This is a repository copy of *Comparison of P2Y12 inhibitors for mortality and stent thrombosis in patients with acute coronary syndromes: Single center study of 10 793 consecutive 'real-world' patients*.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/110640/

Version: Accepted Version

Article:
Gosling, R., Yazdani, M., Parviz, Y. et al. (5 more authors) (2017) Comparison of P2Y12 inhibitors for mortality and stent thrombosis in patients with acute coronary syndromes: Single center study of 10 793 consecutive 'real-world' patients. Platelets, 28 (8). ISSN 0953-7104

https://doi.org/10.1080/09537104.2017.1280601

This is an Accepted Manuscript of an article published by Taylor & Francis in Platelets on 07/03/2017, available online:
http://www.tandfonline.com/10.1080/09537104.2017.1280601.

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

Comparison of $P2Y_{12}$ inhibitors for mortality and stent thrombosis in patients with acute coronary syndromes: single centre study of 10,793 consecutive 'real-world' patients

Authors: Rebecca Gosling[1,2], Momina Yazdani[2], Yasir Parviz[1], Ian R Hall[1], Ever D Grech[1], Julian P Gunn[1,2], Robert F Storey[1,2], Javaid Iqbal[1]

Authors' affiliations:

[1] South Yorkshire Cardiothoracic Centre, Northern General Hospital, Sheffield, UK

[2] Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, UK

Running Title: Comparison of $P2Y_{12}$ inhibitors in ACS patients

Key words: acute coronary syndromes, clopidogrel, ticagrelor, prasugrel, percutaneous coronary intervention, stent thrombosis

Corresponding Author:

Professor Robert F. Storey,

Cardiovascular Research Unit,

Centre for Biomedical Research,

Northern General Hospital,

Herries Road, Sheffield, S5 7AU, United Kingdom

Tel: + 44 114 2159554

Fax: +44 114 2711863

Email: r.f.storey@sheffield.ac.uk

ABSTRACT

Three oral platelet $P2Y_{12}$ inhibitors, clopidogrel, prasugrel and ticagrelor, are available for reducing the risk of cardiovascular death and stent thrombosis in patients with acute coronary syndromes (ACS). We sought to compare the efficacy of these antiplatelet drugs in contemporary practice.

Data were collected for 10,793 consecutive ACS patients undergoing coronary angiography at Sheffield, UK (2009-2015). Since prasugrel use was mostly restricted to the STEMI subgroup, clopidogrel and ticagrelor were compared for all ACS patients and all three agents were compared in the STEMI subgroup. Differences in outcomes were evaluated at 12 months by KM curves and log-rank test after adjustment for independent risk factors.

Of 10,793 patients with ACS (36% STEMI), 43% (4653) received clopidogrel, 11% (1223) prasugrel and 46% (4917) ticagrelor, with aspirin for all. In the overall group, ticagrelor was associated with lower all-cause mortality compared with clopidogrel (adjusted hazard ratio (adjHR) 0.82, 95% confidence intervals (CI) 0.71-0.96, p = 0.01). In the STEMI subgroup, both prasugrel and ticagrelor were associated with a lower mortality compared with clopidogrel (prasugrel vs clopidogrel: adjHR 0.65, CI 0.48-0.89, p = 0.007; ticagrelor vs clopidogrel: adjHR 0.70, CI 0.61-0.99, p = 0.05). Of the 7,595 patients who underwent PCI, 78 (1.0%) had definite stent thrombosis by 12 months. Patients treated with ticagrelor had a lower incidence of definite stent thrombosis compared with clopidogrel (0.6% vs. 1.1%; adjHR 0.51, CI 0.29-0.89, p=0.03). In the STEMI subgroup, there was no significant difference between the three groups (ticagrelor 1.0%, clopidogrel=1.5%, prasugrel=1.6%; p=0.29).

In conclusion, ticagrelor was superior to clopidogrel for reduction of both mortality and stent thrombosis in unselected invasively-managed ACS patients. In STEMI patients, both

ticagrelor and prasugrel were associated with lower mortality compared with clopidogrel but there was no significant difference in the incidence of stent thrombosis.

INTRODUCTION

Antiplatelet agents are the mainstay of treatment for patients with acute coronary syndromes (ACS) [1]. The majority of patients with ACS undergo coronary revascularization with percutaneous coronary intervention (PCI) or, less frequently, coronary artery bypass graft surgery (CABG) [2, 3]. Antiplatelet therapy is vital in these patients to prevent future ischaemic events and, in PCI-treated patients, stent thrombosis [4-8]. The choice of antiplatelet agents for patients with ACS, especially those with ST-segment elevation myocardial infarction (STEMI), remains debatable. It is recommended that all these patients should receive dual antiplatelet therapy for at least 12 months [1]. Aspirin should be continued indefinitely and low dose (75-100 mg daily) is preferred over higher doses. Clopidogrel, a $P2Y_{12}$ inhibitor, was the commonly used 2^{nd} antiplatelet agent in the last decade. However, it is a pro-drug which requires hepatic activation by the cytochrome P450 system and some patients produce ineffective levels of active metabolite leading to poor pharmacodynamic response or 'resistance' [9]. Consequently, newer $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, have been developed in recent years [9]. Prasugrel therapy, compared with clopidogrel, in ACS patients undergoing PCI has significantly reduced rates of ischaemic events, including stent thrombosis, but with an increased risk of bleeding and no significant effect on 1-year mortality [10]. Ticagrelor, a non-thienopyridine $P2Y_{12}$ inhibitor, is an active drug, which, following intestinal absorption, can rapidly achieve adequate levels of platelet inhibition. The PLATO trial has shown that ticagrelor reduces 1-year mortality in patients with ACS, compared with clopidogrel [11]. In PLATO, there was no difference in CABG-related bleeding with ticagrelor compared with clopidogrel but the relative increase in non-CABG-related bleeding, including those managed with planned invasive strategy, was similar to that seen previously with prasugrel [11, 12]. However, there is very limited data on

comparison of newer $P2Y_{12}$ inhibitors with clopidogrel in unselected ACS patients [13]. Furthermore, only one clinical trial with a modest sample size (1230 patients) has directly compared prasugrel with ticagrelor and this has shown no difference in outcomes, although it was terminated early for futility [14], and the results of further comparative efficacy studies are awaited [15]. We aimed to investigate the effect of the introduction of prasugrel and ticagrelor on all-cause mortality and stent thrombosis in this large single-centre, all-comers registry.

METHODS

Study design and population

Data were collected prospectively for consecutive patients attending the cardiac catheterization laboratory of South Yorkshire Cardiothoracic Centre and undergoing coronary angiography between Jan 2009 and June 2015 for the management of ACS. This centre is the only one providing a PCI and CABG service to the population in and around Sheffield, a total of 1.8 million people. For patients undergoing PCI, the procedure and adjunctive pharmacotherapy was at the discretion of the operator, but adhered to relevant local, national, and international guidelines. Consequently, there was a gradual evolution of treatment during the course of the study from use of clopidogrel as the only $P2Y_{12}$ inhibitor in 2009 to introduction of the option of prasugrel in 2010, predominantly for STEMI, followed by the introduction of ticagrelor as first-line therapy in February 2012, according to our previously published protocols that included the prescription of high-intensity statin therapy, angiotensin pathway inhibitors and beta-blockers throughout the study period

[16]. Of particular note, dual antiplatelet therapy for 12 months for all ACS patients was the default approach throughout the study period. After 12 months, patients were prescribed aspirin indefinitely and so, to study the impact of dual antiplatelet therapy on clinical outcomes, follow-up was limited to 12 months. Data on adherence and switching of antiplatelet therapy were not collected and therefore our analysis was based on the intention to treat patients with dual antiplatelet therapy for 12 months. The groups were defined as per the antiplatelet agent prescribed on admission to the catheter laboratory. Any patient who had an event whilst in hospital resulting in a change of antiplatelet were defined as per the original antiplatelet prescribed. Intra-procedural unfractionated heparin, and not bivalirudin, was the default anticoagulation therapy, along with selective use of a glycoprotein IIb/IIIa inhibitor, at the operators' discretion. All patients were treated with 2nd generation drug-eluting stents or bare-metal stents, at the operators' discretion. There were no exclusion criteria. There was increasing provision of a primary PCI service to the population during the course of the study, accounting for a higher proportion of patients with STEMI in the later years.

