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Ticagrelor monotherapy versus 1-year dual antiplatelet therapy in patients with and without acute coronary syndromes: A systematic review and individual patient level meta-analysis of randomised trials

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Summary

Background: One-year dual antiplatelet therapy (DAPT) remains the standard of care after coronary stenting and/or acute coronary syndrome (ACS).

Methods: We performed an individual patient level meta-analysis of randomised trials comparing DAPT de-escalation to ticagrelor monotherapy vs. continuing DAPT for 12 months after coronary drug-eluting stent implantation on centrally-adjudicated endpoints. The three ranked co-primary endpoints were a composite of all-cause death, myocardial infarction, or stroke (major adverse cardiovascular or cerebrovascular events, MACCE) tested for non-inferiority in the per-protocol population, Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding, and all-cause death, tested for superiority in the intention-to-treat population.

Findings: Six trials were identified that randomised patients to ticagrelor monotherapy or DAPT beginning 78 (31-92) days after intervention, with follow-up assessed for the next 334 (329−365) days. Among 23,256 per-protocol patients, MACCE occurred in 297 (2·81%) with ticagrelor monotherapy and 332 (3·20%) with DAPT (hazard ratio [HR] 0·91, 95% CI 0·78 to 1·07; P=0·004 for non-inferiority; τ^2<0·001). Among 24,407 intention-to-treat patients, the risks of BARC 3 or 5 bleeding (0·89% versus 2·10%; HR 0·43, 95% CI 0·34 to 0·54; P<0·001 for superiority; τ^2=0·079) and all-cause death (0·88% versus 1·24%; HR 0·76, 95% CI 0·59 to 0·98; P=0·034 for superiority; τ^2<0·001) were lower with ticagrelor monotherapy. Trial sequential analysis showed conclusive evidence of non-inferiority for MACCE and superiority for bleeding among the overall and ACS populations. The treatment effects were heterogeneous by sex for MACCE and all-cause death, indicating possible benefit in females with ticagrelor monotherapy, and by clinical presentation for bleeding, indicating benefit in ACS with ticagrelor monotherapy.

Interpretation: There is conclusive evidence that DAPT de-escalation to ticagrelor

monotherapy does not increase ischaemic risk and lowers major bleeding compared with 1-year DAPT, especially in ACS. Ticagrelor monotherapy might also be associated with a mortality benefit, particularly among females, warranting further investigation (PROSPERO, CRD42024506083).

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Key words: ticagrelor; dual antiplatelet therapy; meta-analysis; acute coronary syndrome; stent.

INTRODUCTION

Dual antiplatelet therapy (DAPT) is currently recommended as the default antiplatelet regimen after coronary drug-eluting stent (DES) implantation, especially after acute coronary syndrome (ACS).[1,2] Some studies have shown that after DAPT for a few weeks to a few months, de-escalation in the potency of platelet inhibition to a strategy of $P2Y_{12}$ inhibitor monotherapy does not increase ischaemic risk and is associated with less bleeding compared with continuation of standard DAPT.[3-11] These individual studies are difficult to interpret because they differ in study designs, patient populations, type of $P2Y_{12}$ inhibitors, and lack of study power to precisely estimate the treatment effect on relevant individual endpoints such as mortality or stent thrombosis and/or in various treatment subgroups. Meta-analyses of some these studies exist, but their interpretation remains limited by the absence of individual patient data (IPD) or the failure to include all available studies.[12-16]

Given the paucity and incompleteness of data on prasugrel and clopidogrel monotherapy, respectively, and the availability of newer trials with ticagrelor monotherapy, we reviewed and analysed all available randomised evidence on DAPT de-escalation to ticagrelor monotherapy and performed an IPD meta-analysis in patients with and without ACS after coronary DES implantation.

METHODS

A systematic review and IPD level meta-analysis of randomised trials with centrally adjudicated endpoints was performed to evaluate the comparative efficacy and safety of ticagrelor monotherapy 90 mg b.i.d. after short-term DAPT versus 12-month DAPT in patients undergoing treated with coronary DES. Trials evaluating monotherapy with different $P2Y_{12}$ inhibitors versus DAPT with stratified randomisation by type of $P2Y_{12}$ inhibitor were considered, and exclusively included patients assigned to ticagrelor monotherapy or DAPT. Trials that included patients with an indication for long-term oral anticoagulation were

excluded.[17] No further restrictions were imposed for trial selection. Methods and reporting follow the Preferred Reporting Items for a Systematic Review and Meta-analysis of IPD (PRISMA) guidelines.[18] The study protocol was prospectively registered with PROSPERO (CRD42024506083).

Search strategy

Two investigators (MV, SH) determined trial eligibility criteria; a third investigator (MH) was involved for arbitration in case of disagreement. Randomised controlled trials were identified by searching Ovid Medline, Embase, and a website (www.tctmd.com) on May 20, 2024. Reference lists of identified articles were hand searched for additional studies. No language restriction was applied. Detailed search strategy is reported in the **appendix (pp 3−4)**.

