but not all studies (10–12).

These limitations fostered the development of novel drugs with a more consistent and predictable antiplatelet efficacy compared to clopidogrel. So far, prasugrel and ticagrelor showed the most promising results in large, phase III clinical trials, where both drugs have been compared against the current standard treatment with clopidogrel in order to gain approval by regulatory agencies. Prasugrel is a third-generation thienopyridine, which has to be converted to an active form before binding irreversibly to the ADP receptor and inhibiting platelet aggregation (13). Ticagrelor is a direct-acting and reversible inhibitor of the ADP receptor, that has a shorter half-life and requires twice-daily dosing (14). Both new
drugs have a rapid onset of action and are not affected by CYP2C19 polymorphisms. Alternatively, an increase of clopidogrel dosage has been proposed to tackle clopidogrel hypo-responsiveness, which was also tested in large clinical trials (2, 15, 16).

To date, these treatment strategies have been predominantly compared against standard-dose clopidogrel but not against each other, so that the selection of any among newer antiplatelet strategies cannot be based on direct comparisons.

In areas where treatments of interest have not been directly compared network meta-analysis may provide such comparative information (17). A key difference between traditional and network meta-analysis is the choice of the comparator: While in traditional meta-analysis all included studies compare the same intervention with the same comparator (e.g. placebo), network meta-analysis includes multiple pairwise comparisons across a range of interventions. Thus, all available evidence can be taken into account from both direct and indirect comparisons, multiple treatments can be compared simultaneously and it does not depend on a common chosen comparator treatment.

In this study, we aimed to indirectly compare prasugrel, ticagrelor, high- and standard-dose clopidogrel in patients scheduled for PCI by network meta-analysis. As recommended we incorporated this network meta-analysis in a standardised systematic review procedure with performance of a traditional meta-analysis (18).

Methods

Search strategy

A systematic literature review was performed with the help of a medical information scientist using an OVID interface for the electronic databases EMBASE and MEDLINE through May 24th, 2011. Relevant randomised controlled trials were identified by a combination of medical subject headings without subheading restrictions and key words including the following terms: cardiovascular disease, stents, angioplasty, percutaneous coronary intervention, platelet aggregation inhibitors, clopidogrel (high-dose OR high dose OR 150), prasugrel, ticagrelor. In addition, hand-searching of bibliographies of included articles, relevant systematic and non-systematic reviews and selected cardiovascular journals was performed to identify possible references not otherwise found. No language or time restrictions were enforced. Reviews for the advisory committee of the American Food and Drug Administration (FDA), Division of Cardiovascular and Renal Products, on prasugrel and ticagrelor (19, 20), and entries into the clinicaltrials.gov database were also used as a source of information.

Inclusion/exclusion criteria and study selection

Inclusion criteria comprised randomised controlled trials (RCT) enrolling patients scheduled for and/or undergoing PCI with percutaneous coronary intervention to any of the following treatments on top of aspirin: high- and standard-dose clopidogrel, prasugrel and ticagrelor. Minimum duration of follow-up was pre-defined as two weeks. High-dose clopidogrel was defined as a maintenance dose of clopidogrel at least twice the standard dose (75 mg). For multi-dose trials, only the dosage, which is equivalent to the one for which approval was sought at regulatory boards in North America and Europe was included, i.e. prasugrel 10 mg daily (60 mg loading dose) and ticagrelor 90 mg bid (180 mg loading dose). If none of these were used, the most similar dosage would be chosen. For cross-over trials, results from the pre-cross-over phase were included.

A subgroup analysis was performed comprising only studies in patients with acute coronary syndrome (ACS).

Outcomes

Primary efficacy outcome was all-cause death. In addition, data on CV death, myocardial infarction (MI), stroke, and stent thrombosis were extracted. We also analysed the composite end point of major adverse cardiac events (MACE) as defined in the included clinical trials. When stent thrombosis (ST) was categorised according to the definition of the Academic Research Consortium (21), definite or probable ST was chosen, otherwise ST was included as described in the clinical trial. One study captured clinical target vessel thrombosis instead of ST (22).