Data Collection

Demographic, clinical, and angiographic data were collected prospectively. Renal failure was defined as creatinine level of >200 µmol/L and cardiogenic shock as systolic blood pressure <100 mmHg along with signs or symptoms of hypoperfusion. The outcome data were collected using the national mortality database and the hospital electronic database and patient records for South Yorkshire Cardiothoracic Centre. Other patient records were not available for this analysis and so we were not able to assess non-fatal ischaemic and bleeding outcomes. The Academic Research Consortium (ARC) criteria were used to define

definite stent thrombosis [17] and our data were based on the assumption that survivors of stent thrombosis would present or be referred back to our catheter laboratory since this is the only PCI centre for the region and there was no change in this arrangement during the course of the data collection. The cases were adjudicated by review of the angiography films by two cardiologists independently and, in cases of difference of opinion, by a third cardiologist as a referee.

Data analysis

Data are presented as mean ± SD or as percentages (proportions) unless stated otherwise. Analysis was carried out using Student's t-test or one-way ANOVA for continuous variables and Chi-squared or Fisher's exact test for categorical variables. Variables with significant trend ($p \leq 0.1$) were entered in a Cox proportional hazards model to identify factors independently associated with mortality and stent thrombosis. Difference in outcomes among patients receiving different $P2Y_{12}$ inhibitors was evaluated by Kaplan-Meier survival curves and log-rank test. Clopidogrel and ticagrelor were compared for all ACS patients and all three agents were compared in the STEMI subgroup. All statistical analyses were performed using SPSS version 21 (IBM SPSS Inc., New York, USA) and R software version-2.13.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

During the study period, 10,793 patients with ACS underwent coronary angiography. The mean age was 63.6 ± 12.7 years; 70% of the patients were males and 15% had diabetes.

About two-thirds (64%) of the procedures were performed for non-ST elevation acute coronary syndrome (NSTE-ACS) and the remaining (36%) were for STEMI. Of all ACS patients, 43% (n=4653) received clopidogrel, 46% (n=4917) received ticagrelor and 11% (n=1223) received prasugrel. Of the prasugrel-treated patients, 93% (n=1136) had STEMI and only 7% (n=87) had NSTE-ACS so only the STEMI cohort was included in the analyses. ACS patients treated with clopidogrel were slightly older but less frequently had STEMI or renal failure compared to those treated with ticagrelor (Table 1). This partly reflected an increasing provision of primary PCI for STEMI during the years in which prasugrel and then ticagrelor were introduced as options.

Of the 3920 (36%) of patients who underwent coronary angiography for STEMI, the mean age was 62.9 ± 12.9, 73% were male and 12% had diabetes. 29% (n=1130) received clopidogrel, 29% (n=1136) prasugrel and 42% (n=1654) ticagrelor. Differences were noted in some clinical characteristics between the three groups (Table 2): prasugrel-treated patients were younger and clopidogrel-treated patients older than those treated with ticagrelor; prior history of stroke/TIA was more common in clopidogrel-treated patients; and cardiogenic shock was more common in ticagrelor-treated patients.

All-cause mortality at one year

Of the 10,793 patients with ACS, 787 (7.3%) died within one year. The use of ticagrelor was associated with significantly lower all-cause mortality at 1-year compared with clopidogrel (Figure 1A). The use of clopidogrel was an independent risk factor for mortality in multiple regression analysis (Table 3). After adjustment for the independent risk factors, there was still lower mortality in patients treated with ticagrelor (Figure 1B).

Of the 3920 patients with STEMI, 340 (8.7%) died within one year. The use of prasugrel and ticagrelor (vs clopidogrel) was associated with significantly lower all-cause mortality at 1-year (Figure 1C). After adjustment for independent risk factors, there was still lower mortality in patients treated with prasugrel and ticagrelor compared with clopidogrel (Figure 1D).

Incidence of definite stent thrombosis

Out of all ACS patients, 7595 (70%) were treated with PCI. Out of these patients, 2880 (38%) patients received clopidogrel and 3493 (46%) ticagrelor. The remaining 1222 (16%) received prasugrel.

Among PCI-treated ACS patients, 78 (1.0%) developed definite stent thrombosis within 12 months. Of these, 24 (31%) were acute (<24 hours), 32 (41%) subacute (1-30 days) and 22 (28%) late (31-365 days). Half of the stent thrombosis events in patients treated with prasugrel or ticagrelor were acute whereas about one-quarter of these events were acute in clopidogrel-treated patients (Table 4).

The use of ticagrelor was associated with a lower incidence of definite stent thrombosis at one year compared with clopidogrel (Figure 2A). Clopidogrel was an independent risk factor for definite stent thrombosis in multiple regression analysis (Table 5). After adjustment for independent risk factors, there was still lower risk of stent thrombosis in ticagrelor-treated patients (Figure 2B).

Of the 3881 patients undergoing PCI for STEMI, 51 (1.3%) developed stent thrombosis within 12 months. There was no significant difference in the incidence of stent thrombosis between clopidogrel-, prasugrel- and ticagrelor-treated patients in unadjusted **(**Figure 2C) or

adjusted analysis (Figure 2D).

DISCUSSION

In this 'real-world' registry of 10,793 patients with ACS, we found that ticagrelor was associated with a reduction in mortality compared with clopidogrel in invasively-managed ACS patients, including after we had adjusted for differences in baseline characteristics that were attributable to increasing provision of primary PCI for STEMI during the study period and contraindications to the use of ticagrelor or prasugrel. Additionally, both ticagrelor and prasugrel were associated with a reduction in mortality compared to clopidogrel in the STEMI cohort. In all ACS patients, ticagrelor was also associated with lower rates of stent thrombosis compared to clopidogrel; however, there was no significant difference in the STEMI subgroup.

