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ORIGINAL RESEARCH

Risk of Major Bleeding With Potent Antiplatelet Agents After an Acute Coronary Event: A Comparison of Ticagrelor and Clopidogrel in 5116 Consecutive Patients in Clinical Practice

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BACKGROUND: Major bleeding after acute coronary syndrome predicts a poor outcome but is challenging to define. The choice of antiplatelet influences bleeding risk.

METHODS AND RESULTS: Major bleeding, subsequent myocardial infarction (MI), and all-cause mortality to 1 year were compared in consecutive patients with acute coronary syndrome treated with clopidogrel (n=2491 between 2011 and 2013) and ticagrelor (n=2625 between 2012 and 2015) in 5 English hospitals. Clinical outcomes were identified from national hospital episode statistics. Bleeding and MI events were independently adjudicated by 2 experienced clinicians, blinded to drug, sequence, and year. Bleeding events were categorized using Bleeding Academic Research Consortium 3 to 5 and PLATO (Platelet Inhibition and Patient Outcomes) criteria and MI by the Third Universal Definition. Multivariable regression analysis was used to adjust outcomes for case mix. The median age was 68 years and 34% were women. 39% underwent percutaneous coronary intervention and 13% coronary artery bypass graft surgery. Clinical outcome data were 100% complete for bleeding and 99.7% for MI. No statistically significant difference was seen in crude or adjusted major bleeding for ticagrelor compared with clopidogrel (Bleeding Academic Research Consortium 3–5, hazard ratio [HR], 1.23; 95% CI, 0.90–1.68; P=0.2, PLATO major adjusted HR, 1.30; 95% CI, 0.98–1.74; P=0.07) except in the non-coronary artery bypass graft cohort (n=4464), where bleeding was more frequent with ticagrelor (Bleeding Academic Research Consortium 3–5, adjusted HR, 1.58; 95% CI, 1.09–2.31; P=0.017; and PLATO major HR, 1.67; 95% CI, 1.18–2.37; P=0.004). There was no difference in crude or adjusted subsequent MI (adjusted HR, 1.20; 95% CI, 0.87–1.64; P=0.27). Crude mortality was higher in the clopidogrel group but not after adjustment, using either Cox proportional hazards or propensity matched population (HR, 0.90; 95% CI, 0.76–1.10; P=0.21) as was the case for stroke (HR, 0.82; 95% CI, 0.52–1.32; P=0.42).

CONCLUSIONS: This observational study indicates that the apparent benefit of ticagrelor demonstrated in a clinical trial population may not be observed in the broader population encountered in clinical practice.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02484924.

Key Words: acute coronary syndrome ■ antiplatelet ■ bleeding

CLINICAL PERSPECTIVE

What Is New?

- In this national multicenter study of clinical practice, using adjudicated internationally recognized end points for myocardial infarction and bleeding, we have demonstrated no improvement in vascular events in the global population but a hazard for major bleeding in patients medically treated with ticagrelor compared with clopidogrel.

What Are the Clinical Implications?

- The benefits of potent antiplatelets on vascular events in clinical practice appear blunted. The risk: benefit ratio in patients in medically treated acute coronary syndrome does not favor potent antiplatelets and should influence treatment decisions.
- Understanding balance of risk between subsequent myocardial infarction and major bleeding is important and requires further research in clinical practice and particularly in patients with acute coronary syndrome who do not undergo coronary revascularization.

Nonstandard Abbreviations and Acronyms

BARC   Bleeding Academic Research Consortium
HES   hospital episode statistics
MINAP Myocardial Infarction National Audit Programme
PLATO Platelet Inhibition and Patient Outcomes

Clopidogrel had been the antiplatelet of choice to be used in combination with aspirin following acute coronary syndrome (ACS).[1] However, its poor oral bioavailability and large interindividual differences in platelet inhibition led to development of newer antiplatelet agents.[2] Ticagrelor is a novel non-thienopyridine $P2Y_{12}$ inhibitor that has gained approval on the overall net or positive outcomes from the PLATO (Platelet Inhibition and Patient Outcomes) study.[3] A benefit of ticagrelor over clopidogrel was observed in ischemic end points and all-cause death with similar rates of major bleeding (the risk of non-coronary artery bypass graft (CABG) related major bleeding [PLATO criteria] was increased with ticagrelor: 4.5% versus 3.8%, *P*=0.03). Following the PLATO trial, ticagrelor replaced clopidogrel as first-line therapy for many centers in the United Kingdom and Europe. It should be noted that the median age in the study was 62 years, with only 15% of patients being older than 75, <30% being women and <5% suffering with chronic renal disease. Age, female sex, and renal dysfunction are all factors associated with bleeding that are markedly more prevalent in populations with ACS in clinical practice.[4–8] Despite these differences between clinical practice and randomized clinical trials, the major bleeding event rate in PLATO was unusually high for any study of antiplatelets in ACS.[3,9,10] For these reasons, it is conceivable that the net clinical benefit of ticagrelor compared with clopidogrel seen in PLATO may be less marked in real world populations. As far as we are aware no large-scale multicenter studies in clinical practice have used internationally accepted standardized definitions of bleeding, thus limiting their applicability. Additionally, there is very little evidence of outcomes in those managed with medical therapy without coronary revascularization.

We aimed to evaluate the impact of ticagrelor compared with clopidogrel for the treatment of ACS in a national study of clinical practice, including patients treated with medical therapy alone, in terms of major bleeding, subsequent myocardial infarction (MI), stroke, and mortality.

METHODS

Data Sharing

As secondary analyses are in progress, data collected for the study, including individual participant data and a data dictionary defining each field, will not be made available for at least 6 months from publication.

Study Design

We selected consecutive patients treated with ticagrelor for ACS in 5 large hospitals in the northwest of England for inclusion. All 5 hospitals are linked to a cardiothoracic center where percutaneous intervention and coronary artery bypass surgery are performed. There was a gradual transition in the region as each hospital moved from clopidogrel paired with aspirin to ticagrelor with aspirin for the management of ACS between 2012 to 2013. Consecutive patients after this transition who were diagnosed with ACS (ST-segment–elevation MI, non-ST-segment–elevation MI, or unstable angina) and treated with new drug prescriptions for ticagrelor (2012–2015) were identified using MINAP (Myocardial Infarction National Audit Programme), a prospectively collected national database.[11] Demographic, laboratory, and echocardiographic data from each admission were obtained from clinical notes and the MINAP database. An identical process, but retrospectively in a reverse time order fashion, was undertaken to gather a cohort of the same size comprising consecutive patients treated with clopidogrel following an ACS immediately before the transition (2011–2013).

Inclusion criteria were any patient in the specified time period treated for ACS, as identified by MINAP, with either clopidogrel (before the guideline transition date in each individual hospital) or ticagrelor (after the respective transition date). Exclusion criteria included patients already established on the prescribed antiplatelet agent before the ACS event, those under 18 years of age, and patients treated with clopidogrel in the ticagrelor "era." A full list of the inclusion and exclusion criteria can be found in Table S1.

Outcome Measures

The primary outcome measure was defined as major bleeding at 12 months, reported by both Bleeding Academic Research Consortium (BARC) 3 to 5 and PLATO major bleeding definitions.[3,12] The secondary outcome measures were all-cause death at 12 months, subsequent MI, and stroke at 12 months. We also a priori wished to study subsets of patients undergoing revascularization versus those treated medically.

Follow-up was censored 14 days after discontinuation of the antiplatelet drug if this occurred before the 12-month period had elapsed. Follow-up was also censored 14 days after all CABG operations. This was to mitigate bias and crossover based on local surgical practice during the study period where most patients were routinely prescribed clopidogrel post-CABG. Outcome measures were assessed in a time to first event analysis, although this was treated as event/definition specific. For example, a patient first having a major bleed by PLATO criteria but not meeting BARC criteria would remain under follow-up for the possibility of a BARC major bleed.

For screening of potential outcome events and adjudication of clinical outcomes—see Data S1, Table S2.

Ethics

This article conforms to the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals.

The project was registered with the research department of each of the participating 6 hospitals. Each hospital granted consent to undertake this study. Research ethics approval was also gained (National Research Ethics Service Committee Northwest, REC reference:14/NW/1326). In view of the requirement to obtain identifiable data without explicit patient consent, approval was secured from the Health Research Authority Confidential Advisory Group (CAG, ref: 15/CAG/0134). This allowed access to data from any national hospital in England. The protocol was also produced in conjunction with and approved by a regional patient advocacy group (SURE group, Liverpool Heart and Chest Hospital).

Power Calculation

The study was powered on the anticipated difference in bleeding rates between clopidogrel and ticagrelor. The expected rate of bleeding in the clopidogrel group is 5%, based on the balance of existing studies.[1,3,9] At a power of 80% using a significance level of 5% to detect a relative risk of 1.4 the study required 2210 patients per group. Allowing for 10% loss to follow-up, this would require 2456 patients per group to detect a relative risk increase of 40% with ticagrelor compared with clopidogrel. We therefore aimed to include at least 5000 consecutively treated patients, with ≈2500 in each group.

Statistical Analysis

Continuous variables are presented as median (with 25th and 75th percentile) with comparisons made using the Wilcoxon rank sum test. Categorical variables are shown as frequency and percentages with comparisons made using χ^2 tests or the Fisher's exact test as appropriate.

To adjust for differences in baseline characteristics, we generated multilevel Cox proportional hazards models for each of the primary and secondary outcomes. Log-normal frailty survival models were constructed, with the clustered hospital effect incorporated as independent and identically distributed random variables. Variable selection for each model was undertaken using a combination of stepwise selection and assessment of the Akaike information criterion (lower values indicate a better fit) before fitting the final random effects models.

Unadjusted and adjusted hazard ratios (HR) and 95% CI are reported for each outcome. Intrarater agreement was calculated using the Cohen kappa statistic.[13]

In all cases $P<0.05$ was considered significant. The analysis was carried out using the SAS system for Windows v9.3 (SAS Institute, Cary, NC).