Study outcomes

The three ranked co-primary endpoints were the composite of all-cause death, myocardial infarction (MI), or stroke (major adverse cardiovascular or cerebrovascular events, MACCE); Bleeding Academic Research Consortium (BARC) type 3 or 5 bleeding;[19] and all-cause death. Non-fatal components and disease-specific mortality were centrally adjudicated in each trial by an independent clinical events committee. We first assessed the non-inferiority of de-escalation to ticagrelor monotherapy versus continued DAPT for MACCE in the per-protocol population, and then hierarchically assessed the superiority of ticagrelor monotherapy versus DAPT for BARC 3 or 5 bleeding followed by all-cause death in the intention-to-treat population. All outcomes were assessed throughout the duration of the randomised comparison of protocol-mandated de-escalation to ticagrelor monotherapy versus continued DAPT. Secondary endpoints are described in the **appendix** (**p 4**). The definitions used for clinical endpoints were largely consistent across the trials (**appendix, pp 12−16**).

Data extraction and quality assessment

Principal investigators of the eligible trials provided IPD in an anonymised electronic dataset (**appendix, pp 4−5**). Patient level data from 4 trials were available from a previous analysis.[12] In the case of missing data or when inconsistencies were observed, the principal investigators of the trials were contacted. Two investigators (MV, SH) independently assessed the risk of bias by using the revised Cochrane risk-of-bias tool (RoB 2) (**appendix, p 17**).[20] Disagreements were resolved discussion and with a third author (MH) for arbitration. Each trial was approved by the local medical ethics committee; all patients had provided written informed consent for participation in individual trials.

Data synthesis

A one-step approach was pre-specified to model patient level data from included trials simultaneously using a mixed effect Cox regression model with baseline hazards stratified by trial and a random slope to account for variation between trials in treatment effect. Treatment effects were derived as hazard ratios (HR) and 95% CI. The heterogeneity of the treatment effect between trials was quantified using the variance of the random slope τ^2. Sensitivity analyses were based on a two-step approach using the Paule-Mandel estimator to combine trial level estimates. To estimate between trial heterogeneity for the two-step model, I^2 was used. All primary analyses were conducted with censoring of events that occurred during the initial DAPT phase, if present, common to both experimental and control groups. Therefore, only events occurring after the time when the protocol specified the change from DAPT to ticagrelor monotherapy in the experimental group were included. In the T-PASS trial,[7] the days from randomisation to the first visit of out-patient clinic were censored in both groups because de-escalation to ticagrelor monotherapy was scheduled at the first visit of out-patient clinic in the experimental group in the protocol. Data were analysed up to the longest available time point with protocol specified ticagrelor monotherapy in the experimental group and DAPT in the control group.

We first assessed the non-inferiority of ticagrelor monotherapy compared with DAPT on the co-primary endpoint of MACCE at a one-sided α of 0·025 in the per-protocol population. The pre-specified non-inferiority margin of 1·15 on an HR scale preserves 50% of the treatment effect of aspirin versus control reported in patients with prior myocardial infarction for vascular death, myocardial infarction, or stroke.[12,21] If non-inferiority was met, ranked superiority testing of the ticagrelor monotherapy at a two-sided α of 0·05 as for BARC type 3 or 5 bleeding and all-cause death was performed in the intention-to-treat population. For all analyses other than the primary non-inferiority test for MACCE, two-sided P-values for superiority and two-sided 95% CIs were reported to allow conventional interpretation of the results. We conducted trial sequential analyses to determine whether the results were conclusive or futile as to the non-inferiority of ticagrelor for the primary MACCE endpoint and superiority for major bleeding or all-cause death in the overall population and after stratifying patients by clinical presentation (ACS or chronic coronary syndrome [CCS]; appendix p 18).[22]

The per-protocol population excluded ineligible patients (i.e., those violating inclusion/exclusion criteria) and/or those who never received the allocated treatment strategy. The intention-to-treat population included all randomised patients according to their random allocation. Further details on data analysis, including secondary and subgroup analyses are reported in the **appendix (pp 5−6).**

Role of the funding source

This study exclusively received intramural funding by the Cardiocentro Ticino Institute, Ente Ospedaliero Cantonale, Lugano, Switzerland, which had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

RESULTS

A total of 8361 unique citations were screened. Of these, 610 records were considered

potentially eligible during screening of titles and abstracts, and six trials were eligible and provided IPD (**appendix, p 32**), specifically the GLASSY, SMART-CHOICE, TICO, TWILIGHT, T-PASS and ULTIMATE-DAPT trials.[3-8] Trial characteristics and patient populations are described in the **appendix** (**pp 7−16**). The risk of bias assessment identified some concerns in four of the five trials related to the open label allocation of the randomised treatment (**appendix, p 17**). All six studies were sponsored by non-for-profit academic organisations.

A total of 24,562 participants were initially considered for the analysis (**appendix, p 33**). A total of 155 patients (0·6%) were excluded from 4 trials[3,4,5,7] due to premature study termination or death before the time point at which each study protocol specified the implementation of the experimental treatment. Overall, 24,407 patients were available for the intention-to-treat analysis, including 12,199 (50·0%) patients assigned to de-escalation to ticagrelor monotherapy and 12,208 (50·0%) patients assigned to continuation of DAPT (aspirin plus ticagrelor in 10,492 [85·9%] patients and aspirin plus clopidogrel in 1716 [14·1%] patients). A total of 1151 (4·7%) participants were excluded from the per-protocol population (**appendix, p 33**), mainly due to lack of implementation of the allocated treatment. The median DAPT duration before starting monotherapy was 78 (31−92) days, ranging from 12 to 97. The median treatment duration of ticagrelor monotherapy or DAPT after randomisation was 334 (329−365) days.