Dual antiplatelet therapy in the form of aspirin and a $P2Y_{12}$ inhibitor decreases the risks of myocardial infarction, recurrent ischaemia and cardiovascular death in a broad spectrum of ACS patients and reduces the risk of stent thrombosis and its sequelae in PCI-treated patients [18, 19]. The original dual antiplatelet regimen consisted of aspirin plus ticlopidine, which showed superiority to aspirin alone or aspirin plus warfarin [20, 21]. Ticlopidine fell out of favour due to haematological side-effects and was replaced by the safer and equally effective alternative of clopidogrel [18, 22]. However, more contemporary concerns of resistance and drug-drug interactions with clopidogrel have led to the development of the newer oral $P2Y_{12}$ antagonists, prasugrel and ticagrelor [23, 24]. Prasugrel is a pro-drug metabolized to its active form by CYP3A4 and CYP2B6 with a more rapid onset and higher

mean level of platelet inhibition compared to clopidogrel. Patients with ACS undergoing PCI and treated with dual antiplatelet including prasugrel had lower rates of myocardial infarction, urgent target-vessel revascularization, and stent thrombosis as compared to dual antiplatelet therapy with clopidogrel at 15-months follow-up of their index PCI in TRITON-TIMI-38 [10]. This benefit was mostly related to a reduction in the rates of non-fatal myocardial infarction (7.4% with prasugrel vs 9.7% with clopidogrel; HR 0.76; 95% CI 0.67 to 0.85; P<0.001) and lower rates of stent thrombosis (1.1% vs 2.4%; P<0.001). Ticagrelor is a direct-acting, reversibly-binding agent with similarly rapid onset of action compared to clopidogrel and requires twice-daily administration. In the PLATO study, among patients with ACS treated with or without an invasive strategy, there was a reduction in the composite endpoint of death from vascular causes, myocardial infarction or stroke when ticagrelor was included in the dual antiplatelet therapy regimen as compared to clopidogrel (9.8% for ticagrelor vs 11.7% with clopidogrel; HR 0.84; 95% CI 0.77 to 0.92; p<0.001) [11]. Ticagrelor also significantly reduced the rate of stent thrombosis [25]. A recent meta-analysis of the randomized trials has also shown the beneficial effect of new $P2Y_{12}$ inhibitors over clopidogrel [26]. The SWEDEHEART registry confirmed the benefit of ticagrelor (vs clopidogrel) in a real-world registry of 45,073 patients albeit with a higher bleeding rate [13]. Our data from a large all-comers population have further confirmed the benefit of ticagrelor in all ACS patients on both mortality and stent thrombosis that was seen in the clinical trials and recent registry.

Both prasugrel and ticagrelor were associated with reduced mortality compared to clopidogrel in patients with STEMI, however there was no significant difference between the two newer agents (Figures 1D and 2D). For patients with NSTE-ACS, ticagrelor is

recommended in preference to clopidogrel regardless of treatment strategy [1]. In the PLATO trial, ticagrelor was superior to clopidogrel for patients with NSTE-ACS whether treated medically or with revascularization [27, 28]. Whereas the TRITON-TIMI trial showed benefits of prasugrel compared to clopidogrel in patients with NSTE-ACS treated with PCI, the TRILOGY ACS trial found no benefit with prasugrel compared to clopidogrel in patients with medically-treated ACS [29]. Consequently, prasugrel is only recommended for NSTE-ACS managed with PCI. For patients with STEMI managed with primary PCI, both prasugrel and ticagrelor are recommended in preference to clopidogrel for patients without contraindications [3, 30]. Studies of platelet reactivity in STEMI patients have shown similar onsets of action of prasugrel and ticagrelor loading doses, with evidence of both being delayed in some of these patients, at least partly due to morphine treatment [31-34]. We found no significant difference in stent thrombosis rates in the STEMI group with the newer $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) compared to clopidogrel. Furthermore, a higher proportion of the stent thrombosis seen in STEMI occurred acutely (<24 hours) (STEMI 45%, all ACS 31%). This may in part be explained by the increased administration of morphine in these patients. There may potentially be a role of intravenous $P2Y_{12}$ inhibitors in these patients [35, 36].

Our results are also consistent with the PRAGUE-18 study [14], where 1230 patients undergoing primary PCI for ACS were randomly assigned to prasugrel or ticgarelor. There was no significant difference in the primary outcome comprising death, re-infarction, urgent target vessel revascularization, stroke, or serious bleeding observed at 30 days. Currently most centres are using one or other newer $P2Y_{12}$ inhibitor for patients with STEMI treated with primary PCI; however, it may be appropriate to have both drugs available and use one

or the other based on clinical profile of individual patients and relative contraindications or side effects of these drugs. Prasugrel is generally not recommended in older (>75 years) patients and is contraindicated in those with a history of stroke, whereas ticagrelor may be avoided in patients with sinoatrial node dysfunction untreated with permanent pacemaker or with intolerable dyspnoea related to ticagrelor.

Study limitations: This is an observational study, with the data derived from a prospectively compiled registry. Data for bleeding complications, myocardial infarction or stroke were not available and we relied on referral of survivors of stent thrombosis back to our PCI centre for recording of this complication. In addition, some aspects of the data were unconfirmed; for example, we did not evaluate patients' adherence to their antiplatelet treatment and our results are based on antiplatelet prescription at index admission. Rates of stent thrombosis in the STEMI subgroup were low making interpretation difficult. Because of the nature of the registry, we did not include ACS patients who did not undergo coronary angiography and so our results only provide data on ACS patients who are managed invasively.

Conclusion: Ticagrelor is associated with improved survival and a reduction in stent thrombosis compared with clopidogrel in invasively-managed ACS patients. Both ticagrelor and prasugrel are associated with reduced mortality in the STEMI cohort compared with clopidogrel but no significant difference in stent thrombosis was seen in this group. Further head-to-head comparison of prasugrel and ticagrelor for STEMI patients is warranted in an adequately powered clinical trial.

ACKNOWLEDGMENTS

We are grateful to all the interventional cardiologists at South Yorkshire Cardiothoracic Centre. We would also like to thank Louisa Alcock for help with data extraction.

DECLARATION OF INTEREST STATEMENT

RF Storey reports research grants, consultancy fees, and honoraria from AstraZeneca; research grants and consultancy fees from PlaqueTec; and consultancy fees from Aspen, Bayer, ThermoFisher Scientific, Bristol-Myers Squibb/Pfizer alliance, and The Medicines Company. The other authors report no conflicts of interest.

FIGURE LEGENDS

Figure 1. Cumulative incidence of all-cause mortality over 1 year showing (A) unadjusted rates in all ACS patients treated with either clopidogrel or ticagrelor, (B) adjusted rates in all ACS patients treated with either clopidogrel or ticagrelor, (C) unadjusted rates in STEMI patients treated with clopidogrel, prasugrel or ticagrelor, and (D) adjusted rates in STEMI patients treated with clopidogrel, prasugrel or ticagrelor. HR: hazard ratio; CI: confidence intervals.

Figure 2. Cumulative incidence of definite stent thrombosis over 1 year showing (A) unadjusted rates in all ACS patients treated with either clopidogrel or ticagrelor, (B) adjusted rates in all ACS patients treated with either clopidogrel or ticagrelor, (C) unadjusted rates in STEMI patients treated with clopidogrel, prasugrel or ticagrelor, and (D) adjusted rates in STEMI patients treated with clopidogrel, prasugrel or ticagrelor. HR: hazard ratio; CI: confidence intervals.

