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ORIGINAL ARTICLE
Coronary artery disease

Characteristics and outcomes in patients with a prior myocardial infarction treated with extended dual antiplatelet therapy with ticagrelor 60 mg: findings from ALETHEIA, a multi-country observational study

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Background Guidelines recommend extended dual antiplatelet therapy, including ticagrelor 60 mg twice daily, in high-risk post-myocardial infarction (MI) patients who have tolerated 12 months and are not at high bleeding risk. The real-world utilization and bleeding and ischaemic outcomes associated with long-term ticagrelor 60 mg in routine clinical practice have not been well described.

Methods Register and claims data from the USA (Optum Clinformatics, IBM MarketScan, and Medicare) and Europe (Sweden, Italy, UK, and Germany) were extracted. Patients initiating ticagrelor 60 mg ≥12 months after MI, meeting eligibility criteria for the PEGASUS-TIMI (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin – Thrombolysis in Myocardial Infarction 45) 54 trial, were included. The cumulative incidence of the composite of MI, stroke, or all-cause mortality and that of bleeding requiring hospitalization were calculated. Meta-analyses were performed to combine estimates from each source.

Results A total of 7035 patients treated with ticagrelor 60 mg met eligibility criteria. Median age was 67 years and 29% were females; 12% had a history of multiple MIs. The majority (95%) had been treated with ticagrelor 90 mg prior to initiating ticagrelor 60 mg. At 12 months from initiation of ticagrelor 60 mg, the cumulative incidence [95% confidence interval (CI)] of MI, stroke, or mortality was 3.33% (2.73–4.04) and was approximately three-fold the risk of bleeding (0.96%; 0.69–1.33).

Conclusions This study provides insights into the use of ticagrelor 60 mg in patients with prior MI in clinical practice. Observed event rates for ischaemic events and bleeding generally align with those in the pivotal trials, support the established safety profile of ticagrelor, and highlight the significant residual ischaemic risk in this population.

Clinical Trials.gov Registration NCT04568083.

Keywords Long-term ticagrelor • Myocardial infarction • Real-world evidence

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Introduction

Cardiovascular death remains the leading cause of mortality globally with coronary heart disease being a dominant driver, underscoring the need for improved preventive strategies.[1] Patients with coronary artery disease who suffer a myocardial infarction (MI) remain at particularly high risk of subsequent atherothrombotic events years after the event.[2] Antithrombotic strategies have been shown to reduce this risk, including long-term use of the combination of low-dose aspirin and ticagrelor 60 mg twice daily.[3,4]

The broad application of potent antithrombotic strategies for atherothrombotic protection is complicated by the associated bleeding risk.[4] Although pivotal studies have shown overall net benefits in populations selected for clinical trials, clinicians may feel that patients in routine clinical practice may differ in terms of complexity and bleeding risk and that a personalized approach is needed.[5,6] Current clinical guidelines support risk stratification and state that more potent antithrombotic therapy, including ticagrelor 60 mg twice daily, for long-term secondary prevention should be considered in patients at low bleeding risk and high ischaemic risk.[7]

In this context, understanding the utilization of ticagrelor 60 mg twice daily in patients with prior MI in routine clinical practice may offer important insights; however, to date, such use has not been well described. The ALETHEIA (NCT04568083) study was a multinational observational study designed to address this gap. The primary objectives were to describe the demographic, clinical, and treatment characteristics, treatment persistence, and ischaemic and bleeding outcomes in patients with history of MI prescribed ticagrelor 60 mg.

Methods

The design of the ALETHEIA study has been published.[8] In brief, data related to patients with a history of MI receiving ticagrelor 60 mg were extracted from electronic medical record and claims databases in the USA, Germany, Italy, Sweden, and the UK. Data sources encompassed Medicare, Optum Clinformatics, and IBM MarketScan in the USA, Ricerca e Salute (ReS) in Italy, Swedish Prescribed Drug Register linked with National Patient Register and Cause of Death Register, AOK Plus in Germany, and the Clinical Practice Research Datalink (CPRD) linked with the Hospital Episode Statistics and the Office for National Statistics in the UK; further details are available in the ALETHEIA design paper. Cohort definitions and outcomes were pre-specified in a formal statistical analysis plan overseen by an Executive Scientific Advisory Committee. Appropriate ethics board approvals were obtained where necessary. All requirements for data protection and privacy were observed.