For bleeding outcomes, major bleeding was chosen as primary endpoint, minor and major or minor bleeding data were considered as secondary endpoints. Bleeding results classified according to TIMI (Thrombolysis In Myocardial Infarction) criteria were chosen if available (23). Otherwise bleeding results were included as described in the trials. GUSTO severe/moderate bleeding was considered as major, any GUSTO as major or minor bleeding. As some trials also reported non-coronary artery bypass graft (CABG)-related major bleeding separately, an additional analysis was performed using this outcome instead of total major bleeding when reported. Authors were contacted to obtain missing data. If no response was received, analysis was performed without these data.

Data extraction and quality assessment

All information was extracted using a standardised data abstraction form created in Excel® by two independent reviewers (SS, DM). Abstraction included: 1) characteristics of trial participants including severity of disease (e.g. stable or unstable CV disease), the presence of high-on treatment platelet reactivity (HTPR) and proportion of patients actually undergoing PCI; 2) type of intervention including dose (in particular use of a loading dose) and duration of treatment as well as follow-up; 3) results of efficacy and safety outcomes of the intervention. Methodological quality...
assessments were performed using the Cochrane Collaboration’s tool for assessing risk of bias addressing adequacy of randomisation and allocation concealment, blinding (participants/personnel and outcome assessment), completeness of outcome data, selective reporting and the presence of any other bias (24).

Statistical analysis

For traditional meta-analysis, pooled odds ratio (OR) and 95% confidence interval (CI) were calculated for the differences in outcome for each head-to-head comparison based on an intention-to-treat analysis. A formal assessment of statistical heterogeneity was made using the I² test statistics, which quantifies the percentage of the variability that is due to heterogeneity rather than chance (25). Values of 25%, 50%, and 75% were assigned to low, moderate, and high degree of heterogeneity (25). In case of significant heterogeneity (I²>50%), results were pooled using the random effects DerSimonian and Laird model (26), otherwise fixed effects models were performed according to the Mantel-Haenszel method. If one treatment group had zero events, a 0.5 adjustment was automatically made to the numerator. RevMan 5.1 software (Cochrane Collaboration) was used for all analyses. The number needed to treat (NNT) was calculated as the reciprocal of the absolute risk difference. CIs are Newcombe-Wilson hybrid score confidence intervals, without a continuity correction (27).

For network meta-analysis, a binomial, generalised linear mixed model (GLIMMIX) was separately fitted for each outcome to combine direct and indirect evidence and estimate OR and 95% CI. The models included fixed treatment effects and normally distributed random study effects, and were adjusted for mean length of follow-up. All analyses were performed using PROC GLIMMIX as implemented in SAS version 9.2. In a second step, results were validated through a mixed treatment comparison (MTC) using Bayesian statistical methods as introduced by Lu and Ades (28). Posterior distributions for all parameters of the MTC analysis were derived using Gibbs sampling via Markov Chain Monte Carlo simulation in WinBUGS (Version 1.4). Results are presented as OR and 95% credible intervals (CrI). According to prior analyses in the field we anticipated a small number of included trials (29, 30), which limits the applicability of random effects models because vague and weak informative prior distributions of the between-study variance have been shown to exert an unintentionally large degree of influence on any inference (31). Fixed effect models using vague prior distributions for all means were performed, which also allowed ranking of all treatment options by probability being the most efficacious.