Baseline clinical characteristics were balanced between groups (**table 1; appendix, pp 19−21**). The mean age was 63 years, and 5525 (22·6%) were women. A total of 7320 (30·0%) patients had history of diabetes, and 3206 (13·3%) had chronic kidney disease. A history of MI, percutaneous coronary intervention, or coronary artery bypass graft surgery was noted in 4262 (17·5%), 6311 (25·9%), and 1184 (4·9%) patients, respectively. At presentation, ACS, acute MI, and ST-segment elevation MI were identified in 18,135 (74·3%), 11,478 (47·0%), and 4646 (19·0%) patients, respectively. Overall, 3232 (13·8%)

patients were at high risk of bleeding as defined by PRECISE-DAPT score ≥25. Procedural characteristics are shown in the **appendix** (**p 22−26**)**;** a total of 3555 (14·6%) patients had an angiographically-visible thrombus, 5820 (23·8%) patients underwent complex intervention; the median stent length was 30 mm; and 5270 (30·5%) patients received overlapping stents.

The composite MACCE endpoint of all-cause death, MI, or stroke in the per-protocol population occurred in 297 (2·81%) patients with ticagrelor monotherapy and 332 (3·20%) patients with continued DAPT (HR 0·91 [95% CI 0·78 to 1·07]; τ^2<0·001; P=0·004 for non-inferiority) (**figure 1; appendix, p 27**). BARC type 3 or 5 bleeding in the intention-to-treat population occurred in 102 (0·89%) patients with ticagrelor compared with 237 (2·10%) patients with DAPT (HR 0·43 [95% CI 0·34 to 0·54]; τ^2=0·079; P<0·001 for superiority) (**table 2** and **figure 1**). A total of 102 (0·88%) patients with ticagrelor and 135 (1·24%) patients with DAPT died (HR 0·76 [95% CI 0·59 to 0·98]; P=0·034 for superiority, τ^2<0·001) (**table 2** and **figure 1**). The results were similar in the per-protocol and intention-to-treat populations (**figure 1, table 2; appendix, p 27)**.

Trial sequential analyses showed conclusive evidence of non-inferiority for the primary composite endpoint of MACCE and of superiority for BARC type 3 or 5 (**appendix, p 34**). The mortality benefit of ticagrelor monotherapy was inconclusive (**appendix, p 34**).

Treatment-by-sex and treatment-by-diabetes interactions were significant for MACCE, suggesting lower risk with ticagrelor monotherapy in women (HR 0·67 [95% CI 0·49 to 0·93]) but not in men (HR 0·99 [95% CI 0·83 to 1·18]; P-interaction=0·041) and patients with (HR 0·76 [95% CI 0·60 to 0·96]) but not without diabetes (HR 1·03 [95% CI 0·84 to 1·26]; P-interaction=0·043) (**figure 2**).

There was heterogeneity by clinical presentation and type of $P2Y_{12}$ inhibitor in the control group for BARC 3 or 5, suggesting lower rates with ticagrelor in patients with but not without ACS (P-interaction=0·022) and compared with DAPT in form of aspirin and ticagrelor

but not aspirin and clopidogrel (**appendix, p35**).

There was a borderline interaction between the treatment and sex for all-cause death, suggesting greater benefit in women than men (**appendix, p 35**).

Subgroup interactions for MACCE, BARC type 3 or 5 and death were non-significant for other pre-specified subgroups, including age, bleeding risk, PCI complexity, timing of randomisation (≤30 days vs. >30 days), and geographic region of enrollment **(figures 2 and appendix p 35−36).**

The composite of death, MI, or stroke occurred in 229 (2·77%) ACS patients with ticagrelor monotherapy and 261 (3·32%) ACS patients with continued DAPT (HR 0·89 [95% CI 0·74 to 1·06]) (**table 3; appendix, p 37**) and in 86 (2·99%) CCS patients with ticagrelor compared with 87 (3·00%) CCS patients with DAPT (HR 0·98 [95% CI 0·73 to 1·32]) (**appendix, p 28** and **p 38**). BARC 3 or 5 was lower with ticagrelor monotherapy in patients with (0·79% versus 2·37%; HR 0·34 [95% CI 0·26 to 0·45]) but not without (1·14% versus 1·33%; HR 0·86 [95% CI 0·55 to 1·36] ACS (**table 3; appendix, p 28 and p 37−38**). Among ACS patients, 74 (0·86%) with ticagrelor and 101 (1·25%) with DAPT died (HR 0·74 [95% CI 0·55 to 0·99], whereas the corresponding figures for CCS patients were 28 (0·95%) and 34 (1·20%) (HR 0·82 [95% CI 0·50 to 1·35]) (**table 3; appendix, p 28**).