RESULTS

Figure 1 outlines the process used to identify participants for inclusion in the study. Duplicated entries and participants with multiple entries and follow-up periods crossing over led to exclusion of 109 patients. The final cohort consisted of 5116 individual consecutive patients with ACS.

The median age was 68 years (interquartile range 57–78, 30.5% over 75 years) and 34% were women. Coronary revascularization was undertaken as part of
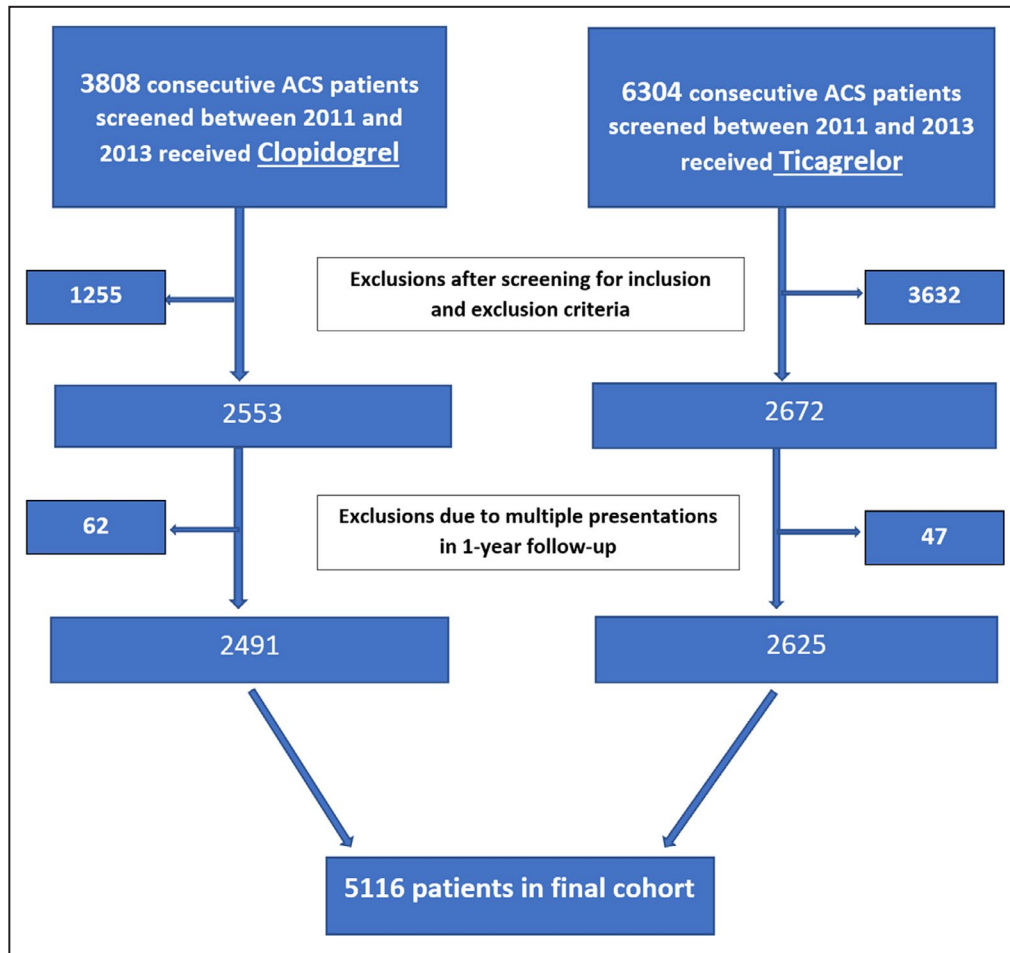
Figure 1. Flowchart of final population.
ACS indicates acute coronary syndrome.

treatment by percutaneous coronary intervention (PCI) in 39% and CABG in 13%.

Table 1 describes the overall patient population split by $P2Y_{12}$ inhibitor. Patients in the clopidogrel arm were significantly older, with a greater proportion of women and with lower estimated glomerular filtration rate. Scores on the Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines scale were significantly higher, and hemoglobin lower, in the clopidogrel arm. Comorbidities including atrial fibrillation, hypertension, cerebrovascular disease, heart failure, and diabetes mellitus were significantly more prevalent in the clopidogrel arm. Triple therapy with warfarin was significantly more common with patients treated with clopidogrel compared with patients treated with ticagrelor. A much lower proportion of patients treated with clopidogrel had normal left ventricular function.

Table S3 illustrates Cox proportional hazard predictors of major bleeding (PLATO and BARC 3–5), subsequent MI, stroke, and mortality at 1 year.

Bleeding Outcomes

1194 *International Classification of Diseases, Tenth Edition (ICD-10)* codes for bleeding/anemia were identified from hospital episode statistics (HES) admitted patient care in the 5116 participants. Bleeding events occurred in 11 UK healthcare institutions. Medical notes were interrogated for all cases with 100% follow-up achieved. After the initial predefined screening process, a total of 284 patient adjudication packs were produced. Figure 2 outlines the process of study outcome derivation.

Adjudication resulted in 213 confirmed major bleeding events (by either BARC or PLATO criteria). Agreement between adjudicators was acceptable (Cohen's K=0.69 for BARC 3–5, 0.65 for PLATO major).

Table 2 and Figures S3 and S4 illustrate rates and temporal nature of bleeding according to definition and $P2Y_{12}$ inhibitor. Bleeding rates were similar (see Figure 3), although, after adjustment for comorbidities and patient demographics, there was a trend to increased PLATO major bleeding in the ticagrelor cohort (HR, 1.30; 95% CI, 0.98–1.74; P=0.07). However, after excluding patients

Table 1.   Patient Characteristics

	All Patients (n=5116)	Clopidogrel (n=2491)	Ticagrelor (n=2625)	*P* Value
Age, y	68 (57, 78)	70 (59, 80)	66 (56, 75)	<0.001
Female sex	1732 (33.9)	936 (37.6)	796 (30.3)	<0.001
eGFR (ml/min/1.73m²)	72.6 (56.7, 88.3)	68.4 (51.6, 84.4)	76.4 (62.1, 91.5)	<0.001
eGFR <15	33 (0.7)	26 (1.0)	7 (0.3)	<0.001
eGFR 15–29	175 (3.4)	115 (4.6)	60 (2.3)	<0.001
eGFR 30–44	476 (9.3)	298 (12.0)	178 (6.8)	<0.001
eGFR 45–59	789 (15.4)	448 (18.0)	341 (13.0)	<0.001
eGFR ≥60	3643 (71.2)	1604 (64.4)	2039 (77.7)	<0.001
Moderate CYP3A4 inhibitors	259 (5.1)	198 (8.0)	61 (2.3)	<0.001
Strong CYP3A4 inhibitors	3 (0.1)	1 (0.1)	2 (0.1)	>0.99
Hemoglobin g/L, (iq range)	138 (124, 150)	136 (121, 149)	140 (127, 151)	<0.001
Low hemoglobin[*]	1399 (27.4)	788 (31.6)	611 (23.3)	<0.001
CRUSADE score	27 (19, 38)	29 (21, 40)	25 (18, 34)	<0.001
CRUSADE score >40	982 (19.2)	594 (23.9)	388 (14.8)	<0.001
Atrial fibrillation	232 (4.5)	156 (6.3)	76 (2.9)	<0.001
Previous acute myocardial infarction	1112 (21.7)	566 (22.7)	546 (20.8)	0.10
Previous angina	1328 (26.0)	695 (27.9)	633 (24.1)	0.002
Hypertension	2438 (47.7)	1275 (51.2)	1163 (44.3)	<0.001
Hypercholesterolemia	1719 (33.6)	829 (33.3)	890 (33.9)	0.64
Peripheral vascular disease	281 (5.5)	134 (5.4)	147 (5.6)	0.73
Cerebrovascular disease	402 (7.9)	236 (9.5)	166 (6.3)	<0.001
Heart failure	252 (4.9)	143 (5.7)	109 (4.2)	0.009
Previous PCI	556 (10.9)	256 (10.3)	300 (11.4)	0.19
Previous CABG	349 (6.8)	175 (7.0)	174 (6.6)	0.57
Diabetes mellitus	1171 (22.9)	577 (23.2)	594 (22.6)	0.65
PCI for index ACS	2019 (39.5)	862 (34.6)	1157 (44.1)	<0.001
CABG for index ACS	652 (12.7)	278 (11.2)	374 (14.3)	<0.001
Aspirin	4996 (97.7)	2389 (95.9)	2607 (99.3)	<0.001
Warfarin	139 (2.7)	95 (3.8)	44 (1.7)	<0.001
Direct oral anticoagulant	3 (0.1)	0 (0)	3 (0.1)	0.25
Left ventricular function				
Normal	2401 (46.9)	1113 (44.7)	1288 (49.1)	0.002
Mild impairment	299 (5.8)	135 (5.4)	164 (6.3)	0.21
Moderate impairment	852 (16.7)	435 (17.5)	417 (15.9)	0.13
Severe impairment	482 (9.4)	267 (10.7)	215 (8.2)	0.002
Unknown	1082 (21.2)	541 (21.7)	541 (20.6)	0.33
ECG changes				
ST depression	1066 (20.8)	526 (21.1)	540 (20.6)	0.63
T wave inversion	1421 (27.8)	641 (25.7)	780 (29.7)	0.002
Q waves	21 (0.4)	11 (0.4)	10 (0.4)	0.74
Bundle branch block	227 (4.4)	128 (5.1)	99 (3.8)	0.02
ST-segment–elevation	718 (14.0)	358 (14.4)	360 (13.7)	0.50
Combination of above	391 (7.6)	251 (10.1)	140 (5.3)	<0.001
Paced	6 (0.1)	5 (0.2)	1 (0.1)	0.12
No ECG changes	1269 (24.8)	571 (22.9)	698 (26.6)	0.002

(*Continued*)

Table 1.   Continued

	All Patients (n=5116)	Clopidogrel (n=2491)	Ticagrelor (n=2625)	*P* Value
Admitting hospital				
Hospital A	997 (19.5)	551 (22.1)	446 (17.0)	<0.001
Hospital B	1000 (19.6)	519 (20.8)	481 (18.3)	0.02
Hospital C	821 (16.1)	336 (13.5)	485 (18.5)	<0.001
Hospital D	1167 (22.8)	525 (21.1)	642 (24.5)	0.004
Hospital E	1131 (22.1)	560 (22.5)	571 (21.8)	0.53

ACS indicates acute coronary syndrome; CABG, coronary artery bypass graft; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the American College of Cardiology/American Heart Association Guidelines; CYP3A4, cytochrome P450 3A4; eGFR, estimated glomerular function rate; and PCI, percutaneous coronary intervention. *low Hb<118g/L (women), <133g/L (men).

who underwent CABG, major bleeding at 1 year by both BARC and PLATO criteria was significantly increased in the ticagrelor cohort at 1 year (Table 3).