Results

Search results

The systematic search strategy yielded 1489 study reports of potential interest after removal of 154 duplicates. A total of 1,449 reports were excluded upon inspection of the title and/or abstract, thus 40 references were screened by full text. The review process is depicted in Figure 1. From the 14 randomised, controlled trials (RCTs) included, nine studies compared high-dose versus standard-dose clopidogrel (including one study reported as conference abstract only) (16, 32–39), two prasugrel versus standard-dose clopidogrel (22, 40), two prasugrel versus high-dose clopidogrel (41, 42), and one trial compared ticagrelor versus standard-dose clopidogrel (43). Only one multi-dose trial was identified (22), and results from the comparison of 10 mg prasugrel maintenance dose with standard-dose clopidogrel were included for analysis. Detailed
Characteristics of the included studies are given in Table 1 and the network of studies is presented in an online appendix (see Suppl. Fig. 1, available online at www.thrombosis-online.com). Five studies comprised only patients with ACS, which were included in the respective subgroup analysis (36, 38–40, 43). Three studies included only patients with high on-clopidogrel treatment platelet reactivity (16, 37, 42), while this information was not available from any other study. The highest number of patients was available for the comparison high versus standard-dose clopidogrel (n=21,150) followed by prasugrel versus standard-dose clopidogrel (n=14,512), ticagrelor versus standard-dose clopidogrel (n=13,408) and prasugrel versus high-dose clopidogrel (n=213). Importantly, three studies in patients with unstable disease (OASIS-7 PCI, TRITON TIMI 38, PLATO invasive) (39, 40, 43) contributed almost 90% of all patients. Detailed results for the main endpoints from these studies including absolute event rates are given in Table 2.

Table 1: Included studies.

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>N</th>
<th>Study design</th>
<th>Maximal follow-up</th>
<th>Population</th>
<th>PCI</th>
<th>Intervention LD/MD mg (duration)</th>
<th>Comparator LD/MD mg</th>
<th>Included end-points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abuzahra (2008)</td>
<td>119</td>
<td>RCT, groups ratio 2:1</td>
<td>30 days</td>
<td>STEMI: 5% NSTE-ACS: 39% SCAD: 56% HTPR: NA</td>
<td>100%</td>
<td>Clopidogrel 600/150 mg (30 days)</td>
<td>Clopidogrel, 300/75 mg</td>
<td>All-cause/CV death, MI, MACE1, stent thrombosis, major/ minor bleeding</td>
</tr>
<tr>
<td>Angiolillo (2008)</td>
<td>40</td>
<td>RCT</td>
<td>60 days, 30 days active phase*</td>
<td>STEMI: 0% NSTE-ACS: 0% SCAD: 100% HTPR: 100%</td>
<td>100%</td>
<td>Clopidogrel 600/150 mg (30 days)</td>
<td>Clopidogrel, 300/75 mg</td>
<td>All-cause/CV death, MI, stroke, stent thrombosis, major/ minor bleeding</td>
</tr>
<tr>
<td>DOSER (2010)</td>
<td>74</td>
<td>RCT, double-blind</td>
<td>1 year</td>
<td>STEMI: 0% NSTE-ACS: 0% SCAD: 100% HTPR: NA</td>
<td>100%</td>
<td>Clopidogrel 600/150 mg (28 days)</td>
<td>Clopidogrel 600/75 mg</td>
<td>MACE1, major/ minor bleeding</td>
</tr>
<tr>
<td>DOUBLE (2010)</td>
<td>54</td>
<td>RCT</td>
<td>1 month</td>
<td>STEMI: 100% NSTE-ACS: 0% SCAD: 0% HTPR: 100%</td>
<td>100%</td>
<td>Clopidogrel 300/150 mg (1 month)</td>
<td>Clopidogrel 300/75 mg</td>
<td>All-cause/CV death, MI, stroke, stent thrombosis, major/ minor bleeding</td>
</tr>
<tr>
<td>GRAVITAS (2011)</td>
<td>2214</td>
<td>RCT, double-blind</td>
<td>6 mo</td>
<td>STEMI: &lt;1% NSTE-ACS: 39% SCAD: 60% HTPR: NA</td>
<td>100%</td>
<td>Clopidogrel 300–600 / 150 mg (6 months)</td>
<td>Clopidogrel 300–600/ 75 mg</td>
<td>All-cause/CV death, MI, MACE2, stent thrombosis, major/ minor bleeding</td>
</tr>
<tr>
<td>Han (2009)</td>
<td>813</td>
<td>RCT</td>
<td>30 days</td>
<td>STEMI: 75% NSTE-ACS: 25% SCAD: 0% HTPR: NA</td>
<td>100%</td>
<td>Clopidogrel 600/150 mg (30 days)</td>
<td>Clopidogrel 600/75 mg</td>
<td>All-cause/CV death, MI, MACE3, stent thrombosis, major/ minor bleeding</td>
</tr>
<tr>
<td>OASIS-7 PCI (2010)</td>
<td>17263</td>
<td>RCT, double-blind</td>
<td>30 days</td>
<td>STEMI: 37% NSTE-ACS: 63% SCAD: 0% HTPR: NA</td>
<td>100%</td>
<td>Clopidogrel 600/150 mg (7 days)</td>
<td>Clopidogrel 300/75 mg</td>
<td>All-cause/CV death, MI, stroke, MACE3, stent thrombosis, major/ minor bleeding</td>
</tr>
<tr>
<td>VASP-02 (2008)</td>
<td>153</td>
<td>RCT, groups ratio 2:3</td>
<td>30 days</td>
<td>STEMI: 0% NSTE-ACS: 0% SCAD: 100% HTPR: NA%</td>
<td>100%</td>
<td>Clopidogrel 300–600/150 mg (30 days)</td>
<td>Clopidogrel 300–600/75 mg, at 14 days 150 mg when HTPR**</td>
<td>CV death, MI, stroke, stent thrombosis, major/ minor bleeding</td>
</tr>
<tr>
<td>Von Beckerath (2007)</td>
<td>60</td>
<td>RCT, double-blind</td>
<td>30 days</td>
<td>STEMI: 0% NSTE-ACS: 0% SCAD: 100% HTPR: NA%</td>
<td>100%</td>
<td>Clopidogrel 600/150 mg (30 days)</td>
<td>Clopidogrel 600/75 mg</td>
<td>All-cause/CV death, MI, stent thrombosis, major/minor bleeding</td>
</tr>
</tbody>
</table>
Overall, a low risk of bias was identified (►Fig. 2). All studies provided adequate sequence generation, addressed outcomes completely and were free of selective reporting bias. Eight studies were designed as double-blind randomised controlled trials (16, 22, 32, 37, 39–41, 43). In five out of six studies without blinding of study medication compliance was checked by pill count (33–35, 38, 42). Seven studies used an independent data safety monitoring board or clinical event committee for outcome adjudication (16, 38, 42). Seven studies used an independent data safety monitoring board or clinical event committee for outcome adjudication (16, 38, 42). While in two studies an independent physician board or clinical event committee for outcome adjudication (16, 38, 42). Seven studies used an independent data safety monitoring board or clinical event committee for outcome adjudication (16, 38, 42).