The stratified treatment effects for three co-primary endpoints in patients with acute MI (**appendix, p 29 and p 39**) and subgroup analyses in patients with ACS, acute MI, or CCS are shown in the **appendix** (**p 40−48**).

Trial sequential analyses showed conclusive evidence of non-inferiority for MACCE and superiority for BARC type 3 or 5 in ACS but not in CCS patients with ticagrelor (**appendix, pp 49−50**).

In pre-specified analyses including clinical events occurring during the initial DAPT phase or excluding patients with primary events during the initial DAPT phase after randomisation in four trials, the results for ischaemic and bleeding endpoints remained entirely consistent (**appendix, p 30−31**). All-cause death occurred in 139 (0·90%) patients treated with

ticagrelor monotherapy and 177 (1·22%) patients treated with continued DAPT (HR 0·79 [95% CI 0·63 to 0·98; P=0·035; τ^2<0·001) including GLOBAL LEADERS instead of GLASSY in the pooled trial dataset.

Discussion

This IPD meta-analysis appraised the totality of available randomised evidence comparing de-escalation from DAPT to ticagrelor monotherapy after a median of 78 days of DAPT (ranging from a few weeks to 3 months) and standard 12-month DAPT in 24,407 patients after drug-eluting coronary stenting. There was conclusive evidence of the non-inferiority of ticagrelor monotherapy compared with DAPT for the composite MACCE endpoint of all-cause death, MI, or stroke in the overall and ACS populations, but not in CCS patients. Similarly, ticagrelor monotherapy was conclusively superior to 12-month DAPT for reducing major bleeding in the overall and ACS populations, but not in CCS patients. Ticagrelor monotherapy was associated with a significant yet inconclusive mortality reduction. Finally, there was heterogeneity of treatment effects for MACCE with respect to sex, with possible benefit in female but not in male patients.

Compared with 12-month DAPT, an abbreviated DAPT regimen after coronary stenting is desirable to reduce bleeding but only if ischaemic risks are not increased.[1,2] In this regard, 3-to-6-month DAPT de-escalation to aspirin monotherapy compared with 12-month DAPT in ACS patients has been associated with reduced bleeding but an increase in adverse ischaemic events.[23] De-escalation to clopidogrel monotherapy after a short course of DAPT was investigated in 3 Asian randomised trials,[4,9,10] and raised concerns over a possible excess of mortality compared with 12-month DAPT.[9] The evidence for de-escalation to prasugrel monotherapy after a short DAPT regimen is limited to observational studies.[24] Conversely, as reported in the present systematic review, six trials in North America, Europe, and Asia have investigated de-escalation to ticagrelor monotherapy after coronary DES.[3-8] Among 24,407 included patients , 18,135 (74·3%) underwent treatment for ACS and 11,478

(47·0%) suffered from acute MI.

Our analysis is unique because it is the only IPD including the totality of evidence and implementing trial sequential analysis in the overall and stratified ACS/CCS populations. It provides solid evidence that de-escalation to ticagrelor monotherapy after a short-term DAPT regimen is not associated with a higher risk of the composite of death, MI, or stroke or mortality alone compared with 12-month DAPT. We pre-specified testing for non-inferiority of ticagrelor monotherapy compared with continued DAPT on MACCE, under the assumption that the former treatment would preserve at least 50% of the treatment effect of aspirin in patients with prior MI. The 97·5% confidence limit for MACCE entailed no greater than 6% of relative risk increase with ticagrelor in the intention to treat population, which fulfilled non-inferiority and was deemed conclusive at trial sequential analysis. This finding in the overall population reflects the treatment effects observed in the large ACS population in which the 97·5% confidence limit for MACCE also entailed no greater than 6% of relative risk increase with ticagrelor, which was deemed conclusive at trial sequential analysis. In some of the included studies, the proportion of patients with ACS due to unstable angina was high, which may reflect the limited availability of high-sensitivity troponin in some centres. To overcome this limitation, we performed a stratified analysis in patients with confirmed MI and found consistent results. We explored the consistency of the treatment effects in various patient subgroups, including patients with or without chronic kidney disease, complex coronary intervention, left main or proximal left anterior descending artery stent implantation, high bleeding risk, and found no evidence of an increased risk of MACCE with ticagrelor in the overall or ACS populations. Patients with diabetes, who experience higher risk of adverse events, derived significant MACCE benefit from ticagrelor monotherapy compared with DAPT continuation, with significant interaction testing. Interaction testing also suggested a heterogeneous treatment effect for MACCE, with preferential benefit in female patients using ticagrelor monotherapy. Elderly patients, in whom a prior trial suggested possible harm with ticagrelor, did not incur a higher risk of MACCE compared with DAPT.[25] Importantly, the

treatment effects of ticagrelor monotherapy in preserving the rates of MACE seen with continued DAPT remained consistent when de-escalation occurred within or beyond 1-month.