REFERENCES

1. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brotons C, Chew DP, Gencer B, Hasenfuss G, Kjeldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2015; 37:267-315.
2. Iqbal J, Serruys PW, Taggart DP. Optimal revascularization for complex coronary artery disease. Nat Rev Cardiol. 2013; 10:635-47.
3. Windecker S, Kolh P, Alfonso F, Collet J-P, Cremer J, Falk V, Filippatos G, Hamm C, Head SJ, Jüni P, Kappetein AP, Kastrati A, Knuuti J, Landmesser U, Laufer G, Neumann F-J, Richter DJ, Schauerte P, Sousa Uva M, Stefanini GG, Taggart DP, Torracca L, Valgimigli M, Wijns W, Witkowski A. 2014 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2014; 35:2541-2619.
4. van Werkum JW, Heestermans AA, Zomer AC, Kelder JC, Suttorp MJ, Rensing BJ, Koolen JJ, Brueren BR, Dambrink JH, Hautvast RW, Verheugt FW, ten Berg JM. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol. 2009; 53:1399-1409.
5. Lagerqvist B, Carlsson J, Fröbert O, Lindbäck J, Scherstén F, Stenestrand U, James SK, Swedish Coronary Angiography and Angioplasty Registry Study Group. Stent thrombosis in Sweden: a report from the Swedish Coronary Angiography and Angioplasty Registry. Circ Cardiovasc Interv. 2009; 2:401-8.
6. Airoldi F, Colombo A, Morici N, Latib A, Cosgrave J, Buellesfeld L, Bonizzoni E, Carlino M, Gerckens U, Godino C, Melzi G, Michev I, Montorfano M, Sangiorgi GM, Qasim A, Chieffo A, Briguori C, Grube E. Incidence and predictors of drug-eluting stent thrombosis during and after discontinuation of thienopyridine treatment. Circulation. 2007; 116:745-54.
7. de la Torre-Hernández JM, Alfonso F, Hernández F, Elizaga J, Sanmartin M, Pinar E, Lozano I, Vazquez JM, Botas J, Perez de Prado A, Hernández JM, Sanchis J, Nodar JM, Gomez-Jaume A, Larman M, Diarte JA, Rodríguez-Collado J, Rumoroso JR, Lopez-Minguez JR, Mauri J, ESTROFA Study Group. Drug-eluting stent thrombosis: results from the multicenter Spanish registry ESTROFA (Estudio ESpañol sobre TROmbosis de stents FArmacoactivos). J Am Coll Cardiol. 2008; 51:986-90.
8. Iqbal J, Sumaya W, Tatman V, Parviz Y, Morton AC, Grech ED, Campbell S, Storey RF, Gunn J. Incidence and predictors of stent thrombosis: a single-centre study of 5,833 consecutive patients undergoing coronary artery stenting. EuroIntervention. 2013; 9:62-9.
9. Storey RF. New $P2Y_{12}$ inhibitors. Heart. 2011; 97:1262-1267.
10. Wiviott S, Braunwald E, McCabe C, Montalescot G, Ruzyllo W, Gottlieb S, Neumann F-J, Ardissino D, De Servi S, Murphy S, Riesmeyer J, Weerakkody G, Gibson C, Antman E. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007; 357:2001-2015.
11. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, for the PLATO Investigators. Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes. N Engl J Med. 2009; 361:1045-1057.

12. Cannon CP, Harrington RA, James S, Ardissino D, Becker R, Emanuelsson H, Husted S, Katus H, Keltai M, Khurmi NS, Kontny F, Lewis BS, Steg PG, Storey RF, Wojdyla D, Wallentin L, the PLATelet inhibition and patient Outcomes (PLATO) investigators. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet. 2010; 375:283-93.
13. Sahlén A, Varenhorst C, Lagerqvist B, Renlund H, Omerovic E, Erlinge D, Wallentin L, James SK, Jernberg T. Outcomes in patients treated with ticagrelor or clopidogrel after acute myocardial infarction: experiences from SWEDEHEART registry. Eur Heart J. 2016; Epub ahead of print.
14. Motovska Z, Hlinomaz O, Miklik R, Hromadka M, Varvarovsky I, Dusek J, Knot J, Jarkovsky J, Kala P, Rokyta R, Tousek F, Kramarikova P, Majtan B, Simek S, Branny M, Mrozek J, Cervinka P, Ostransky J, Widimsky P, PRAGUE-18 Study Group. Prasugrel Versus Ticagrelor in Patients With Acute Myocardial Infarction Treated With Primary Percutaneous Coronary Intervention: Multicenter Randomized PRAGUE-18 Study. Circulation. 2016; 134:1603-1612.
15. Schulz S, Angiolillo DJ, Antoniucci D, Bernlochner I, Hamm C, Jaitner J, Laugwitz KL, Mayer K, von Merzljak B, Morath T, Neumann FJ, Richardt G, Ruf J, Schömig G, Schühlen H, Schunkert H, Kastrati A, Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 Trial Investigators. Randomized comparison of ticagrelor versus prasugrel in patients with acute coronary syndrome and planned invasive strategy--design and rationale of the iNtracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT) 5 trial. J Cardiovasc Transl Res. 2014; 7:91-100.
16. Joshi RR, Hossain R, Morton AC, Ecob R, Judge HM, Wales C, Walker JV, Karunakaran A, Storey RF. Evolving pattern of platelet $P2Y_{12}$ inhibition in patients with acute coronary syndromes. Platelets. 2014; 25:416-422.
17. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es G-A, Gabriel Steg P, Morel M-a, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW, on behalf of the Academic Research Consortium. Clinical End Points in Coronary Stent Trials. Circulation. 2007; 115:2344-2351.
18. Yusuf S, Zhao F, Mehta S, Chrolavicius S, Tognoni G, Fox K. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345:494-502.
19. Steinhubl SR, Berger PB, Mann JT, Fry ET, DeLago A, Wilmer C, Topol EJ, CREDO Investigators. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002; 288:2411-2420.
20. Albiero R, Hall P, Itoh A, Blengino S, Nakamura S, Martini G, Ferraro M, Colombo A. Results of a consecutive series of patients receiving only antiplatelet therapy after optimized stent implantation. Comparison of aspirin alone versus combined ticlopidine and aspirin therapy. Circulation. 1997; 95:1145-1156.
21. Schomig A, Neumann F-J, Kastrati A, Schulen H, Blasini R, Hadamitzky M, Walter H, Zitzmann-Roth E-M, Richardt G, Alt E, Schmitt C, Ulm K. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996; 334:1084-1089.
22. Quinn MJ, Fitzgerald DJ. Ticlopidine and clopidogrel. Circulation. 1999; 100:1667-72.

23. Matetzky S, Shenkman B, Guetta V, Shechter M, Bienart R, Goldenberg I, Novikov I, Pres H, Savion N, Varon D, Hod H. Clopidogrel Resistance Is Associated With Increased Risk of Recurrent Atherothrombotic Events in Patients With Acute Myocardial Infarction. Circulation. 2004; 109:3171-3175.
24. Ahmad S, Storey RF. Development and clinical use of prasugrel and ticagrelor. Curr Pharm Des. 2012; 18:5240-60.
25. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, Emanuelsson H, Finkelstein A, Husted S, Katus H, Kilhamn J, Olofsson S, Storey RF, Weaver WD, Wallentin L. Ticagrelor versus Clopidogrel in Patients with ST-elevation Acute Coronary Syndromes Intended for Reperfusion with Primary PCI ; a PLATelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. Circulation. 2010; 122:2131-41.
26. Verdoia M, Schaffer A, Barbieri L, Cassetti E, Piccolo R, Galasso G, Marino P, Sinigaglia F, De Luca G. Benefits from new ADP antagonists as compared with clopidogrel in patients with stable angina or acute coronary syndrome undergoing invasive management: a meta-analysis of randomized trials. J Cardiovasc Pharmacol. 2014; 63:339-50.
27. Lindholm D, Varenhorst C, Cannon CP, Harrington RA, Himmelmann A, Maya J, Husted S, Steg PG, Cornel JH, Storey RF, Stevens SR, Wallentin L, James SK. Ticagrelor Versus Clopidogrel in Patients With Non-ST-elevation Acute Coronary Syndrome With or Without Revascularization: Results From the PLATO Trial. Eur Heart J. 2014; 35:2083-2093.
28. Wallentin L, Lindholm D, Siegbahn A, Wernroth L, Becker RC, Cannon CP, Cornel JH, Himmelmann A, Giannitsis E, Harrington RA, Held C, Husted S, Katus HA, Mahaffey KW, Steg PG, Storey RF, James SK. Biomarkers in Relation to the Effects of Ticagrelor in Comparison With Clopidogrel in Non–ST-Elevation Acute Coronary Syndrome Patients Managed With or Without In-Hospital Revascularization: A Substudy From the Prospective Randomized Platelet Inhibition and Patient Outcomes (PLATO) Trial. Circulation. 2014; 129:293-303.
29. Roe MT, Armstrong PW, Fox KAA, White HD, Prabhakaran D, Goodman SG, Cornel JH, Bhatt DL, Clemmensen P, Martinez F, Ardissino D, Nicolau JC, Boden WE, Gurbel PA, Ruzyllo W, Dalby AJ, McGuire DK, Leiva-Pons JL, Parkhomenko A, Gottlieb S, Topacio GO, Hamm C, Pavlides G, Goudev AR, Oto A, Tseng C-D, Merkely B, Gasparovic V, Corbalan R, Cinteză M, McLendon RC, Winters KJ, Brown EB, Lokhnygina Y, Aylward PE, Huber K, Hochman JS, Ohman EM. Prasugrel versus Clopidogrel for Acute Coronary Syndromes without Revascularization. N Engl J Med. 2012; 367:1297-309.
30. Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Eur Heart J. 2012; 33:2569-2619.
31. Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, Koutsogiannis N, Damelou A, Tsigkas G, Davlouros P, Hahalis G. Randomized Assessment of Ticagrelor Versus Prasugrel Antiplatelet Effects in Patients with