Subsequent Myocardial Infarction to 1 Year

There were 326 patients with I21 or I22 (acute MI or subsequent MI within 4 weeks of previous MI) as first position *ICD-10* codes identified in HES, after a blanking window of 48 hours from index event date. After interrogation of the medical notes from 12 different English healthcare institutions, 209 adjudication packs were produced. There was only 1 case where the medical notes could not be obtained (99.7% follow-up). The remaining 116 HES admissions with MI codes not put forward for adjudication were excluded because they represented duplicate codes, principally that of the index MI admission.

After adjudication there were 183 (3.6%) confirmed MI (type 1 or 2) events. Agreement between adjudicators was moderate for type 1 MI (K=0.6). A small number of events (second occurrence in same

patient) were removed for the time to first event analysis.

A total of 168 patients suffered any MI, representing 3.3% of the study population. There was no difference in the unadjusted (HR, 1.00; 95% CI, 0.73–1.37; *P*>0.99) or adjusted (HR, 1.20; 95% CI, 0.87–1.64; *P*=0.27) subsequent MI rate for patients treated with ticagrelor compared with patients treated with clopidogrel, by means of Cox proportional hazard adjustment (Table 2, Figure 3). In patients who were revascularized the subsequent MI rate did not differ between those treated with ticagrelor and those treated with clopidogrel (adjusted HR, 1.02; 95% CI, 0.63–1.64; *P*=0.95). In patients who were medically treated there was also no significant difference but a trend toward lower subsequent MI with clopidogrel (adjusted HR, 1.53; 95% CI, 1.00–2.34; *P*=0.051).

Stroke

There were 94 HES admissions identified containing the prespecified stroke *ICD-10* codes. Eight duplicate
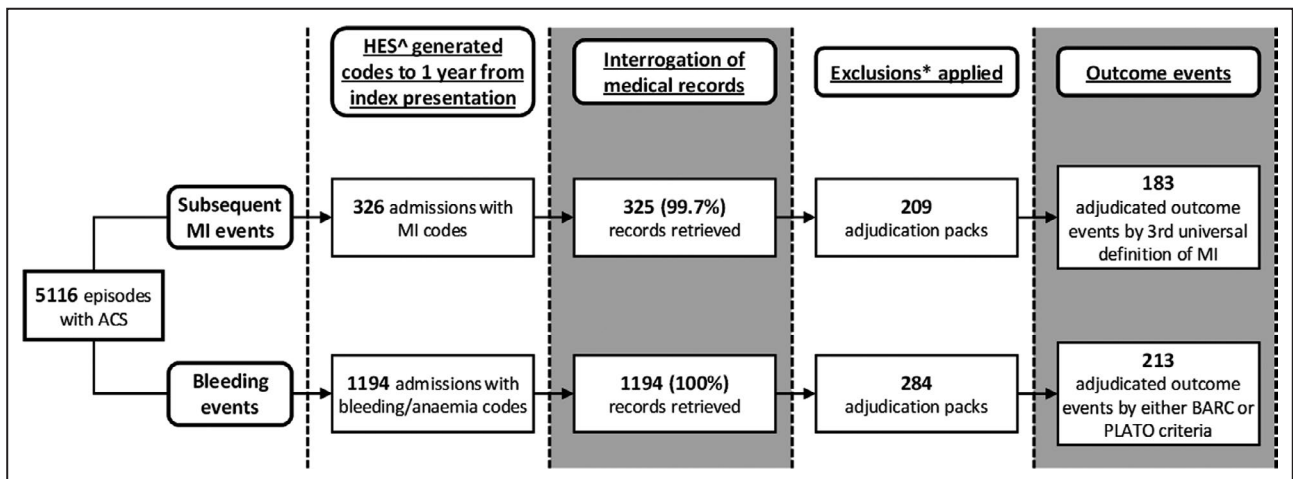
Figure 2.   Flowchart of outcome derivation of subsequent myocardial infarction and bleeding events to 1 year.
^Hospital episode statistics; *Prespecified criteria and duplications. ACS indicates acute coronary syndrome; BARC, Bleeding Academic Research Consortium; HES, hospital episode statistics; MI, myocardial infarction; and PLATO, Platelet Inhibition and Patient Outcomes.

Table 2. Primary and Secondary Outcome Rates (Unadjusted)

	All Patients (n=5116)	Clopidogrel (n=2491)	Ticagrelor (n=2625)	*P* Value
Primary bleeding outcomes at 12 mo				
BARC major bleeding, n (%)	165 (3.7)	80 (3.7)	85 (3.7)	>0.99
BARC 3a	76 (1.8)	42 (2.0)	34 (1.5)	0.23
BARC 3b	50 (1.1)	18 (0.8)	32 (1.4)	0.08
BARC 3c	11 (0.3)	5 (0.2)	6 (0.3)	0.85
BARC 4	28 (0.6)	15 (0.7)	13 (0.5)	0.59
BARC 5	18 (0.4)	8 (0.4)	10 (0.4)	0.73
PLATO major bleeding, n (%)	193 (4.3)	90 (4.2)	103 (4.5)	0.61
PLATO fatal/life-threatening bleeding	101 (2.3)	44 (2.0)	57 (2.5)	0.32
PLATO other major bleeding	92 (2.1)	46 (2.2)	46 (2.0)	0.77
Secondary outcomes at 12 mo, n (%)				
Subsequent myocardial infarction	159 (3.7)	76 (3.7)	83 (3.8)	0.86
Type 1 myocardial infarction	145 (3.5)	69 (3.4)	76 (3.5)	0.83
Type 2 myocardial infarction	18 (1.6)	10 (0.5)	8 (0.4)	0.55
Stroke, n (%)	78 (1.7)	48 (2.2)	30 (1.3)	0.02
Ischemia or unspecified stroke	73 (1.6)	46 (2.1)	27 (1.1)	0.01
Hemorrhagic stroke	5 (0.1)	2 (0.1)	3 (0.1)	0.70
All-cause mortality	606 (12.9)	378 (16.3)	228 (9.5)	<0.001

BARC indicates Bleeding Academic Research Consortium; and PLATO, Platelet Inhibition and Patient Outcomes.

codes and 8 second events in the same patients were removed, leaving a total of 78 stroke events in the time to first event analysis. This represents 1.5% of the patients in the cohort suffering a stroke in the 12-month follow-up period. The unadjusted total (hemorrhagic and ischemic) stroke rate was significantly greater with clopidogrel than ticagrelor (2.2% versus 1.3%, *P*=0.02) but not after adjustment (Table 2, Figure 3). These findings were confirmed in the propensity matched population. (Table S4).

Mortality

Table 2 and Figure 3 demonstrate the unadjusted and adjusted mortality for the clopidogrel and ticagrelor arms. After adjustment both by Cox proportional hazards modeling or by propensity score (Table S4) there was no difference in mortality at 12 months.

Propensity Matching

We tested the robustness of our analysis by performing additional propensity analysis. A total of 1954 matching pairs were selected (n=3908). Table S4 details the matched pairs in terms of demographics and comorbidities. Figure S1 illustrates dot plots of standardized mean differences in the clopidogrel and ticagrelor treatments in covariates, before and after matching. Figure S2 illustrates degree of matching of covariates, by P2Y$_{12}$ inhibitor, by a mirrored histogram. Figures S3 through S7 illustrates propensity matched Kaplan-Meier curves for bleeding, mortality, and subsequent MI and supports the results using Cox proportional hazards modelling.