### Direct meta-analysis results

Results from direct meta-analysis are shown in the supplementary material (see ►Suppl. Table 1 and ►Suppl. Fig. 2, available online at www.thrombosis-online.com). Based on this data, NNT with 95% CIs were calculated, which are also presented in ►Suppl. Table 1 (available online at www.thrombosis-online.com). Statistical heterogeneity assessed by I² statistic was zero or not estimable for all outcomes except for MACE (47%) and major bleeding (48%) for the comparison high versus low-dose clopidogrel and stroke (28%) for the comparison prasugrel versus low-dose clopidogrel. As statistical heterogeneity was below the predefined cut-off (I²>50%) and even zero for many outcomes, in which case fixed and random effect models yield identical results, findings from fixed effect models are reported. Only one large phase III clinical trial was included for the comparison ticagrelor versus standard-dose clopidogrel (PLATO Invasive) (43), and ticagrelor was the only agent to significantly reduce the primary outcome all-cause death as well as CV death. The NNT with ticagrelor to avoid one death was 109. The informative value of the direct comparison prasugrel versus high-dose clopidogrel was limited by the low number of events in small study populations. Compared to standard-dose clopidogrel, all three treatment strategies significantly reduced the risk of MI, MACE and stent thrombosis. The NNT to avoid one of these outcomes was lowest with prasugrel (MI: NNT 47, MACE: NNT 49, stent thrombosis: NNT 85) compared to high-dose clopidogrel (MI: NNT 197, MACE: NNT 143, stent thrombosis: NNT 144) and ticagrelor (MI: NNT 83, MACE: NNT 64, stent thrombosis: NNT 128). Major bleeding was significantly increased by prasugrel, minor bleeding by high-dose clopidogrel, and both strategies were associated with higher major or minor bleeding risk in comparison to standard-dose clopidogrel. The number