ST-Segment–Elevation Myocardial Infarction. Circulation: Cardiovascular Interventions. 2012; 5:797-804.
32. Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, Carrabba N, Santini A, Gensini GF, Abbate R, Antoniucci D. Comparison of Prasugrel and Ticagrelor Loading Doses in ST-Segment Elevation Myocardial Infarction Patients: RAPID (Rapid Activity of Platelet Inhibitor Drugs) Primary PCI Study. J Am Coll Cardiol. 2013; 61:1601-1606.
33. Silvain J, Storey RF, Cayla G, Esteve JB, Dillinger JG, Rousseau H, Tsatsaris A, Baradat C, Salhi N, Hamm CW, Lapostolle F, Lassen JF, Collet JP, Ten Berg JM, Van't Hof AW, Montalescot G. P2Y12 receptor inhibition and effect of morphine in patients undergoing primary PCI for ST-segment elevation myocardial infarction. The PRIVATE-ATLANTIC study. Thromb Haemost. 2016; 116:369-378.
34. Thomas MR, Morton AC, Hossain R, Chen B, Luo L, Shahari NN, Hua P, Beniston RG, Judge HM, Storey RF. Morphine delays the onset of action of prasugrel in patients with prior history of ST-elevation myocardial infarction. Thromb Haemost. 2016; 116:96-102.
35. Bhatt DL, Stone GW, Mahaffey KW, Gibson CM, Steg PG, Hamm CW, Price MJ, Leonardi S, Gallup D, Bramucci E, Radke PW, Widimský P, Tousek F, Tauth J, Spriggs D, McLaurin BT, Angiolillo DJ, Généreux P, Liu T, Prats J, Todd M, Skerjanec S, White HD, Harrington RA. Effect of Platelet Inhibition with Cangrelor during PCI on Ischemic Events. N Engl J Med. 2013; 368:1303-13.
36. Storey RF, Sinha A. Cangrelor for the management and prevention of arterial thrombosis. Expert Rev Cardiovasc Ther. 2016; 14:991-9.

Table 1: Clinical characteristics of all ACS patients stratified by antiplatelet.

Characteristic	**Clopidogrel N = 4653**	**Ticagrelor N = 4917**	**P**
Age (years)	64.4 (+/-12.9)	63.5 (+/-12.7)	<0.001
Male	3166 (68%)	3466 (70%)	0.009
STEMI	1130 (24%)	1654 (34%)	<0.001
Renal impairment	45 (1%)	107 (2%)	<0.001
Diabetes mellitus	687 (15%)	798 (16%)	0.05
Previous stroke/TIA	143 (3%)	144 (3%)	0.68
Previous PCI	320 (7%)	359 (7%)	0.42
Previous CABG	149 (3%)	141 (3%)	0.34
GP IIb/IIIa inhibitor	581 (12%)	634 (13%)	0.55
LMS >50%	340 (7.3%)	226 (4.6%)	<0.001
Hypertension	1882 (40%)	2140 (44%)	0.002
Dyslipidaemia (treated)	2144 (46%)	1903 (39%)	<0.001
3-vessel disease	1002 (22%)	745 (15%)	<0.001
PCI	2880 (62%)	3353 (68%)	<0.001
No. of vessels attempted	1.2 +/- 0.48	1.2 +/- 0.47	0.801
No. of stents used	1.59+/- 0.92	1.47+/- 0.87	<0.001
Referred for CABG	458 (10%)	292 (6.2%)	<0.001

STEMI: ST-elevation myocardial infarction; TIA: transient ischaemic attack; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery; GP: glycoprotein; LMS: Left main stem

Table 2: Clinical characteristics of ST-elevation myocardial infarction patients according to antiplatelet therapy.

Characteristic	**Clopidogrel N = 1130**	**Prasugrel N = 1136**	**Ticagrelor N = 1654**	**P**
Age (years)	65.2 +/- 13.7	60.8 +/- 11.7	62.8 +/-12.9	<0.001
Male	804 (71%)	870 (77%)	1189 (72%)	0.005
Renal impairment	12 (1%)	7 (1%)	23 (1%)	0.144
Diabetes mellitus	141 (13%)	121 (11%)	216 (13%)	0.147
Hypertension	413 (37%)	388 (34%)	593 (36%)	0.477
Dyslipidaemia	444 (39%)	419 (37%)	470 (29%)	<0.001
Previous stroke/TIA	57 (5%)	32 (2.8%)	40 (2%)	<0.001
Previous PCI	76 (7%)	78 (7%)	139 (8%)	0.172
Previous CABG	19 (2%)	16 (1%)	24 (1%)	0.805
Cardiogenic shock	23 (2%)	18 (2%)	64 (4%)	<0.001
GP IIb/IIIa inhibitors	391 (35%)	364 (32%)	529 (32%)	0.299
LMS >50%	61 (5.4%)	31 (2.7%)	53 (3.2%)	0.001
3-vessel disease	234 (21%)	181 (16%)	208 (13%)	<0.001
PCI	1130 (100%)	1135 (100%)	1616 (98%)	<0.001
No. of vessels attempted	1.12+/- 0.39	1.10 +/- 0.35	1.09 +/- 0.39	0.139
No. of stents used	1.54+/-0.81	1.50 +/- 0.82	1.35+/-0.77	<0.001
Referred for CABG	0 (0%)	0 (0%)	7 (0.4%)	<0.001

TIA: transient ischaemic attack; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery; LMS: Left main stem; GP: Glycoprotein

Table 3: Independent predictors of mortality in all acute coronary syndrome patients

Variable	HR	95% CI	p
Cardiogenic shock	7.006	5.247-9.353	<0.001
Renal impairment	3.048	2.199 – 4.226	<0.001
Emergency procedure	2.396	1.959 – 2.929	<0.001
LMS disease	1.693	1.350 – 2.124	<0.001
3-vessel disease	1.358	1.054-1.750	0.02
Clopidogrel	1.188	1.020-1.382	0.03
Age (years)	1.057	1.050 – 1.064	<0.001
STEMI	0.805	0.649-0.999	0.05
Dyslipidaemia (treated)	0.796	0.681 – 0.932	0.004