Outcomes in Patients Revascularized Compared With Those on Medical Therapy Alone

Figures S8 and S9 illustrates outcomes according to whether coronary intervention took place, revascularization (PCI or CABG) versus no coronary revascularization. The principal finding in this categorization was the increased incidence of crude and adjusted PLATO major bleeding with ticagrelor in those treated medically. There was also evidence of increased bleeding after adjustment for BARC 3 to 5 bleeding. There was a signal for an increased incidence of MI with ticagrelor (adjusted HR, 1.53; 95% CI, 0.99–2.34; *P*=0.05). For those patients undergoing revascularization there was no signal for increased
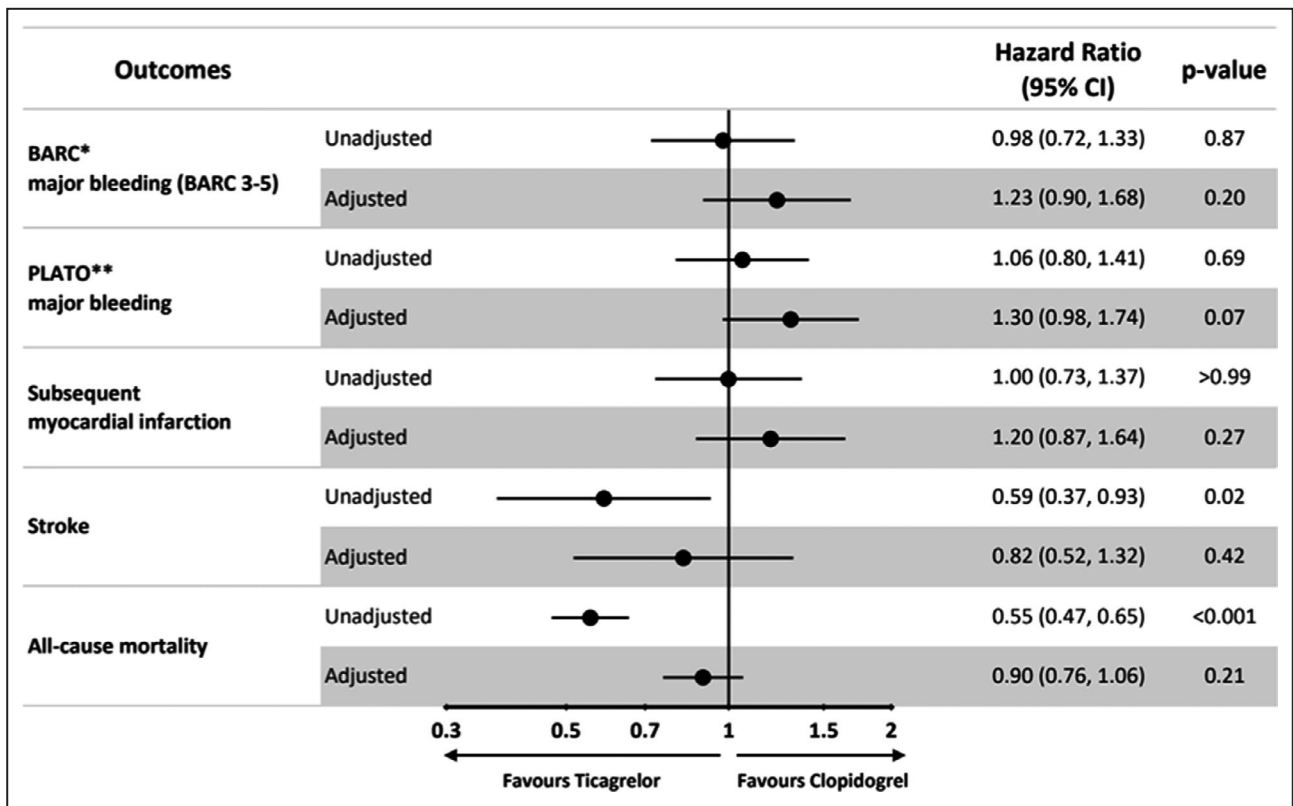
Figure 3. Unadjusted and adjusted Cox proportional hazard ratios for primary and secondary outcomes at 12 months.
*BARC indicates Bleeding Academic Research Consortium; and **PLATO, Platelet Inhibition and Patient Outcomes.

bleeding but with no evidence for a reduction in MI or stroke either.

DISCUSSION

As far as we are aware this is the first large-scale multicenter study to assess the effects of potent antiplatelet agents in clinical practice using adjudicated hard end points including internationally recognized bleeding and MI definitions. Participants were identified from 5 centers but readmissions for bleeding and MI were tracked, using HES data, to 11 and 12 healthcare facilities respectively, throughout England.

Our results provide some reassurance about the bleeding risk of ticagrelor compared with clopidogrel in a "real world" population. Results mirrored those of the PLATO study with no overall difference but an increase in bleeding in patients who were not treated with CABG. Bleeding incidence rates were slightly lower than estimates used for power sampling. However, by comparison mortality was 2.5 times greater in this study as compared with PLATO.[3] There were a total of 645 deaths at 1 year (12.6%) compared with 905 deaths (4.9%) in the PLATO study, suggesting adequate power to determine signal for all-cause mortality. This analysis also highlights differences between the PLATO clinical trial population and one

Table 3. Major Bleeding (Excluding Patients Undergoing Coronary Artery Bypass Surgery)

	All Patients (n=4464)	Clopidogrel (n=2213)	Ticagrelor (n=2251)	Unadjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)	P Value
BARC (Bleeding Academic Research Consortium) major bleeding (BARC 3–5)	123 (3.0)	55 (2.8)	68 (3.2)	1.15 (0.80–1.64)	0.45	1.52 (1.06–2.18)	0.024
PLATO (Platelet Inhibition and Patient Outcomes) major bleeding	145 (3.5)	63 (3.2)	82 (3.9)	1.22 (0.88–1.70)	0.23	1.56 (1.11–2.18)	0.01

encountered in clinical practice. It is possible competing pathologies and noncardiac causes of mortality, such as solid organ cancers and cerebrovascular disease, may have blunted any potential benefit of ticagrelor. The incidence of subsequent MI was similar to previous studies, both from observational[2] and randomized controlled trials but surprisingly lower than PLATO,[3] which was a lower risk population. There was no signal of benefit in terms of crude or adjusted MI or in adjusted mortality. Although deaths may have been sufficient to grant confidence in the results, the study was not powered for subsequent MI. Nonetheless, there was no signal of benefit with ticagrelor for subsequent MI.

We found a clear (both crude and adjusted) increase in bleeding (PLATO major bleeding criteria) in patients medically treated with ticagrelor compared with clopidogrel. (Figure S9) This differs from the PLATO study, where there was no significant difference in bleeding between clopidogrel or ticagrelor in the subgroup of patients who were medically treated.[15]

We used a hybrid approach, combining initial screening via *ICD-10* coding in HES for bleeding and MI, followed by detailed assessment of medical notes and subsequent adjudication using internationally accepted standardized definitions for bleeding and MI. It is possible that both bleeding and, less likely, subsequent MI were missed in HES. There is some evidence that bleeding can be missed using administrative data.[7] However, the accuracy of clinical coding and HES data has undoubtedly improved over time and studies now demonstrate favorable accuracy when using HES data to identify cardiovascular outcomes in trials.[16,17] Face-to-face interview or telephone contact with individual consented patients, as is standard in randomized controlled trials, are robust means of ascertaining completeness of follow-up. However, we used a wide range of codes, not solely codes denoting intracerebral bleeds or upper gastrointestinal bleeds but also including anemia. The aim of this was to increase our sensitivity for identifying possible bleeding in HES.

One must be cautious about asserting causation in observational studies.[18] We sought to test the robustness of any association by undertaking the analyses both by Cox proportional hazard analysis and by a propensity score matched population. We also undertook to reduce bias by central coordination of adjudication and blinding to sequence, year, and drug. The completeness of follow-up and the national scope of this study emphasize that the observational nature of the study is not compounded by limitations in other aspects. It is important to emphasize the implications in this analysis relate to the differences in clinical practice to that of a clinical trial population with a consequent weakening of net positive outcomes. The results cannot refute nor do they contradict PLATO[3] or PEGASUS[19] (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) outcomes.

The SWEDEHEART[20] (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry was another large observational study that used *ICD-10* coding data alone for outcome event. In that study, there was a blanking period for 1 month applied for subsequent MI that could result in missed MI, particularly with regard to acute stent thrombosis, which is heavily weighted in frequency to the first month after PCI. Also, it is difficult to compare bleeding risk due to differences in bleeding definition between *ICD-10* codes that related to hemorrhagic stroke, gastrointestinal bleeding, anemia-related bleeding, and other bleeding. It is not clear how many of these patients with admission coded bleeding would fulfill accepted standardized international definitions such as BARC or PLATO. It is noteworthy that only 18% of events with bleeding/anemia codes fulfilled major bleeding definitions when assessed by experienced clinicians and an adjudication committee in our study. (Table S1, Figure 2). Nonetheless, our results are consistent with the SWEDEHEART study to the extent that there was no reduction in MI or stroke but differ in so far as there was no reduction in all-cause death.

Our results are consistent with several other studies, which were restricted to patients who were revascularized, which suggested no benefit with ticagrelor compared to clopidogrel.[21–23]

Improvements in design of stents with thinner struts in later generation drug eluting stents could blunt the benefit of a more potent antiplatelet in terms of reduction of acute stent thrombosis and subsequent MI.[24]

This multicenter study of clinical practice in ACS, with specific focus on antiplatelet therapy, has implications for treatment with potent antiplatelets, particularly with respect to those treated medically (Figure S9). Individualized treatment based on risk scores,[25] antiplatelet testing,[26] or genotyping[27] for clopidogrel appears intuitive. However the validity of risk scores for both MI and bleeding outcomes in clinical practice is questionable; antiplatelet testing has been associated with mixed results[26,28] and the largest study of genotyping clopidogrel response was overall negative for improving outcomes.[29] Analysis of larger registries, with common definitions for end points, are warranted to corroborate these findings.

Limitations

There are clear limitations when comparing two drugs in an observational study.

Temporal changes in treatment and management are an important confounder to consider, and these remain unadjusted. However, details of the temporal changes in local interventional practice and treatments indicate that if anything patients treated with ticagrelor (latter years) would be more likely to be a beneficiary of temporal changes in treatments rather than the converse.

There was a trend toward increased radial compared with femoral access for PCI between 2011 and 2015, which is likely to reduce bleeding risk (93.2% radial procedures in 2015 versus 79.6% in 2011). Also, there was greater use of beating heart (off-pump) surgery in the latter years of this study (ticagrelor treated period) and this is likely to have reduced the risk of major bleeding. The greater use of second-generation drug eluting stents (79.4–98.2% in 2011 and 2015 respectively) in the regional tertiary center are also likely to have reduced the tendency to stent thrombosis and consequent MI, favoring ticagrelor. The clopidogrel cohort, as anticipated, represented a "higher risk" population with a greater incidence of major comorbidities and higher average age. This was also reflected in the higher numbers of MINAP entries that needed to be screened to achieve the required numbers in the ticagrelor arm (Figure 1). This is likely due to several factors, not least local prescribing practices whereby ticagrelor may be actively avoided in the elderly or high bleeding risk populations. As this was anticipated, we planned from the outset to employ both Cox proportional analysis and propensity scoring to adjust for differences in the populations. We acknowledge that these techniques cannot fully adjust for hidden confounders. Nonetheless, given that the differences in the populations described would likely favor the ticagrelor arm, we believe our results to be meaningful.