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**Table 1: Continued**

| Comparison prasugrel vs. standard-dose clopidogrel | JUMBO-TIMI 26 (2005) | 904, groups ratio 4:4:5:5 | RCT, double-blind, multidose | 30 days | STEM: 0% NS-T-ACS: 40% SCAD: 60% HTPR: NA | 99% | Prasugrel 60/10 mg (30 days) | Clopidogrel 300/75 mg | All-cause death, MI, stroke, MACE4, CTVT, major/minor bleeding |
| | TRITON-TIMI 38 (2007) | 13008 | RCT, double-blind | 15 mo | STEM: 26% NS-T-ACS: 74% SCAD: 0% HTPR: NA | 99% | Prasugrel 60/10 mg (15 months) | Clopidogrel 300/75 mg | All-cause/CV death, MI, stroke, MACE4, stent thrombosis, major/minor bleeding |

| Comparison prasugrel vs. high-dose clopidogrel | Alexopoulos (2011) | 71 | RCT, cross-over | 60 days (30 days precross-over*) | STEM: 47% NS-T-ACS: 23% SCAD: 30% HTPR: 100% | 100% | Clopidogrel 300–600 mg LD/ Prasugrel 10 mg (30 days) | Clopidogrel 300–600/150 mg | All-cause/CV death, MI, stroke, MACE4, stent thrombosis, major/minor bleeding |
| | PRINCIPLE-TIMI 44 (2007) | 201 | RCT, double-blind cross-over | 29 days (15 days precross-over*) | STEM: 0% NS-T-ACS: 0% SCAD: 100% HTPR: NA | 55% | Prasugrel 60/10 mg (15 days) | Clopidogrel 600/150 mg | All-cause/CV death, MI, stroke, MACE4, stent thrombosis, major/minor bleeding |

| Comparison ticagrelor vs. standard-dose clopidogrel | PLATO invasive (2009) | 13008 | RCT, double-blind | 12 months | STEM: 49% NS-T-ACS: 51% SCAD: 0% HTPR: NA | 77% | Ticagrelor 180–270/180 mg (12 months) | Clopidogrel 300–600/75 mg | All-cause/CV death, MI, stroke, MACE4, stent thrombosis, major/minor bleeding |

- PCI, percutaneous coronary intervention; LD, loading dose; MD, daily maintenance dose; RCT, randomised controlled trial; STEM, ST-elevation myocardial infarction; NS-T-ACS, non ST-elevation acute coronary syndrome; SCAD, stable coronary artery disease; HTPR, high on-treatment platelet reactivity; CV, cardiovascular; MI, myocardial infarction; CTVT, clinical target vessel thrombosis; MACE, major adverse cardiovascular event. *Included in meta-analysis. **Excluded from meta-analysis. Definitions as used in the included trials: Composite of CV death, MI, target vessel revascularisation; Composite of CV death, MI, stent thrombosis; Composite of CV death, MI, stroke; Composite of all-cause death, MI, stroke, recurrent myocardial ischaemia requiring hospitalisation, clinical target vessel thrombosis.
needed to harm for one extra major or minor bleeding was 94 and 90 with prasugrel and high-dose clopidogrel, respectively. Non CABG-related major bleeding could be elicited from four trials (OASIS-7 PCI, JUMBO, TRITON, PLATO Invasive), and the observed increase of bleeding reached statistical significance for the comparison prasugrel versus standard-dose clopidogrel.

**Network meta-analysis results**

Results comparing prasugrel, ticagrelor and high-dose clopidogrel against each other by combining direct and indirect evidence are given in Figure 2 A and B. Further, results derived from direct and indirect comparisons are shown as simplified graphs in Suppl. Figure 2 (available online at www.thrombosis-online.com). Ticagrelor was associated with a non-significant reduction of the primary outcome all-cause mortality when compared to prasugrel and high-dose clopidogrel. No superiority of any treatment strategy over the other was seen for CV mortality, MI, stroke and MACE. For stent thrombosis, prasugrel was associated with a significantly lower risk compared to ticagrelor, while the reduced risk compared to high-dose clopidogrel did not reach statistical significance when analysed with GLIMMIX.