LMS: left main stem; STEMI: ST-elevation myocardial infarction

Table 4: Incidence and timing of definite stent thrombosis according to antiplatelet therapy

	Clopidogrel	**Prasugrel**	**Ticagrelor**	**P value**
All PCI-treated ACS patients, n	2880	-	3353	
Definite ST, n (%)	33 (1.1%)	-	21 (0.6%)	0.02
Acute (% of total)	11 (33%)	-	6 (29%)	
Sub-acute (% of total)	15 (45%)	-	5 (24%)	
Late (% of total)	7 (21%)	-	10 (48%)	
All PCI-treated STEMI patients, n	1130	1136	1654	
Definite ST, n (%)	17 (1.5%)	18 (1.6%)	16 (1%)	0.29
Acute (% of total)	6 (26%)	11 (61%)	6 (38%)	
Sub-acute (% of total)	7 (48%)	5 (28%)	4 (25%)	
Late (% of total)	4 (26%)	2 (11%)	6 (38%)	

PCI: percutaneous coronary intervention; ACS: acute coronary syndromes; ST: stent thrombosis; STEMI: ST-elevation myocardial infarction

Table 5: Independent predictors of definite stent thrombosis within 12 months

Variable	HR	95% CI	p
STEMI	2.232	1.286-3.872	0.004
Diabetes	2.191	1.189-4.037	0.01
Clopidogrel	2.057	1.187-3.565	0.01
Age	0.967	0.947-0.987	0.001

STEMI: ST-elevation myocardial infarction

Fig. 1A

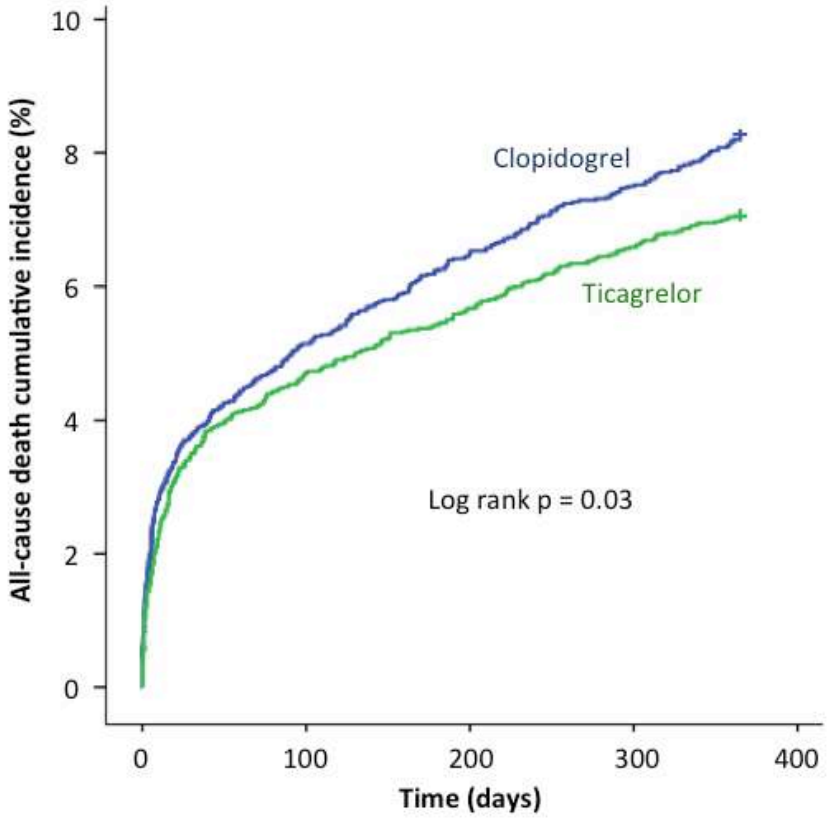

All-cause death cumulative incidence (%)
10
8
6
4
2
0
Clopidogrel
Ticagrelor
Log rank p = 0.03
0
100
200
300
400
Time (days)

Fig. 1B

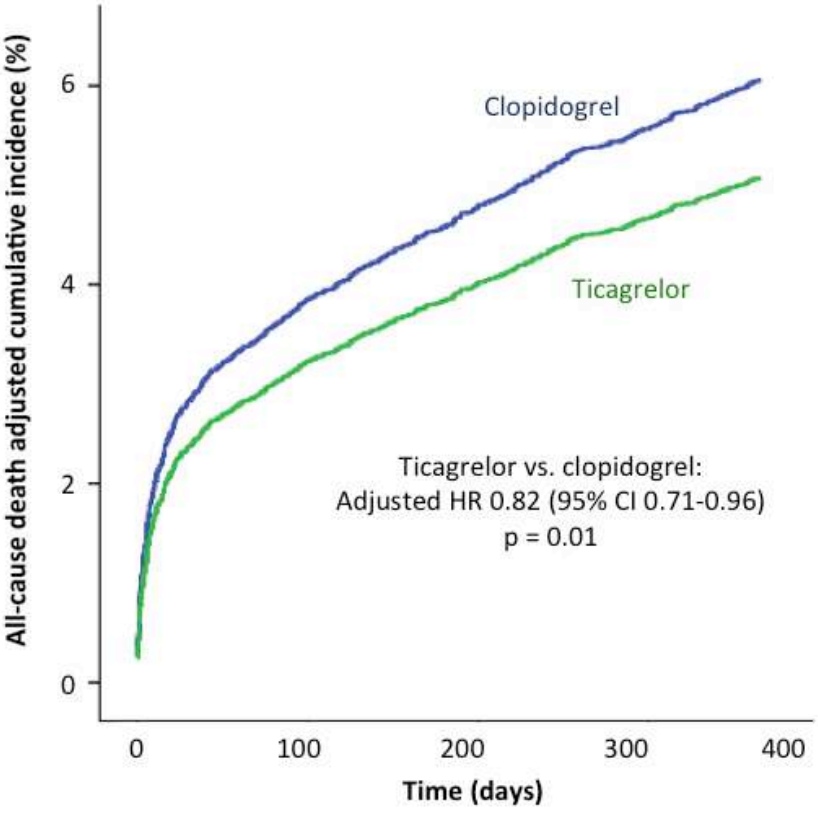

All-cause death adjusted cumulative incidence (%)
6
4
2
0
Clopidogrel
Ticagrelor
Ticagrelor vs. clopidogrel:
Adjusted HR 0.82 (95% CI 0.71-0.96)
p = 0.01
0
100
200
300
400
Time (days)