We did not seek to validate the ACS diagnosis on index admission, which triggered the original prescription of antiplatelets. The benefit of antiplatelets will be blunted in the absence of plaque rupture but the bleeding risk remains. However, this is likely to have affected both clopidogrel and ticagrelor time periods. Furthermore, MINAP is regularly audited with particular reference to ACS diagnosis.[11] The adjudicated subsequent MI rate for ROBOT-ACS (The Risk of Major Bleeding With Novel Anti-platelets: A Comparison of Ticagrelor With Clopidogrel in a Real World Population of 5000 Patients Treated for Acute Coronary Syndrome) is 3.3% in the year following index presentation, which is broadly similar to contemporaneous randomized controlled trials[14] and registry data.[2]

We had insufficient power to detect true differences in acute stent thrombosis, subsequent MI, or revascularization. A study to detect a reduction of acute stent thrombosis in the first month following PCI (from 0.48% to 0.25% using contemporary frequencies of acute stent thrombosis) would require recruitment of >18 000 patients.[2]

Our sample size was slightly underpowered considering the lower than expected event rate of major bleeds in clinical practice compared with PLATO. This is despite the much higher risk population. A number of antiplatelet studies have demonstrated a clear association of bleeding with age and in particular age >75.[6,7] The difference observed may be because of the use of different bleeding definitions in studies and alternate methods of outcome derivation (eg, HES data).

Although we did not measure compliance, we were able to analyze over 1000 patients with bleeding or MI codes to ascertain during hospital admission if there was compliance or if the antiplatelet was still being taken. We adjusted for this in our analysis. Compliance, or lack thereof, is likely to have a greater impact on patients treated with ticagrelor for 2 main reasons: a twice daily dosage schedule and a propensity to induce dyspnea.[30] Reversible binding to $P2Y_{12}$ receptors with a shorter half-life implies less antiplatelet effect if there is partial compliance.[31] Lack of compliance may have particularly affected patients who were medically treated (as there are fewer aids for compliance) in those not undergoing PCI. This may explain no reduction in MI (Figure S5).

SUMMARY

In clinical practice ticagrelor does not appear to increase overall bleeding following ACS. However, compared with clopidogrel, there is an increase in major bleeding in patients not undergoing coronary revascularization. However, we could not discern any reduction in MI, stroke, or mortality at 1 year after adjustment for case mix.

This study underscores the differences in clinical practice and a clinical trial population with implications for a blunting of net benefit outcomes with potent antiplatelets.

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SUPPLEMENTAL MATERIAL

Data S1.

Details of follow-up, adjudication of clinical outcomes

Follow-up

Screening for potential outcome events

Patient outcome events, occurring at any hospital in England (population 60 million), were tracked from Hospital Episode Statistics (HES), using their NHS number as a unique identifier. In England, HES admitted patient care (APC) data is routinely collected for all patient admissions, with coding for all diagnoses (ICD-10) and procedures (OPCS-4). [31-33] For the purposes of the primary bleeding relating outcomes, readmissions to hospital that contained an ICD-10 code for bleeding or anaemia in any diagnostic position were identified. For the main secondary outcome measure of myocardial infarction, all readmissions that contained an MI code in the primary diagnostic position were collected. See Table S2 for full list of ICD-10 codes used for each outcome event.

Adjudication of clinical outcomes

All admissions identified from HES using the relevant pre-specified ICD-10 codes were screened for potential major bleeds. This involved detailed review of corresponding medical notes by at least two independent cardiologists or physicians (LM, MM, DW, TH, MR, AE). If the event occurred at an institution in England other than those directly involved in the study, medical notes were formally requested with evidence of necessary approvals. There was an expectation that HES would identify a very large number of potential events, many of

which would not represent significant or major bleeding. Therefore, each admission was screened before being put forward for formal adjudication based on predetermined criteria. These were designed to remove events that were trivial or clearly not going to meet the definitions of major/significant bleeding. These criteria were: chronic anaemia which preceded drug commencement with no drop in haemoglobin (i.e. <2g/dL change) and no clinical evidence of bleeding, uncomplicated epistaxis, catheter related haematuria or uncomplicated access site haematoma/bleeding ('uncomplicated' was defined as not requiring intervention, no haemoglobin drop, no transfusion and no haemodynamic compromise). Details of the nature of events screened out in this phase were still recorded in the database. For all other events, a formal anonymised adjudication pack was produced detailing patient history, observations, discharge summaries, haemoglobin trends, biochemistry, the results of any imaging such as echocardiograms, ultrasound abdomens, CT scans, upper and lower gastrointestinal endoscopies and other relevant investigations. Transfusion details (the number, dates and sequence of) were also included. Events were censored if $P2Y_{12}$ inhibitor was stopped or not taken >14 days before bleeding event or if they occurred >14 days after coronary artery bypass surgery.

There was central co-ordination of adjudication and outcomes with password protected files. Adjudicators were blinded to year of event and investigational drug (clopidogrel or ticagrelor). Random ID generation ensured time sequence was blinded. These files were sent simultaneously and in a blinded fashion to two experienced clinicians. Clear instructions were provided (together with definitions) to adjudicate bleeding events according to BARC 3-5 bleeding and PLATO major bleeding criteria. Discrepant adjudications were scrutinised by a third senior clinician (consultant cardiologist or haematologist) experienced in clinical trial end point adjudication. An adjudication committee oversaw bleeding events with insufficient information or ambiguity.

A similar but separate process was undertaken for ascertainment of MI events. The medical notes of any admissions identified from HES APC as containing the relevant ICD-10 codes were screened by the research team. Any event with at least one cardiac biomarker greater than 99th percentile was put forward for formal independent blinded adjudication by the generation of adjudication packs containing all necessary Events were then adjudicated using the Third Universal Definition for myocardial infarction by two experienced clinicians.

Ascertainment of stroke events was again derived from HES using the pre specified ICD-10 codes (see supplementary materials). We considered a stroke code occurring in any diagnostic position in HES to be indicative of an event. Clear duplicate events were removed based on comparison of admission/discharge dates in HES. Stroke events were not further adjudicated and are reported as defined by HES codes only.

Death was determined by tracking via the Demographics Batch Service (DBS) which is part of the Personal Demographics Service (PDS).

Table S1. Inclusion/Exclusion Criteria.

Inclusion Criteria
1. Patient commenced on clopidogrel for ACS prior to change of ACS policy at each recruiting site, or ticagrelor for same indication afterwards.
Exclusion Criteria
1. Patient already taking the study drug in question (clopidogrel or ticagrelor) prior to the ACS event
2. Patients under 18 years of age
3. Patients in whom the drug is stopped during the same hospital admission due to clinical judgement dictating that it is no longer indicated (this does not apply to patients in whom a bleeding event is the precipitant for stopping the drug, or patients who die or have a bleeding event within 7 days of drug cessation- both of whom will be included).
4. Patients in whom the study drug may have been switched to an alternative drug for the same indication during the original hospital admission (assuming they to do not meet the clauses set out in criterion 3).
5. Patients prescribed clopidogrel in the ticagrelor time period (or "era") will not be included.

Table S2. Bleeding, MI and Stroke codes used to screen for events in HES.

ICD-10 CODE (ADULTS)	MEANING
BLEEDING	
D50	Iron Deficiency Anaemia
D62	Acute posthaemorrhagic anaemia
H356	Retinal Haemorrhage
I60	Subarachnoid haemorrhage
I61	Intracerebral haemorrhage
I62	Subdural/other intracranial haemorrhage
I850	Oesophageal Varices with bleeding
K226	Mallory Weiss syndrome
K25. (0,2,4,6)	Gastric Ulcer with bleeding
K26. (0,2,4,6)	Duodenal Ulcer with bleeding
K27. (0,2,4,6)	Peptic Ulcer with bleeding
K28. (0,2,4,6)	Gastrojejunal ulcer with bleeding
K290	Haemorrhagic Gastritis
K625	Haemorrhage of anus and rectum
K92. (0,1,2)	Haematemesis/melaena/GI haemorrhage unspecified
N93. (8,9)	Other abnormal uterine and vaginal bleeding
R04	Haemorrhage from respiratory passages
R31	Unspecified haematuria
R58	Haemorrhage not elsewhere classified
S065	Traumatic subdural haemorrhage
S066	Traumatic subarachnoid haemorrhage
S068	Other traumatic intracranial haemorrhage
T792	Traumatic secondary and recurrent haemorrhage
T810	Haemorrhage and haematoma complicating a procedure, not elsewhere
T828	Other specified complications of cardiac and vascular prosthetic devices, implants and grafts (haemorrhage)
MYOCARDIAL INFARCTION	
I21	Acute MI
I22	Subsequent MI (within 4 weeks of previous MI)
STROKE	
I60	Subarachnoid Haemorrhage
I61	Intracerebral Haemorrhage
I63	Cerebral Infarction
I64	Stroke not specified as ischaemia or infarction

Table S3. Cox proportional hazard model predictors of primary and secondary endpoints (admitting hospital was entered as a random effect in all models).