Mortality and cardiovascular mortality were lower with ticagrelor monotherapy compared with continued DAPT. This finding was deemed inconclusive, but reassures that ticagrelor is not associated with an excess of fatal events compared with standard DAPT. The lower risk of mortality with ticagrelor in the overall population was most notable in female patients, who were under-represented across studies but derived significant mortality benefit from ticagrelor. The apparent differential sex-specific treatment effect of ticagrelor on mortality does not seem to be explained by lower major bleeding risk, as both relative and absolute risk reductions for major bleeding were consistent across sexes. The observed mortality benefit and whether a between-sex disparity exist (and if so, the underlying mechanism) require additional research.[26]

The risk of major bleeding was more than halved with ticagrelor monotherapy in the overall and ACS populations, whereas it did not differ compared with DAPT in the smaller CCS group. This finding most likely reflects differences in the type of DAPT in the control arm, mainly consisting of aspirin and ticagrelor among ACS and aspirin and clopidogrel among CCS patients, as well as the limited study power in CCS patients. This and previous observations suggest that ticagrelor monotherapy is a preferable treatment option than DAPT in ACS but not clearly in CCS patients,[12] given the uncertain preservation of ischaemic benefit and bleeding risk mitigation profile in the latter group. Conversely, the relative risk of major bleeding was consistently reduced by more than 60% in ACS patients, with and without high bleeding risk features. This observation suggests that de-escalation to ticagrelor should not be reserved to high bleeding risk patients, but rather offered to the entire spectrum of ACS patients, although acknowledging that the number of patients to treat for benefit with ticagrelor was halved to 31 in patients at high bleeding risk based on the PRECISE-DAPT score.[27,28]

This study has limitations. First, this analysis included four open label studies. However, all studies implemented blinded central endpoint adjudication, and endpoint definitions were consistent across trials.[3-8] Second, although ticagrelor was consistently administered in the experimental group, either clopidogrel or ticagrelor were given with aspirin in CCS patients in the DAPT group. Moreover, 6-month rather than 12-month DAPT is recommended in CCS patients. As we did not correct for multiplicity, the findings on secondary endpoints and subgroup analyses are hypothesis-generating. The trial sequential analysis was pre-specified for the three co-primary endpoints in the overall study population; the stratified findings in ACS/CCS patients are post-hoc. Four studies included Asian patients only. However, the study population included 13,034 (53.4%) non-Asian and 11,373 (46.6%) Asian patients, with no heterogeneity of treatment effects by geography. Our study does not clarify whether early (within 1 month) or late (beyond 1 and up to 3 months) de-scalation is preferable as both time frames preserved MACCE and lowered bleeding risks. The comparative treatment effects of ticagrelor monotherapy and other de-escalation modalities remain unclear. The absolute rate of ischemic or fatal events across the included studies is lower compared with some ACS trials, which included patients early after presentation. Patients with clinical instability or at high likelihood of early events might have been excluded or included only after clinical stabilisation. However, events occurring during the early DAPT phase, common to both treatment groups, are confounders to the research question.

Finally, the present results do not apply to de-escalation to prasugrel monotherapy or to the comparative treatment effects of ticagrelor monotherapy or DAPT in form of aspirin and prasugrel (which has not been studied in randomised trials). Nor has de-escalation to ticagrelor been compared with de-escalation to clopidogrel, a strategy that may be particularly relevant in patients with CCS.

In summary, the present IPD meta-analysis provides conclusive evidence that de-

escalating from DAPT to ticagrelor monotherapy at a few weeks to a few months after coronary DES implantation preserves the fatal and non-fatal ischaemic risk and halves major bleeding compared with 1-year DAPT in ACS patients. There was a significant yet inconclusive mortality benefit with ticagrelor, particularly among females, warranting further investigations. Among CCS patients, the benefits and risks of DAPT escalation to ticagrelor monotherapy compared with continued DAPT remains inconclusive.

Research in context

Evidence before this study

We searched Ovid Medline, EMBASE, and two websites (www.tctmd.com, www.escardio.org) without language restrictions for randomised trials reported up to May 20, 2024, that compared $P2Y_{12}$ monotherapy with dual antiplatelet therapy (DAPT) after coronary revascularisation. Most of the evidence showed similar risk of ischaemic events and lower risk of bleeding with $P2Y_{12}$ inhibitor monotherapy compared with conventional DAPT. However, individual trials were not designed to assess whether the $P2Y_{12}$ inhibitor specific treatment effects. A previous IPD meta-analysis of six trials observed that $P2Y_{12}$ inhibitor monotherapy was associated with a similar risk of death, myocardial infarction, or stroke and a lower risk of bleeding compared with DAPT, irrespective of baseline risks and type of $P2Y_{12}$ inhibitor. However, in the subsequent STOPDAPT-2 ACS trial, clopidogrel monotherapy after 1- to 2-month DAPT failed to achieve non-inferiority to standard DAPT in patients undergoing drug-eluting stent implantation for acute coronary syndrome. This finding was confirmed in a recent meta-analysis, which suggested that the treatment effect of $P2Y_{12}$ inhibitor monotherapy could depend on the type of $P2Y_{12}$ inhibitor. Since this previous meta-analysis, two large randomised controlled studies assessed the role of ticagrelor monotherapy compared with standard 12-month DAPT in patients with acute coronary syndrome.