Fig. 1C

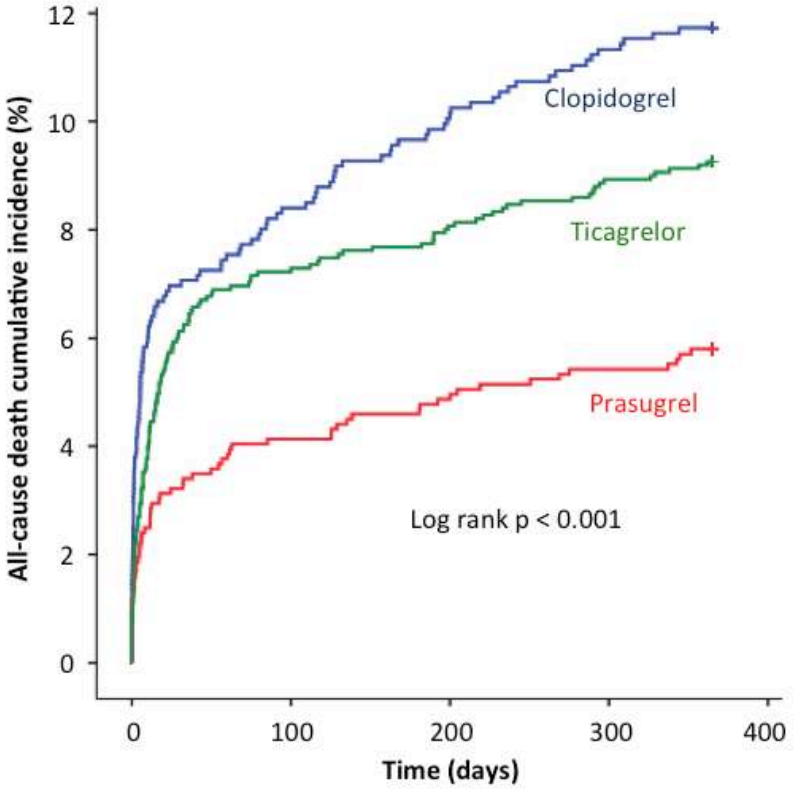

All-cause death cumulative incidence (%)
12
10
8
6
4
2
0
Clopidogrel
Ticagrelor
Prasugrel
Log rank p < 0.001
0
100
200
300
400
Time (days)

Fig. 1D

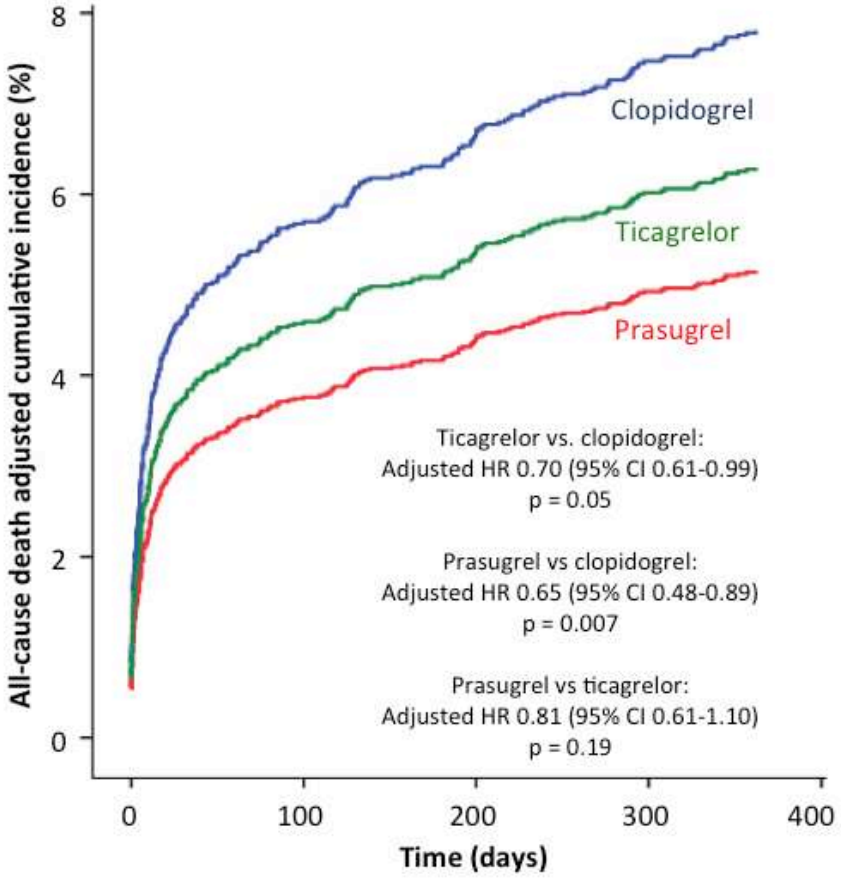

All-cause death adjusted cumulative incidence (%)
8
6
4
2
0
Clopidogrel
Ticagrelor
Prasugrel
Ticagrelor vs. clopidogrel:
Adjusted HR 0.70 (95% CI 0.61-0.99)
p = 0.05
Prasugrel vs clopidogrel:
Adjusted HR 0.65 (95% CI 0.48-0.89)
p = 0.007
Prasugrel vs ticagrelor:
Adjusted HR 0.81 (95% CI 0.61-1.10)
p = 0.19
0
100
200
300
400
Time (days)

Fig. 2A

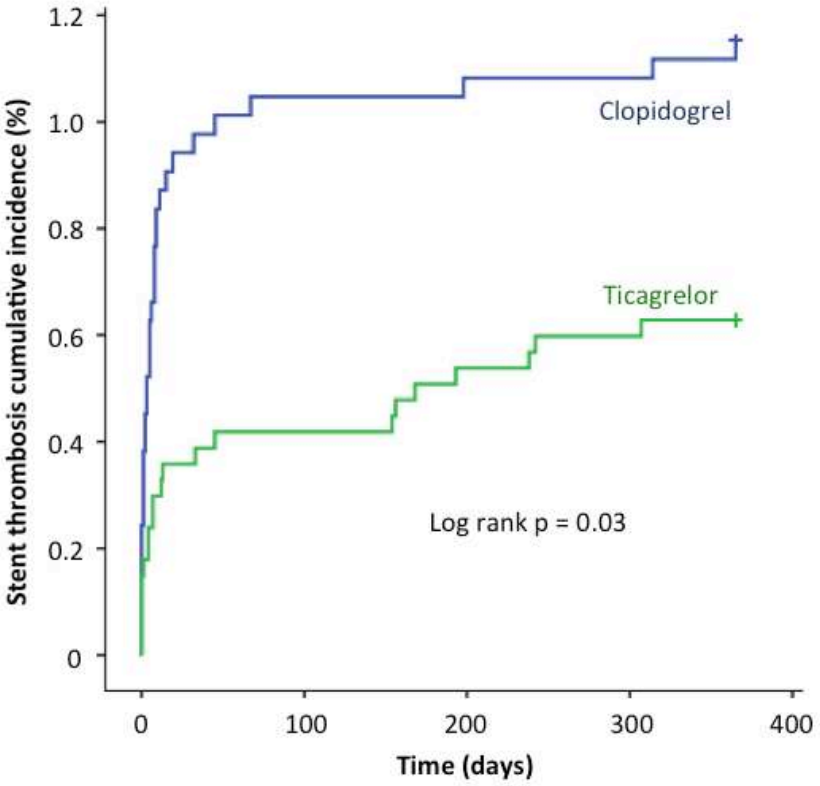

Stent thrombosis cumulative incidence (%)
1.2
1.0
0.8
0.6
0.4
0.2
0
Clopidogrel
Ticagrelor
Log rank p = 0.03
0
100
200
300
400
Time (days)