Covariate	BARC bleeding		PLATO bleeding		Subsequent MI		Stroke		Mortality	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Ticagrelor	1.229 (0.897, 1.683)	0.20	1.303 (0.975, 1.742)	0.07	1.196 (0.870, 1.644)	0.27	0.824 (0.516, 1.317)	0.42	0.896 (0.756, 1.063)	0.21
Age (years)	1.031 (1.017, 1.045)	<0.001	1.030 (1.017, 1.044)	<0.001	1.025 (1.010, 1.040)	<0.001	1.039 (1.017, 1.061)	<0.001	1.063 (1.054, 1.072)	<0.001
Female sex	-		-		-		-		0.720 (0.603, 0.860)	<0.001
eGFR	-		-		-		0.983 (0.972, 0.994)	0.002	-	
Haemoglobin	0.987 (0.979, 0.996)	0.003	0.984 (0.977, 0.992)	<0.001	0.983 (0.975, 0.992)	<0.001	-		0.993 (0.988, 0.997)	0.003
CRUSADE score	-		-		-		-		1.034 (1.026, 1.042)	<0.001
AF	1.788 (1.038, 3.080)	0.04	-		-		-		-	
Previous AMI	-		-		1.777 (1.273, 2.481)	<0.001	-		1.260 (1.051, 1.511)	0.01
Hypertension	-		-		1.721 (1.204, 2.461)	0.003	-		-	
Hypercholesterolaemia	-		-		-		-		0.737 (0.613, 0.886)	0.001
Cerebrovascular Disease	-		-		-		1.919 (1.082, 3.403)	0.03	-	
Heart Failure	-		-		2.051 (1.301, 3.232)	0.002	-		1.483 (1.166, 1.885)	0.001
Previous PCI	-		-		-		-		0.608 (0.430, 0.859)	0.005
Diabetes	-		-		1.610 (1.158, 2.240)	0.005	-		-	
LVEF: Moderate impairment	1.704 (1.224, 2.373)	0.002	1.628 (1.179, 2.248)	0.003	-		-		-	
LVEF: Severe impairment	-		-		-		-		1.646 (1.343, 2.018)	0.003
ECG: ST depression	1.667 (1.177, 2.360)	0.004	1.615 (1.185, 2.202)	0.002	-		-		1.312 (1.094, 1.573)	<0.001
ECG: T wave inversion	-		-		0.640 (0.432, 0.947)	0.03	-		-	
ECG: Combination	-		-		0.396 (0.174, 0.902)	0.03	-		-	

Table S4. Patient characteristics in propensity matched cohort.

	Clopidogrel (n = 1954)	Ticagrelor (n = 1954)	p-value
Age (years)	67 (57, 78)	67 (57, 76)	0.82
Female sex	661 (33.8)	646 (33.1)	0.60
eGFR	71.9 (57.8, 87.2)	73.0 (58.0, 87.7)	0.50
Moderate CYP3A4 inhibitors	60 (3.1)	61 (3.1)	0.91
Strong CYP3A4 inhibitors	1 (0.1)	2 (0.1)	0.56
Haemoglobin	138 (124, 150)	139 (126, 150)	0.23
CRUSADE score	27 (19, 37)	27 (19, 36)	0.40
Co-morbidities			
AF	71 (3.6)	69 (3.5)	0.85
Previous AMI	418 (21.4)	397 (20.3)	0.40
Previous Angina	502 (25.7)	484 (24.8)	0.51
Hypertension	933 (47.8)	925 (47.3)	0.79
Hypercholesterolaemia	678 (34.7)	679 (34.8)	0.97
Peripheral Vascular Disease	102 (5.2)	102 (5.2)	>0.99
Cerebrovascular Disease	138 (7.1)	138 (7.1)	>0.99
Heart Failure	98 (5.0)	88 (4.5)	0.44
Previous PCI	217 (11.1)	197 (10.1)	0.30
Previous CABG	132 (6.8)	128 (6.6)	0.80
Diabetes	448 (22.9)	457 (23.4)	0.73
PCI for index ACS	782 (40.0)	790 (40.4)	0.78
CABG for index ACS	249 (12.7)	253 (13.0)	0.84
Aspirin	1943 (99.4)	1936 (99.1)	0.13
Warfarin	40 (2.1)	38 (1.9)	0.81
DOAC	0 (0)	1 (0.1)	-
Left ventricular function			
Mild impairment	112 (5.7)	99 (5.1)	0.36
Moderate impairment	328 (16.8)	320 (16.4)	0.73
Severe impairment	175 (9.0)	182 (9.3)	0.69
ECG changes			
ST depression	414 (21.2)	394 (20.2)	0.43
T wave inversion	545 (27.9)	549 (28.1)	0.89
Q waves	6 (0.3)	8 (0.4)	0.59
BBB	92 (4.7)	86 (4.4)	0.65
ST elevation	287 (14.7)	291 (14.9)	0.86
Combination of above	129 (6.6)	133 (6.8)	0.78
Paced	1 (0.1)	1 (0.1)	>0.99
Admitting hospital			
Hospital A	402 (20.6)	390 (20.0)	0.62
Hospital B	362 (18.5)	374 (19.1)	0.62
Hospital C	302 (15.5)	315 (16.1)	0.55
Hospital D	446 (22.8)	445 (22.8)	0.97
Hospital E	442 (22.6)	430 (22.0)	0.64

Figure S1. Standardised mean differences in patient characteristics for both unmatched and propensity matched patient groups.
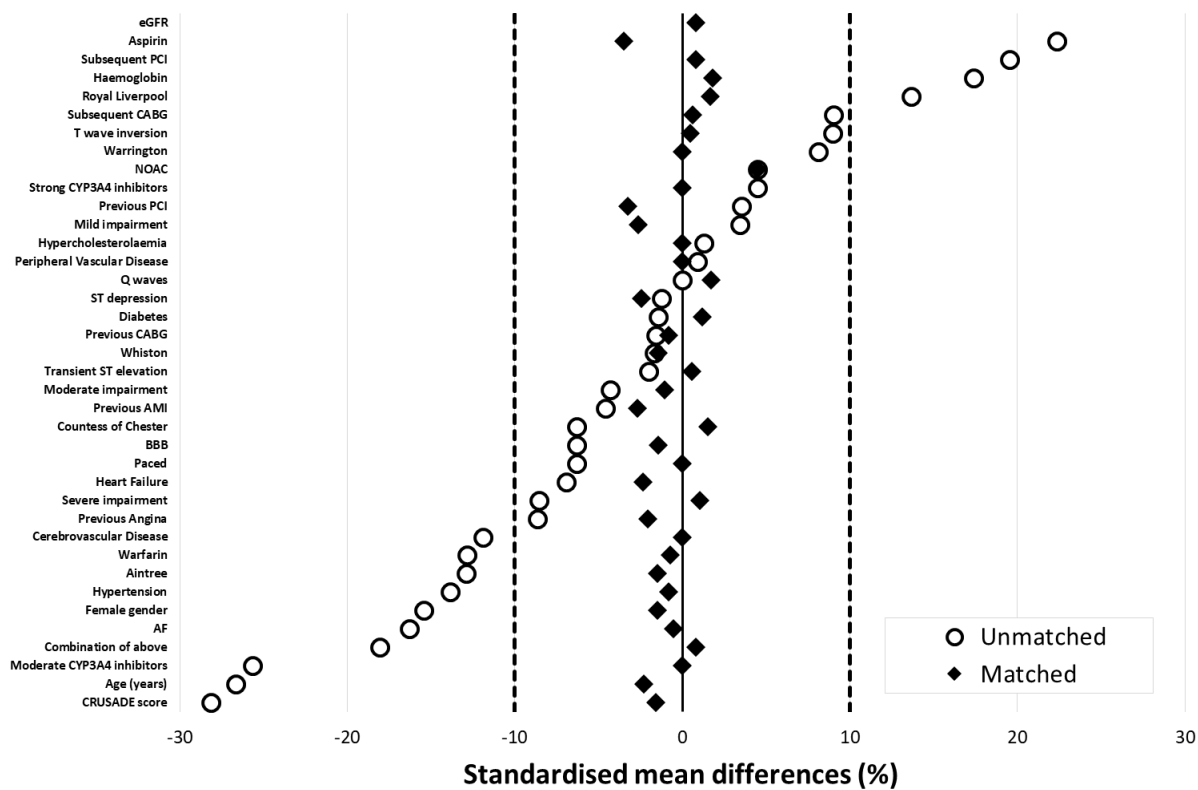
Figure S2. Mirrored histogram chart showing distribution of propensity scores in the unmatched (white bars) and matched (colored bars) patient groups.
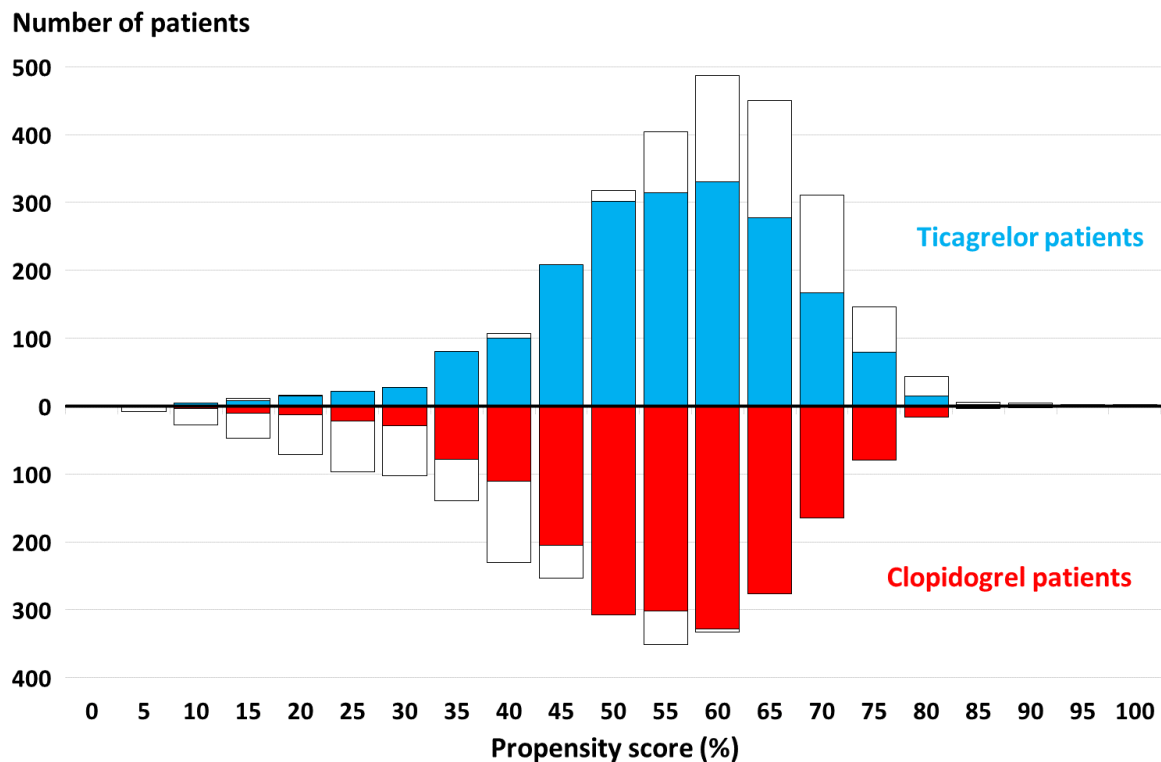
Figure S3. Kaplan-Meier chart for freedom from major bleeding in matched groups (BARC 3-5 criteria).