Added value of this study

We analysed all available randomised evidence on DAPT de-escalation to ticagrelor monotherapy and performed an IPD meta-analysis in patients with and without acute coronary syndrome after coronary drug-eluting stent implantation. Six trials with 23,820 randomised patients were identified. De-escalation to ticagrelor monotherapy was implemented 78 (31-92) days after intervention. For the three ranked co-primary endpoints, a composite of all-cause death, myocardial infarction, or stroke (major adverse

cardiovascular or cerebrovascular events, MACCE) met non-inferiority. The risks of BARC 3 or 5 bleeding and all-cause death were lower with ticagrelor monotherapy. Trial sequential analysis showed conclusive evidence of non-inferiority for MACCE and superiority for bleeding among the overall and acute coronary syndrome populations. The treatment effects were heterogeneous by sex for MACCE, indicating benefit in females with ticagrelor monotherapy, and by clinical presentation for BARC 3 or 5 bleeding, indicating benefit in acute coronary syndrome with ticagrelor monotherapy.

Implications of all the available evidence

With the totality of available evidence, this study shows conclusively that DAPT de-escalation to ticagrelor monotherapy occurring between one to three months after coronary stenting does not increase ischaemic risk and lowers major bleeding compared with 1-year DAPT, especially in acute coronary syndrome. Ticagrelor monotherapy might also be associated with a mortality benefit, particularly among females, warranting further investigation

Contributors

Marco Valgimigli, designed the study, analysed and interpreted data, drafted and approved the final manuscript.

Sung-Jin Hong and Felice Gragnano, analysed and interpreted data, revised and approved the final manuscript.

Konstantina Chalkou, Bruno R da Costa and Dik Heg have accessed and verified the data, analysed and interpreted data, revised and approved the final manuscript.

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All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

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All other authors declare no competing interests.

Data Sharing

Anonymised SIDNEY-4 individual patient data are stored at the Department of Clinical Research, University of Bern, in Switzerland and will be available for sharing after written approval from all individual study principal investigators and institutional review board, when necessary. Requests should be addressed to marco.valgimigli@eoc.ch. The analytic code, individual study protocols (which were individually previously published), SIDNEY-4 protocol (available at PROSPERO, CRD42024506083) and individual study case report forms can be requested to marco.valgimigli@eoc.ch.

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Table 1. Baseline characteristics

	Overall population N=24407	Ticagrelor monotherapy N=12199	DAPT N=12208	P-value
Included Study				
GLASSY	7509 (30·8%)	3753 (30·8%)	3756 (30·8%)	
SMART-CHOICE	536 (2·2%)	273 (2·2%)	263 (2·2%)	
TICO	3004 (12·3%)	1499 (12·3%)	1505 (12·3%)	
TWILIGHT	7119 (29·2%)	3555 (29·1%)	3564 (29·2%)	
T-PASS	2839 (11·6%)	1419 (11·6%)	1420 (11·6%)	
ULTIMATE-DAPT	3400 (13·9%)	1700 (13·9%)	1700 (13·9%)	
Age, years	63·4 ± 10·6 (n=24407)	63·4 ± 10·6 (n=12199)	63·3 ± 10·5 (n=12208)	0·693
Age ≥65 years	11473/24407 (47·0%)	5769/12199 (47·3%)	5704/12208 (46·7%)	0·376
Sex (Female)	5525/24407 (22·6%)	2771/12199 (22·7%)	2754/12208 (22·6%)	0·771
Height, m	169·1 ± 8·9 (n=24360)	169·1 ± 8·9 (n=12179)	169·1 ± 8·9 (n=12181)	0·649
Weight, Kg	77·4 ± 16·4 (n=24370)	77·5 ± 16·5 (n=12183)	77·3 ± 16·4 (n=12187)	0·443
Body mass index, kg/m²	27·0 ± 4·7 (n=24353)	27·0 ± 4·7 (n=12177)	27·0 ± 4·7 (n=12176)	0·637
Geographic region				0·998
Asia	11373 (46·6%)	5689 (46·6%)	5684 (46·6%)	0·908
North America	2972 (12·2%)	1484 (12·2%)	1488 (12·2%)	0·969
Western Europe	7892 (32·3%)	3939 (32·3%)	3953 (32·4%)	0·880
Eastern Europe	2170 (8·9%)	1087 (8·9%)	1083 (8·9%)	0·928
Diabetes	7320/24406 (30·0%)	3691/12198 (30·3%)	3629/12208 (29·7%)	0·364
Insulin treated diabetes	1681/24014 (7·0%)	821/12000 (6·8%)	860/12014 (7·2%)	0·336
Current cigarette smoker	7107/24402 (29·1%)	3503/12196 (28·7%)	3504/12206 (29·5%)	0·167