For bleeding outcomes, prasugrel was associated with an increased risk of major and minor or major bleeding compared to ticagrelor but no differences were found compared to high-dose clopidogrel. Ticagrelor exhibited a significantly lower risk of major or minor bleeding compared to high-dose clopidogrel. No significant differences were seen for any other bleeding outcome. In particular, risk of non CABG-related major bleeding did not differ significantly between the three novel antiplatelet strategies.

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**Table 2: Main endpoints and data as reported in OASIS-7 PCI, TRITON TIMI-38 and PLATO invasive.**

<table>
<thead>
<tr>
<th>Endpoint, events (%)</th>
<th>Study (year)</th>
<th>High-dose</th>
<th>Standard clopidogrel</th>
<th>HR (95%CI)</th>
<th>Prasugrel</th>
<th>Standard clopidogrel</th>
<th>HR (95%CI)</th>
<th>Ticagrelor</th>
<th>Standard clopidogrel</th>
<th>HR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint1</td>
<td>OASIS-7 PCI (2010)</td>
<td>330/8560 (3.9%)</td>
<td>392/8703 (4.5%)</td>
<td>0.86 (0.74, 0.98)</td>
<td>643/6813 (9.9%)</td>
<td>781/6795 (12.1%)</td>
<td>0.81 (0.73, 0.90)</td>
<td>569/6732 (9.0%)</td>
<td>668/6676 (10.7%)</td>
<td>0.84 (0.75, 0.94)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>TRITON TIMI 38 (2007)</td>
<td>166/8560 (1.9%)</td>
<td>179/8703 (2.1%)</td>
<td>0.94 (0.76, 1.16)</td>
<td>188/6813 (3.0%)</td>
<td>197/6795 (3.2%)</td>
<td>0.95 (0.78, 1.16)</td>
<td>252/6732 (3.9%)</td>
<td>311/6676 (5.0%)</td>
<td>0.81 (0.68, 0.95)</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>PLATO invasive (2009)</td>
<td>172/8560 (2.0%)</td>
<td>226/8703 (2.6%)</td>
<td>0.79 (0.64, 0.96)</td>
<td>475/6813 (7.3%)</td>
<td>620/6795 (9.5%)</td>
<td>0.76 (0.67, 0.85)</td>
<td>328/6732 (5.3%)</td>
<td>406/6676 (6.6%)</td>
<td>0.80 (0.69, 0.92)</td>
</tr>
<tr>
<td>Stent thrombosis2</td>
<td>OASIS-7 PCI (2010)</td>
<td>136/8560 1.6%</td>
<td>199/8703 2.3%</td>
<td>0.69 (0.56, 0.87)</td>
<td>68/6422 (1.1%)</td>
<td>142/6422 (2.4%)</td>
<td>0.48 (0.36, 0.64)</td>
<td>104/4949 (2.2%)</td>
<td>142/4928 (3.0%)</td>
<td>0.73 (0.57, 0.94)</td>
</tr>
<tr>
<td>Total major bleeding3</td>
<td>TRITON TIMI 38 (2007)</td>
<td>81/8560 1.0%</td>
<td>60/8703 0.7%</td>
<td>1.36 (0.97, 1.90)</td>
<td>170/6421 (2.5%)</td>
<td>117/6716 (1.7%)</td>
<td>1.46* (1.15, 1.85)</td>
<td>476/6651 (7.9%)</td>
<td>476/6585 (7.9%)</td>
<td>1.00 (0.88, 1.14)</td>
</tr>
<tr>
<td>Non CABG rel. major bleeding3</td>
<td>PLATO invasive (2009)</td>
<td>71/8560 0.8%</td>
<td>54/8703 0.6%</td>
<td>1.34* (0.94, 1.91)</td>
<td>146/6421 (2.4%)</td>
<td>111/6716 (1.8%)</td>
<td>1.32 (1.03, 1.68)</td>
<td>160/6651 (2.8%)</td>
<td>130/6585 (2.3%)</td>
<td>1.23 (0.98, 1.55)</td>
</tr>
</tbody>
</table>

*Death from cardiovascular causes, non-fatal MI, non-fatal stroke. **Definite or probable stent thrombosis as defined by the Academic Research Consortium (ARC). ***According to Thrombolysis in Myocardial Infarction (TIMI) criteria. HR, hazard ratio; MI, myocardial infarction; * Ratio is odds ratio, rather than hazard ratio.