Cumulative probability of freedom from BARC 3-5 bleeding

Log-rank p-value = 0.52

Follow up (months)

Numbers at risk

Clopidogrel	1954	1612	1528	1483	1440
Ticagrelor	1954	1582	1506	1471	1436
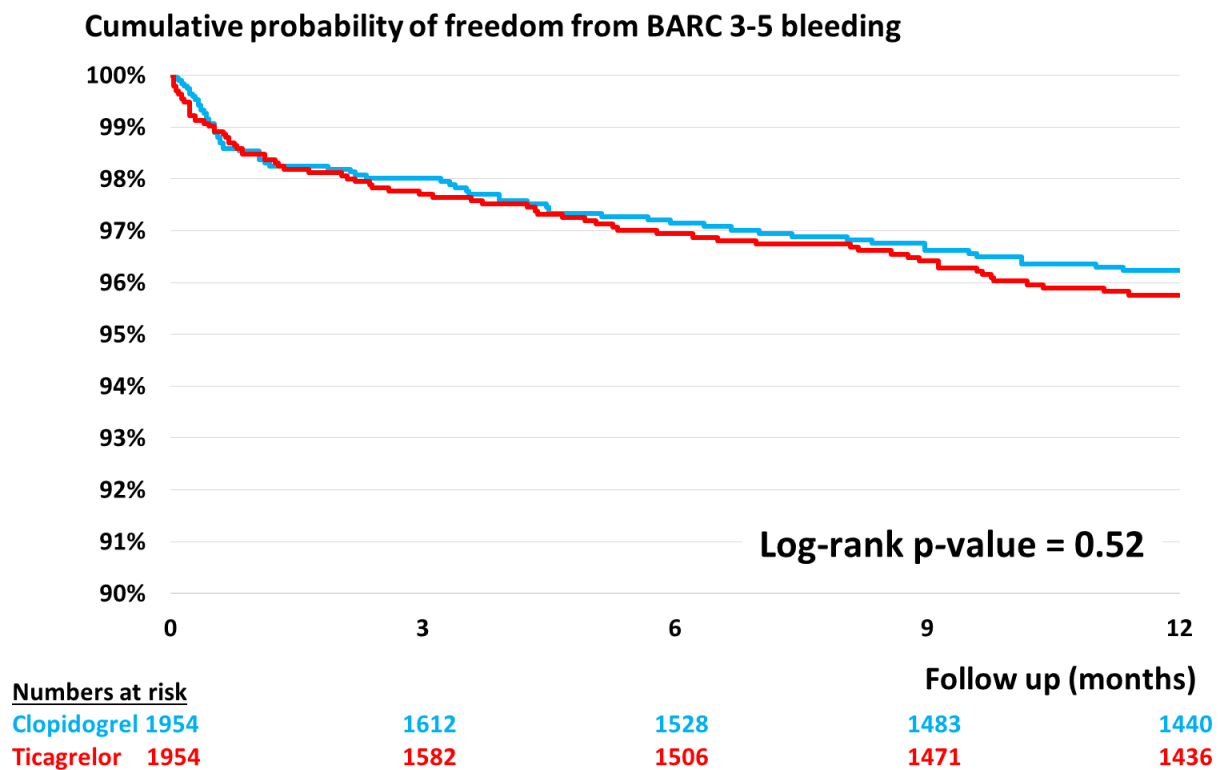
Figure S4. Kaplan-Meier chart for freedom from major bleeding in matched groups (PLATO criteria).

Cumulative probability of freedom from PLATO major bleeding

Log-rank p-value = 0.28

Follow up (months)

Numbers at risk

Clopidogrel	1954	1609	1525	1479	1434
Ticagrelor	1954	1578	1498	1463	1427
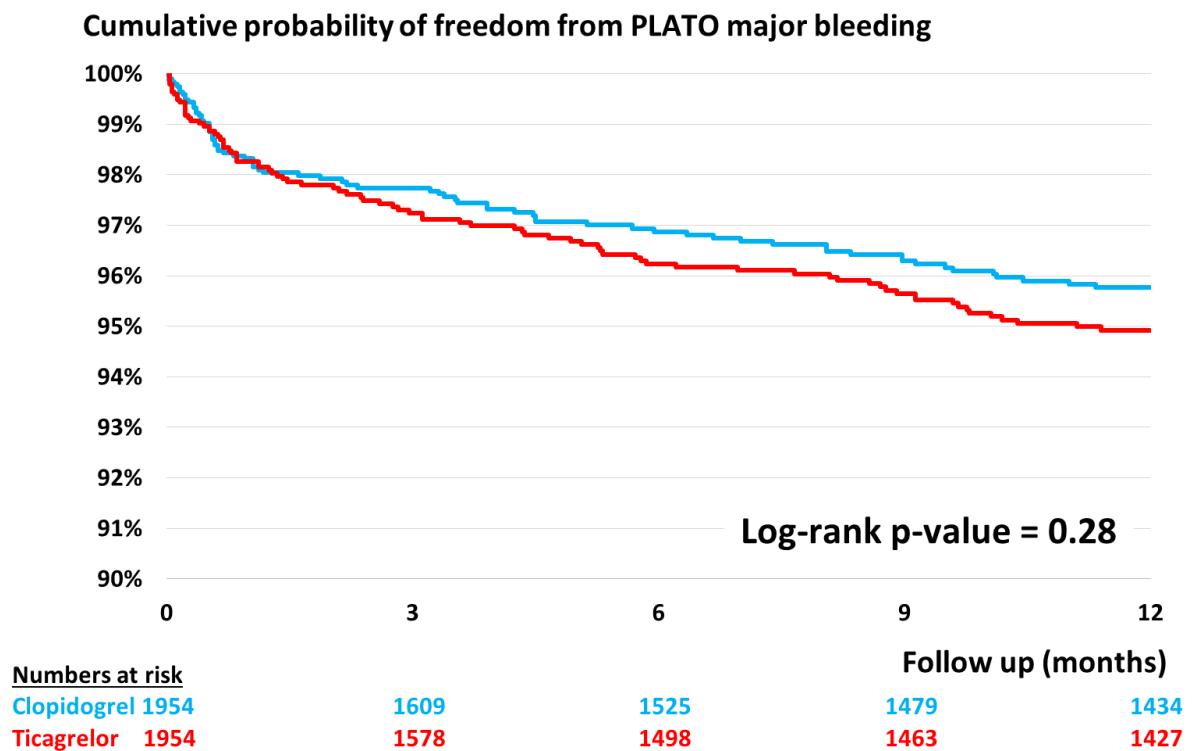
Figure S5. Kaplan-Meier chart for freedom from subsequent MI in matched groups.

Cumulative probability of freedom from MI

Log-rank p-value = 0.19

Follow up (months)

Numbers at risk

	0	3	6	9	12
Clopidogrel	1954	1606	1529	1482	1438
Ticagrelor	1954	1575	1501	1457	1422
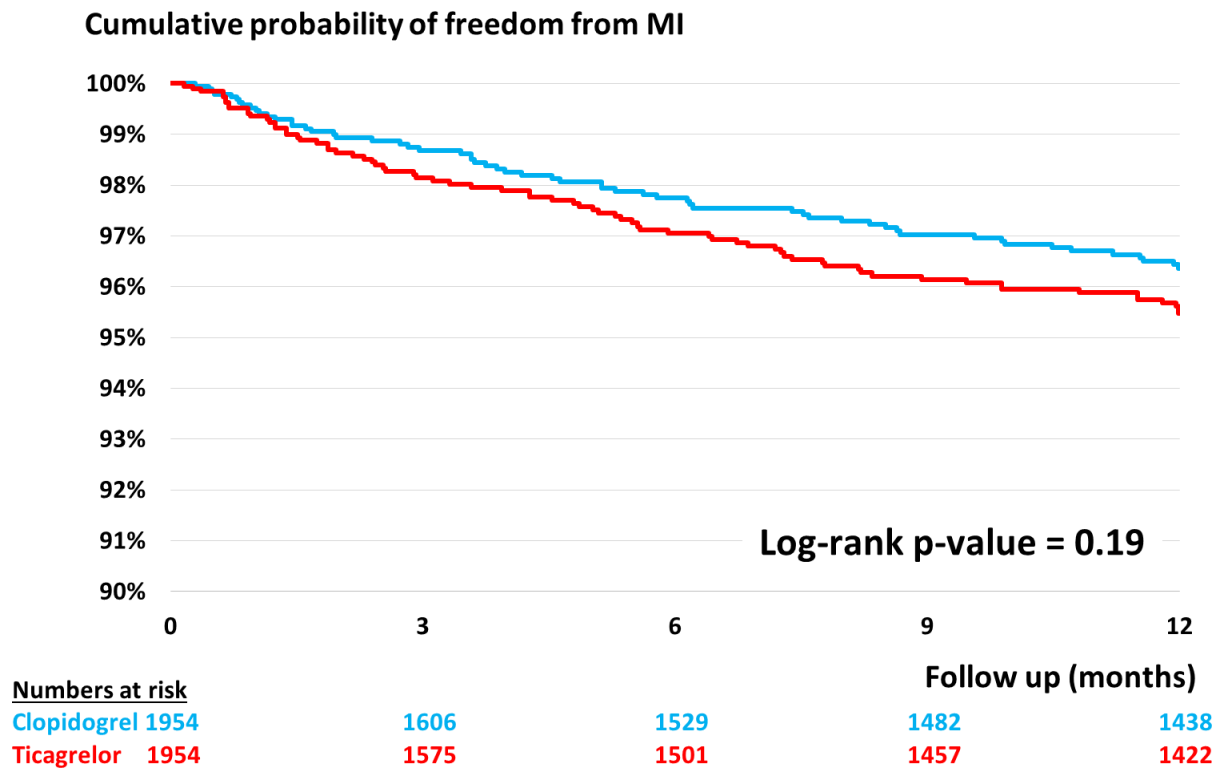
Figure S6. Kaplan-Meier chart for freedom from stroke in matched groups.