Hypercholesterolaemia	13933/24140 (57·7%)	6916/12063 (57·3%)	7017/12077 (58·1%)	0·226
Hypertension	15837/24386 (64·9%)	7918/12190 (65·0%)	7919/12196 (64·9%)	0·969
Liver disease	189/21032 (0·9%)	89/10507 (0·8%)	100/10525 (1·0%)	0·428
Peripheral artery disease	1194/18530 (6·4%)	572/9262 (6·2%)	622/9268 (6·7%)	0·138
Previous myocardial infarction	4262/24398 (17·5%)	2119/12192 (17·4%)	2143/12206 (17·6%)	0·716
Previous PCI	6311/24402 (25·9%)	3133/12197 (25·7%)	3178/12205 (26·0%)	0·530
Previous CABG	1184/24402 (4·9%)	580/12196 (4·8%)	604/12206 (4·9%)	0·484
Prior stroke	725/24399 (3·0%)	361/12193 (3·0%)	364/12206 (3·0%)	0·921
Prior bleeding	168/21555 (0·8%)	92/10772 (0·9%)	76/10783 (0·7%)	0·213
History of chronic kidney disease	3206/24106 (13·3%)	1596/12046 (13·2%)	1610/12060 (13·3%)	0·818
Chronic lung disease	804/20727 (3·9%)	402/10356 (3·9%)	402/10371 (3·9%)	0·983
Clinical presentation				
Acute coronary syndrome	18135/24405 (74·3%)	9051/12198 (74·2%)	9084/12207 (74·4%)	0·700
ST-elevation MI	4646/18135 (25·6%)	2342/9051 (25·9%)	2304/9084 (25·4%)	0·434
Non-ST-elevation MI	6832/18135 (37·7%)	3438/9051 (38·0%)	3394/9084 (37·4%)	0·391
Unstable angina	6657/18135 (36·7%)	3271/9051 (36·1%)	3386/9084 (37·3%)	0·116
Chronic coronary syndrome	6270/24405 (25·7%)	3147/12198 (25·8%)	3123/12207 (25·6%)	0·700
Aspirin on admission	17339/24405 (71·0%)	8646/12198 (70·9%)	8693/12207 (71·2%)	0·567
PRECISE-DAPT score*	15·3 ± 8·8 (n=23394)	15·4 ± 8·8 (n=11674)	15·3 ± 8·8 (n=11720)	0·601
PRECISE-DAPT score ≥25	3232/23394 (13·8%)	1618/11674 (13·9%)	1614/11720 (13·8%)	0·844
Creatinine clearance, mL/min	87·0 (72·0–101·6) (n=24012)	87·2 (72·1–101·8) (n=11999)	86·8 (71·8–101·5) (n=12013)	0·270
Haemoglobin, g/dL	14·1 ± 2·5 (n=23691)	14·1 ± 2·2 (n=11834)	14·1 ± 2·8 (n=11857)	0·834
Left ventricular ejection fraction, %	55·3 ± 10·9 (n=13755)	55·2 ± 10·8 (n=6890)	55·4 ± 11·0 (n=6865)	0·431

CABG=coronary artery bypass graft; DAPT=dual antiplatelet therapy; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; MI=myocardial infarction;

PCI=percutaneous coronary intervention; SMART-CHOICE=Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; TICO=Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome; T-PASS=Ticagrelor monotherapy in patients treated with new-generation drug-eluting stents for acute coronary syndrome; TWILIGHT=Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention; ULTIMATE-DAPT=Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes. *Includes five items: age, creatinine clearance, white blood cell count, haemoglobin, and history of bleeding.

Table 2. Clinical outcomes in the intention-to-treat population

	Ticagrelor monotherapy (N=12199)	DAPT (N=12208)	HR (95% CI)	P-value	τ^2
Primary outcomes					
Death, MI or stroke	315 (2·82%)	348 (3·24%)	0·91 (0·78–1·06)	0·216	<0·001
BARC type 3 or 5 bleeding	102 (0·89%)	237 (2·10%)	0·43 (0·34–0·54)	<0·001	0·079
All-cause death	102 (0·88%)	135 (1·24%)	0·76 (0·59–0·98)	0·034	<0·001
Secondary outcomes					
Cardiovascular death	64 (0·56%)	90 (0·82%)	0·70 (0·51–0·97)	0·031	<0·001
Non-cardiovascular death	38 (0·32%)	45 (0·42%)	0·85 (0·55–1·30)	0·447	<0·001
MI	177 (1·58%)	180 (1·65%)	0·99 (0·80–1·21)	0·895	<0·001
Stroke	64 (0·58%)	61 (0·57%)	1·05 (0·74–1·49)	0·777	<0·001
Ischaemic stroke	48 (0·43%)	48 (0·41%)	1·00 (0·67–1·50)	0·989	0·028
Haemorrhagic stroke	10 (0·10%)	6 (0·05%)	1·67 (0·61–4·60)	0·320	<0·001
Death or MI	265 (2·35%)	296 (2·73%)	0·90 (0·76–1·06)	0·202	<0·001
BARC type 2, 3 or 5 bleeding	316 (2·85%)	566 (5·14%)	0·55 (0·48–0·63)	<0·001	0·091
BARC type 5 bleeding	5 (0·04%)	6 (0·05%)	0·83 (0·25–2·74)	0·765	<0·001
Definite or probable stent thrombosis	29 (0·27%)	36 (0·33%)	0·81 (0·50–1·32)	0·389	<0·001
Definite stent thrombosis	24 (0·22%)	30 (0·28%)	0·77 (0·45–1·32)	0·340	<0·001
Probable stent thrombosis	5 (0·05%)	6 (0·05%)	0·50 (0·13–2·01)	0·329	<0·001
TIMI bleeding major	51 (0·45%)	119 (1·06%)	0·43 (0·31–0·59)	<0·001	0·43
TIMI bleeding minor	162 (1·49%)	299 (2·67%)	0·54 (0·44–0·65)	<0·001	<0·001
TIMI bleeding major or minor	212 (1·94%)	414 (3·72%)	0·51 (0·43–0·60)	<0·001	0·090
Net adverse clinical event†	397 (3·81%)	543 (5·28%)	0·73 (0·64–0·83)	<0·001	0·047

* P value for non-inferiority=0·004 of ticagrelor monotherapy versus DAPT in the per-protocol population.