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MTC models using Bayesian statistical methods yielded consistent results (Suppl. Table 2, available online at www.thrombosis-online.com) with similar point estimates for treatment effects in comparison to those obtained by GLIMMIX. Also, the level of...
statistical significance did not change except for a significant reduction of stent thrombosis by prasugrel when compared to high-dose clopidogrel (OR 0.68, 95% CI 0.48, 0.97).

Analysing the probability of a ranking order of the effectiveness of treatment strategies, prasugrel was identified as most potent agent to prevent stent thrombosis, while ticagrelor showed best results for all-cause mortality (Table 3). Regarding safety, ticagrelor was ranked first for all bleeding outcomes except non CABG-related major bleeding where standard-dose clopidogrel clearly performed best (Table 3).

### Subgroup analysis in patients with ACS

A subgroup analysis in patients with ACS included five studies (36, 38–40, 43) comprising the three major clinical trials as depicted in Table 2. Subgroup corroborated the main findings as shown in Figure 2 A and B. Due to a lower precision with a smaller number of trials confidence intervals tended to be larger in this subgroup analysis.

#### Table 3: Probability each treatment performs best for each outcome. A) Efficacy outcomes. B) Bleeding outcomes.

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>All-cause mortality</th>
<th>CV mortality</th>
<th>MI</th>
<th>Stroke</th>
<th>MACE</th>
<th>Stent thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel</td>
<td>0.08</td>
<td>0.25</td>
<td>0.49</td>
<td>0.15</td>
<td>0.46</td>
<td>0.98</td>
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<tr>
<td>Ticagrelor</td>
<td>0.80</td>
<td>0.63</td>
<td>0.20</td>
<td>0.11</td>
<td>0.23</td>
<td>0.01</td>
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<tr>
<td>High-dose clopidogrel</td>
<td>0.12</td>
<td>0.11</td>
<td>0.31</td>
<td>0.65</td>
<td>0.31</td>
<td>0.01</td>
</tr>
<tr>
<td>Standard-dose clopidogrel</td>
<td>0</td>
<td>0</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Major bleeding</th>
<th>Minor bleeding</th>
<th>Major or minor bleeding</th>
<th>Non CABG-related major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel</td>
<td>0</td>
<td>0.03</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>0.48</td>
<td>0.55</td>
<td>0.61</td>
<td>0.04</td>
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<tr>
<td>High-dose clopidogrel</td>
<td>0.13</td>
<td>0</td>
<td>0</td>
<td>0.05</td>
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<tr>
<td>Standard-dose clopidogrel</td>
<td>0.39</td>
<td>0.42</td>
<td>0.39</td>
<td>0.89</td>
</tr>
</tbody>
</table>

CV, cardiovascular. MI, myocardial infarction. MACE, major adverse cardiovascular event. CABG, coronary artery bypass graft.
Discussion

In traditional meta-analysis, all three novel antiplatelet strategies (high-dose clopidogrel, prasugrel, ticagrelor) significantly reduced non-fatal ischaemic endpoints compared to standard-dose clopidogrel, while only ticagrelor showed mortality benefits. Furthermore, only ticagrelor did not increase bleeding risk compared with standard low-dose clopidogrel. In network meta-analysis indirectly comparing the three novel strategies against each other, prasugrel performed best for the reduction of stent thrombosis reaching statistical significance in comparison to ticagrelor, but ticagrelor showed the most favourable bleeding profile.