Cumulative probability of freedom from stroke

Log-rank p-value = 0.30

Follow up (months)

Numbers at risk

	0	3	6	9	12
Clopidogrel	1954	1610	1535	1488	1448
Ticagrelor	1954	1588	1521	1490	1459
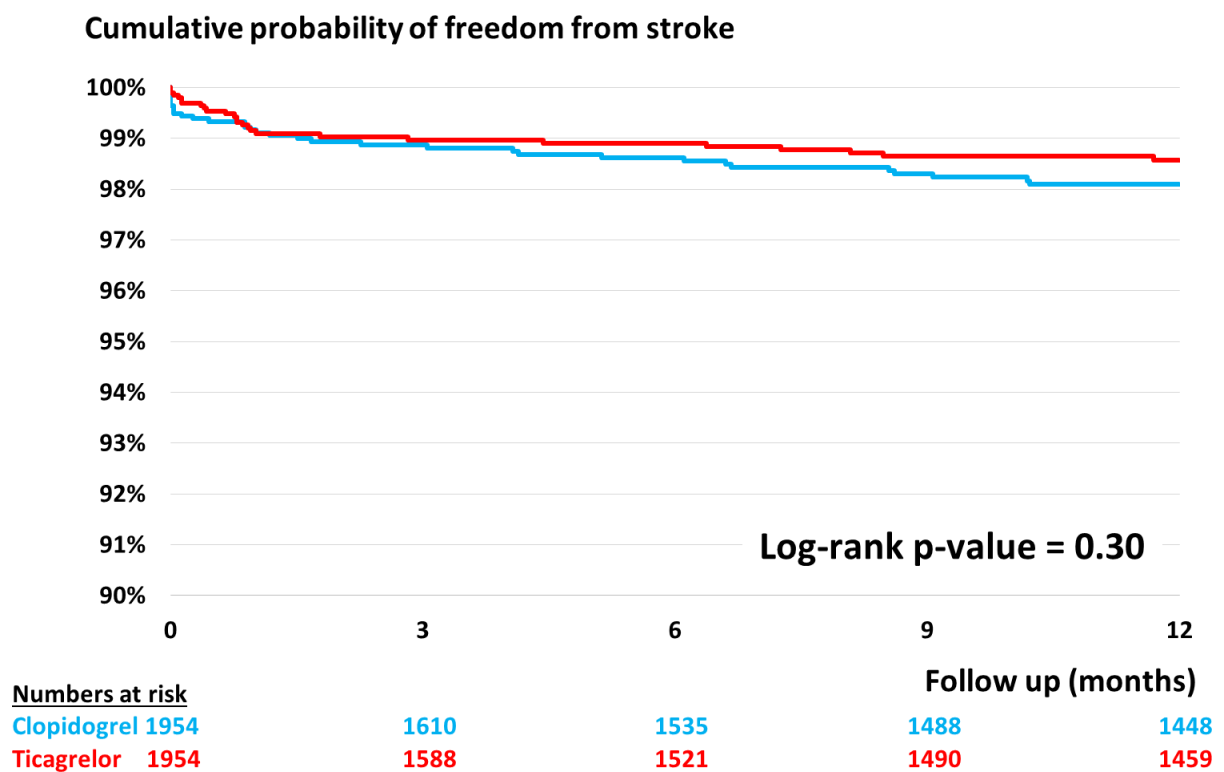
Figure S7. Kaplan-Meier chart for survival in matched groups.

Cumulative probability of survival

Log-rank p-value = 0.10

Follow up (months)

Numbers at risk

	0	3	6	9	12
Clopidogrel	1954	1623	1549	1507	1468
Ticagrelor	1954	1598	1532	1499	1470
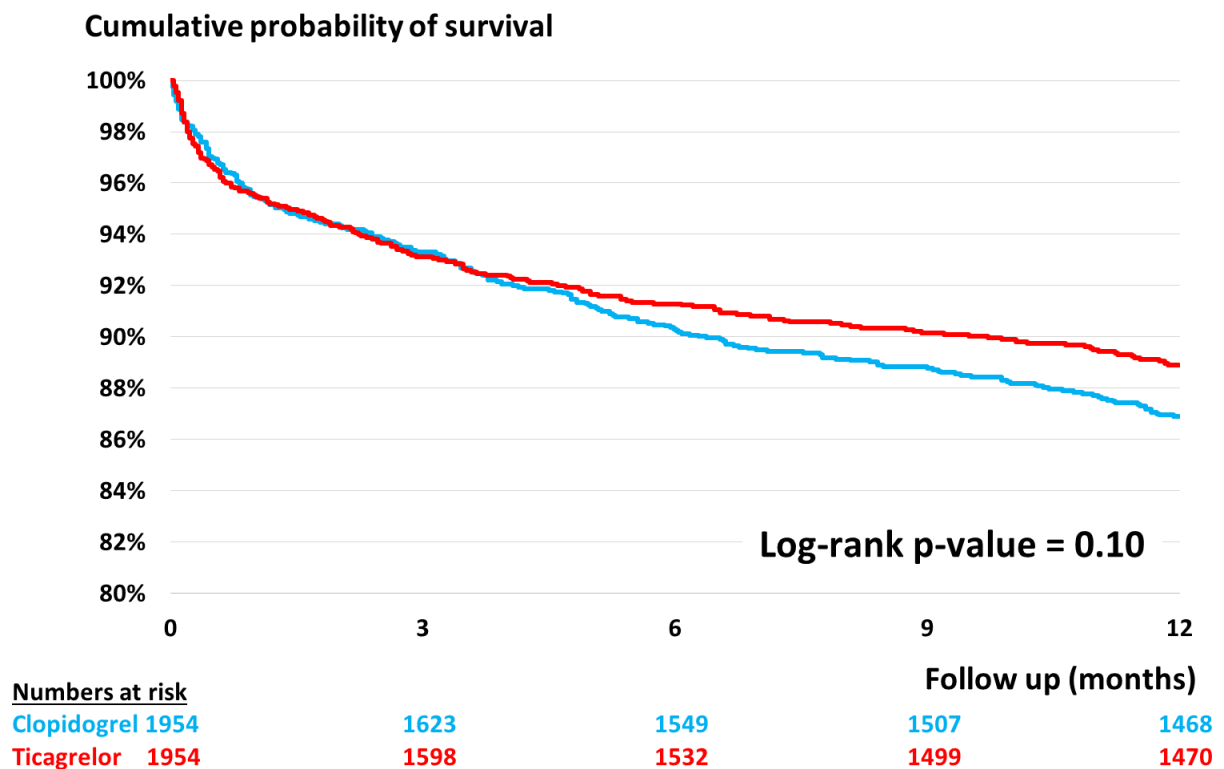
Figure S8. Forest plot of hazard ratios for revascularized patients (CABG and PCI).

Outcomes		Hazard Ratio (95% CI)	p-value
BARC* major bleeding (BARC 3-5)	Unadjusted	0.67 (0.44, 1.03)	0.07
	Adjusted	0.78 (0.51, 1.19)	0.25
PLATO** major bleeding	Unadjusted	0.73 (0.49, 1.09)	0.12
	Adjusted	0.82 (0.55, 1.22)	0.32
Subsequent myocardial infarction	Unadjusted	0.88 (0.55, 1.42)	0.60
	Adjusted	1.02 (0.63, 1.64)	0.95
Stroke	Unadjusted	0.97 (0.47, 1.99)	0.93
	Adjusted	1.26 (0.61, 2.63)	0.54
All-cause mortality	Unadjusted	0.69 (0.42, 1.13)	0.14
	Adjusted	0.84 (0.51, 1.38)	0.48

Favours Ticagrelor — Favours Clopidogrel

Figure S9. Forest plot of hazard ratios for medically managed patients (no revascularisation).

Outcomes		Hazard Ratio (95% CI)	p-value
BARC* major bleeding (BARC 3-5)	Unadjusted	1.47 (0.94, 2.28)	0.09
	Adjusted	1.90 (1.21, 2.98)	0.01
PLATO** major bleeding	Unadjusted	1.58 (1.05, 2.38)	0.03
	Adjusted	2.12 (1.39, 3.24)	<0.001
Subsequent myocardial infarction	Unadjusted	1.18 (0.78, 1.79)	0.44
	Adjusted	1.53 (1.00, 2.34)	0.051
Stroke	Unadjusted	0.44 (0.24, 0.84)	0.01
	Adjusted	0.57 (0.30, 1.08)	0.09
All-cause mortality	Unadjusted	0.67 (0.56, 0.80)	<0.001
	Adjusted	0.96 (0.80, 1.14)	0.63

0.2 0.3 0.5 0.7 1 1.5 2 2.5 3 3.5

← Favours Ticagrelor   Favours Clopidogrel →