† Net adverse clinical event was defined as composite of all-cause death, myocardial infarction, stroke, and BARC type 3 or 5 bleeding.

BARC=Bleeding Academy Research Consortium; DAPT=dual antiplatelet therapy; MI=myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction.

Table 3. Clinical outcomes for patients with acute coronary syndrome in the intention-to-treat population

	Ticagrelor monotherapy (N=9051)	DAPT (N=9084)	HR (95% CI)	P-value	τ^2
Primary outcomes					
Death, MI or stroke	229 (2·77%)	261 (3·32%)	0·89 (0·74–1·06)	0·181	<0·001
BARC type 3 or 5 bleeding	67 (0·79%)	196 (2·37%)	0·34 (0·26–0·45)	<0·001	<0·001
All-cause death	74 (0·86%)	101 (1·25%)	0·74 (0·55–0·99)	0·045	<0·001
Secondary outcomes					
Cardiovascular death	44 (0·52%)	66 (0·81%)	0·66 (0·45–0·96)	0·032	<0·001
Non-cardiovascular death	30 (0·34%)	35 (0·44%)	0·86 (0·53–1·39)	0·533	<0·001
MI	125 (1·51%)	135 (1·71%)	0·94 (0·74–1·20)	0·605	0·019
Stroke	53 (0·65%)	49 (0·63%)	1·09 (0·74–1·60)	0·674	0·003
Ischaemic stroke	38 (0·46%)	36 (0·41%)	1·06 (0·67–1·67)	0·799	0·034
Haemorrhagic stroke	10 (0·13%)	6 (0·07%)	1·67 (0·61–4·61)	0·318	<0·001
Death or MI	189 (2·26%)	219 (2·75%)	0·87 (0·72–1·06)	0·165	<0·001
BARC type 2, 3 or 5 bleeding	186 (2·25%)	422 (5·25%)	0·44 (0·37–0·52)	<0·001	<0·001
BARC type 5 bleeding	5 (0·06%)	5 (0·06%)	1·00 (0·29–3·47)	0·996	<0·001
Definite or probable stent thrombosis	18 (0·24%)	26 (0·34%)	0·70 (0·38–1·28)	0·244	<0·001
Definite stent thrombosis	13 (0·17%)	22 (0·30%)	0·55 (0·27–1·12)	0·099	<0·001
Probable stent thrombosis	5 (0·07%)	4 (0·05%)	0·50 (0·09–2·71)	0·418	<0·001
TIMI bleeding major	33 (0·40%)	97 (1·19%)	0·34 (0·23–0·51)	<0·001	0·195
TIMI bleeding minor	103 (1·25%)	230 (2·79%)	0·45 (0·36–0·57)	<0·001	<0·001
TIMI bleeding major or minor	136 (1·65%)	324 (3·98%)	0·42 (0·34–0·51)	<0·001	0·004
Net adverse clinical event*	282 (3·73%)	418 (5·61%)	0·68 (0·58–0·79)	<0·001	0·036

* Net adverse clinical event was defined as composite of all-cause death, myocardial infarction, stroke, and BARC type 3 or 5 bleeding.

BARC=Bleeding Academy Research Consortium; DAPT=dual antiplatelet therapy; MI=myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction.

Figure Legends

Figure 1. Kaplan-Meier estimates for co-primary endpoints and hazard ratios for individual trials and the pooled population

BARC=Bleeding Academy Research Consortium; CI=confidence interval; DAPT=dual antiplatelet therapy; GLASSY=GLOBAL LEADERS Adjudication Sub-Study; HR=hazard ratio; MI=myocardial infarction; SMART-CHOICE=Smart Angioplasty Research Team: Comparison Between P2Y12 Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; TICO=Ticagrelor Monotherapy After 3 Months in the Patients Treated With New Generation Sirolimus-eluting Stent for Acute Coronary Syndrome; TWILIGHT=Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention; T-PASS=Ticagrelor monotherapy in patients treated with new-generation drug-eluting stents for acute coronary syndrome; ULTIMATE-DAPT=Ticagrelor alone versus ticagrelor plus aspirin from month 1 to month 12 after percutaneous coronary intervention in patients with acute coronary syndromes.

Figure 2. Subgroup analyses for the primary composite endpoint of all-cause death, myocardial infarction, or stroke

ACS=acute coronary syndrome; CCS=chronic coronary syndrome; CKD=chronic kidney disease; DAPT=dual antiplatelet therapy; HR=hazard ratio; LAD=left anterior descending artery; PCI=percutaneous coronary intervention.