A previous analysis performing an adjusted indirect comparison according to Bucher (44) between ticagrelor and prasugrel in patients with ACS (29) also found that prasugrel decreased stent thrombosis and increased bleeding rates compared to ticagrelor. In our study, we chose network analysis to overcome the limitations of simple pair-wise comparisons and the need of a common comparator for all included trials (45). Therefore, we could extend the investigated treatment strategies to high-dose clopidogrel and integrate information from trials beyond those using standard-dose clopidogrel as active comparator.

A mixed treatment comparison using Bayesian methods not only confirmed our findings but also allowed ranking of treatments: Prasugrel outperformed both ticagrelor and high-dose clopidogrel with respect to reduction of stent thrombosis with a 98% probability of performing best. On the other hand, ticagrelor was ranked first for reduction of mortality and bleeding except for non-CABG-related major bleeding. The consistency of findings from a previously published study (29), our own Bayesian analysis, and our generalised linear mixed models indicates that the latter represent a valid technique for network meta-analysis. Of note, it has been recently demonstrated that adjusted indirect comparisons and mixed treatment comparisons show a similar relative performance (46).

Caveats and limitations

The validity of indirect comparisons is determined by trial similarity (47), so that differences in study populations, interventions, and outcome definition are potential sources of biases or errors. As regards differences in study populations, the three large, phase III clinical trials (OASIS-7 PCI, TRITON, and PLATO Invasive, see Table 2) and two smaller ones included patients with ACS, while all other trials included stable or mixed study populations, resulting in almost 90% ACS patients in our analysis. Thus, our results have to be interpreted with particular caution for non-ACS patients, although it seems likely that these drugs will be increasingly used off-label in patients with stable CAD (48). With respect to differences in interventions, the favourable outcome of prasugrel for stent thrombosis might at least in part be due to different loading strategies of ADP-antagonist administration: As regards loading dose of the active control group, patients in PLATO Invasive received up to 600 mg clopidogrel, while patients in TRITON and OASIS-7 PCI received a maximum of 300 mg clopidogrel. As regards timing of loading, in TRITON prasugrel or clopidogrel were given mostly after coronary anatomy was known, while in PLATO Invasive and OASIS-7 PCI loading dose was given earlier (before angiography).

Aspirin dosage might also be a confounder, as a significant interaction of ticagrelor and high-dose aspirin has been postulated as potential explanation for the lack of a ticagrelor benefit in the North American study population (49). A further issue represents length of follow-up, which was adjusted for in our analysis.

While outcome definitions of thrombotic and CV events are similar throughout most of the included trials, definitions of bleeding events differ substantially. Therefore, in order to limit heterogeneity of bleeding definitions we utilised the TIMI bleeding classification wherever reported in the included studies. Beyond diverse definitions, bleeding rates are also influenced by trial design. The observed superiority of ticagrelor over prasugrel for total major bleeding was diminished when CABG-related bleeding events were excluded. Due to its design, more CABG procedures were performed in PLATO invasive compared to the other trials. Therefore, the high number of CABG procedure-related bleeds in both groups most likely weakened the trend towards more spontaneous bleeding associated with ticagrelor, which might have contributed to the favourable bleeding profile of ticagrelor in our analysis.

Despite the fact that these novel antiplatelet strategies represent a substantial progress for patients requiring PCI, the differential role and indication of each of these novel antiplatelet strategies are not clear, yet. Although, in the lack of direct comparisons no definite recommendations for individual patient management can be made, our indirect comparison might suggest preferences of one antiplatelet strategy over another in specific situations. For example, our data suggest advantages for prasugrel in reduction of stent thrombosis in patients with high thrombotic and low bleeding risk, especially during 30 days post PCI, whereas advantages as regards long term outcome are suggested for ticagrelor.
Our analysis also indicates that high-dose clopidogrel is more effective than standard-dose clopidogrel and represents a valid alternative for many patients in particular in the light of economic restraints and the increasing availability of generic clopidogrel. In conclusion, network meta-analysis suggests potentially relevant differences in efficacy and bleeding risk between novel antplatelet treatments. However, definite conclusions about superiority of one drug over another could only be drawn from randomised trials directly comparing the specific agents.

Conflicts of interest
None declared.

References