Fig. 2B

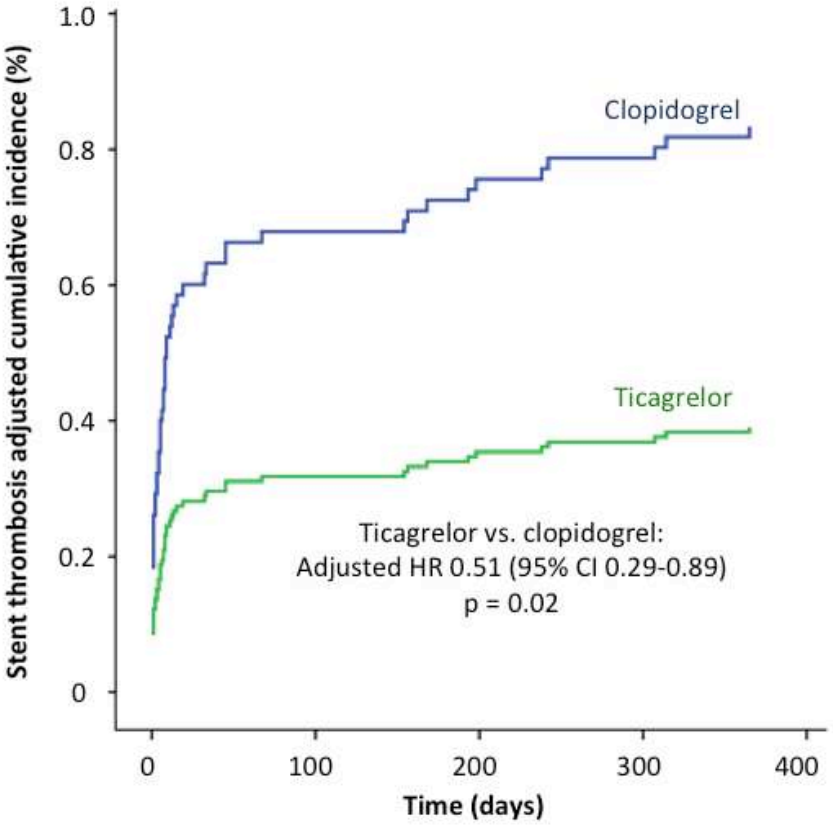

Stent thrombosis adjusted cumulative incidence (%)
1.0
0.8
0.6
0.4
0.2
0
Clopidogrel
Ticagrelor
Ticagrelor vs. clopidogrel:
Adjusted HR 0.51 (95% CI 0.29-0.89)
p = 0.02
0
100
200
300
400
Time (days)

Fig. 2C

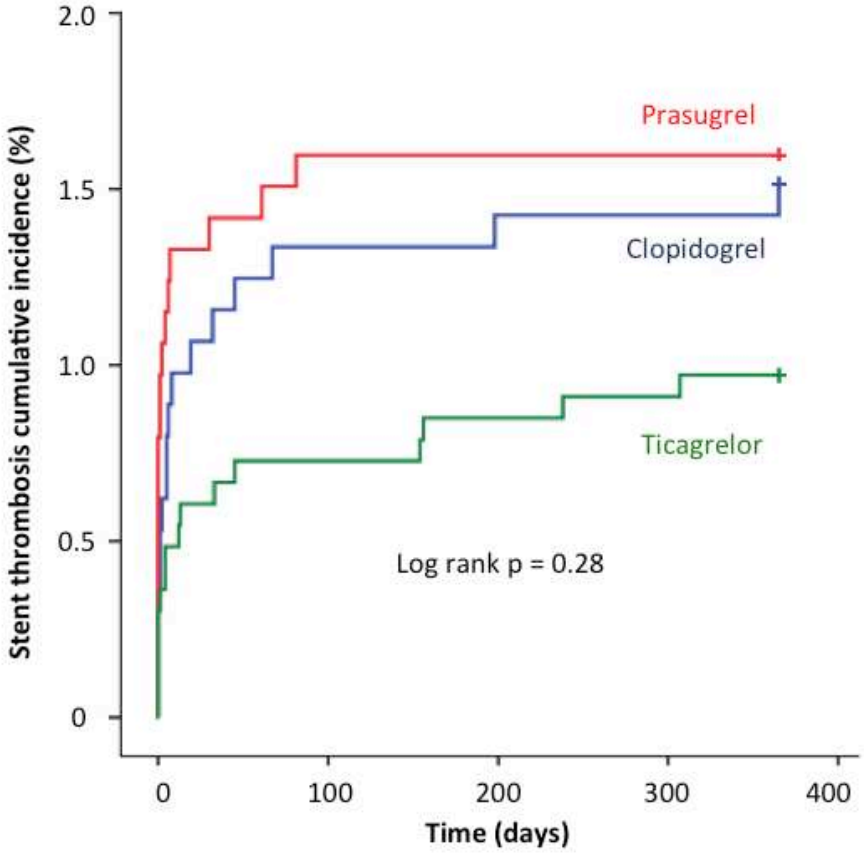
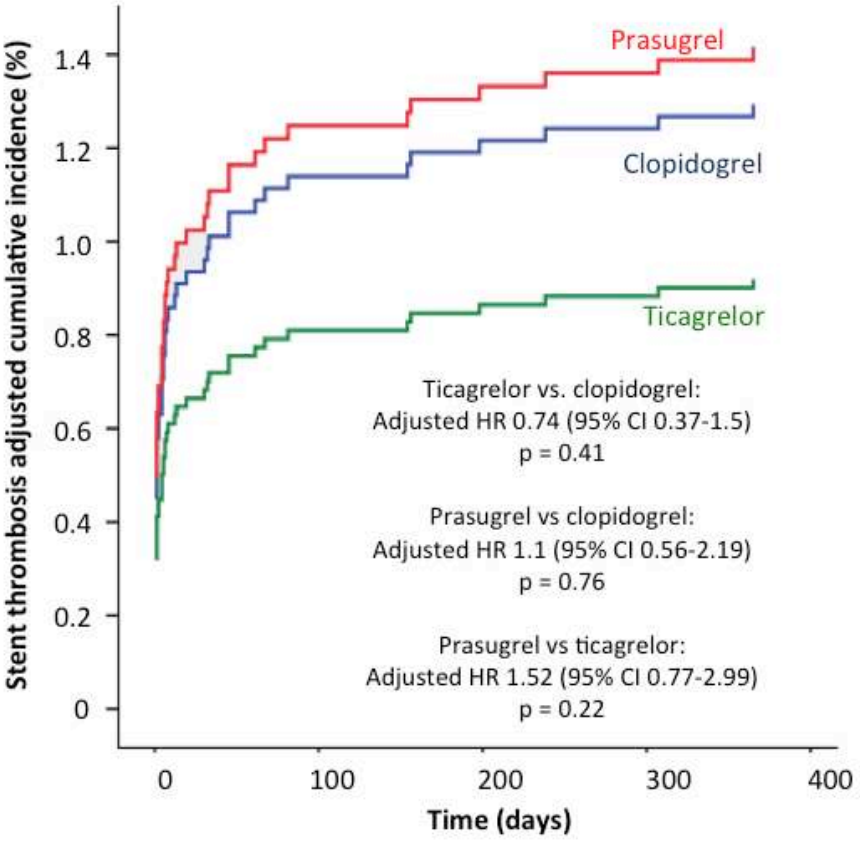

Stent thrombosis cumulative incidence (%)
2.0
1.5
1.0
0.5
0
Prasugrel
Clopidogrel
Ticagrelor
Log rank p = 0.28
0
100
200
300
400
Time (days)

Fig. 2D


Stent thrombosis adjusted cumulative incidence (%)
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0
Prasugrel
Clopidogrel
Ticagrelor
Ticagrelor vs. clopidogrel:
Adjusted HR 0.74 (95% CI 0.37-1.5)
p = 0.41
Prasugrel vs clopidogrel:
Adjusted HR 1.1 (95% CI 0.56-2.19)
p = 0.76
Prasugrel vs ticagrelor:
Adjusted HR 1.52 (95% CI 0.77-2.99)
p = 0.22
0
100
200
300
400
Time (days)