Study population

The study population was defined as patients who had a first prescription of ticagrelor 60 mg 12 months or more from their qualifying MI. The date of this first prescription was defined as their index date. The qualifying MI was defined as the occurrence of hospitalization with a primary ICD-10 or ICD-9 code of MI during a pre-specified eligibility period. Aligned with eligibility criteria for the PEGASUS-TIMI 54 trial, patients were excluded if they were receiving anticoagulation, had history of ischaemic stroke or intracranial haemorrhage, had gastrointestinal bleeding within 6 months of the index date, had severe renal or liver dysfunction, or were receiving a potent CYP3A4 inhibitor. In addition, to allow capture of baseline characteristics, those with $\leq$1 year of available data prior to the qualifying MI were also excluded. To contextualize the characteristics of the ticagrelor cohort, patient characteristics were also described among patients with no $P2Y_{12}$ inhibitor (e.g. aspirin monotherapy or no therapy) and among those prescribed a different $P2Y_{12}$ inhibitor (e.g. clopidogrel or prasugrel) but otherwise fulfilling the eligibility criteria.

Outcomes

Treatment persistence was assessed up to 24 months from index and calculated based on package size and number of days between prescription refills. Adherence was assessed within the first 12 months and defined using the medication possession ratio (MPR), which is the days supplied divided by the 12-month assessment period multiplied by 100. A threshold of 5000 patient-years on treatment with ticagrelor 60 mg was pre-specified for analysis of clinical outcomes to ensure adequate precision. The primary outcome was hospitalization for bleeding and the secondary outcome was a composite, including hospitalization for MI or stroke, and all-cause mortality. Two of the US data sources (Optum and MarketScan) were limited in ascertainment of death so analyses, including mortality, excluded these two data sources. The definitions of outcomes are listed in Supplementary material online, *Table S1*.

Statistics

Baseline characteristics were summarized using standard descriptive statistics. The sample size weighting method was used to pool patient characteristics across data sources. Characteristics that were not collected among all sources or that had insufficient numbers could not be pooled. Outcomes were analysed as time to first event on treatment, with cumulative incidence calculated at pre-specified timepoints using the Kaplan–Meier (KM) method. Patients were censored at treatment discontinuation. Pooled KM curves for bleeding requiring hospitalization and the CV composite outcomes were generated from monthly lifetables from each data source by weighting based on the number of patients at risk at each time point. Meta-analyses were applied to generate the pooled cumulative incidence at 12 and 24 months for the bleeding and CV composite outcomes across data sources. Fixed-effect (FE) and random-effect (RE) models were used, with the FE model as the primary for reporting. Heterogeneity was assessed using I^2 and the Q-statistic.

Results

The CONSORT diagram is presented in *Figure 1*. A total of 19 365 patients were hospitalized with a primary diagnosis of MI and subsequently prescribed ticagrelor 60 mg during the study period. Of those, 4948 (26%) received their prescription earlier than 12 months from their qualifying MI and were excluded from the analysis, leaving 14 417 with prior MI who were prescribed ticagrelor 60 mg 12 or more months after the qualifying MI. Of those, 3770 had an exclusion based on PEGASUS-TIMI 54 entry criteria (most often, need for anticoagulation or prior stroke) and 3612 had less than 1 year of available look-back for baseline data and were excluded, leaving 7035 in the final study population. This population included 2225 (32%) from Europe and the remainder from the USA. The 7035 patients contributed a total of 6573 person-years on treatment (thus exceeding the pre-defined threshold of 5000). The calendar year of initiation of ticagrelor 60 mg treatment is shown in *Figure 2*.

A total of 527 445 were hospitalized for a qualifying MI but did not receive ticagrelor 60 mg. Of those who met eligibility based on PEGASUS-TIMI 54 criteria and had sufficient look-back time, 40 696 were treated with a non-ticagrelor $P2Y_{12}$-inhibitor and 130 178 were on no $P2Y_{12}$-inhibitor at 15 months after their MI.

Baseline characteristics

Baseline characteristics are shown in *Table 1*. At the index date (date of first prescription of ticagrelor 60 mg) in the ticagrelor cohort, the median age was 67 years, 29% were female, and 78% had two or more ischaemic risk factors. Dyslipidaemia and hypertension were prevalent, 33% had diabetes, 29% had heart failure, 24% had peripheral artery disease, and 16% had chronic kidney disease. In terms of other

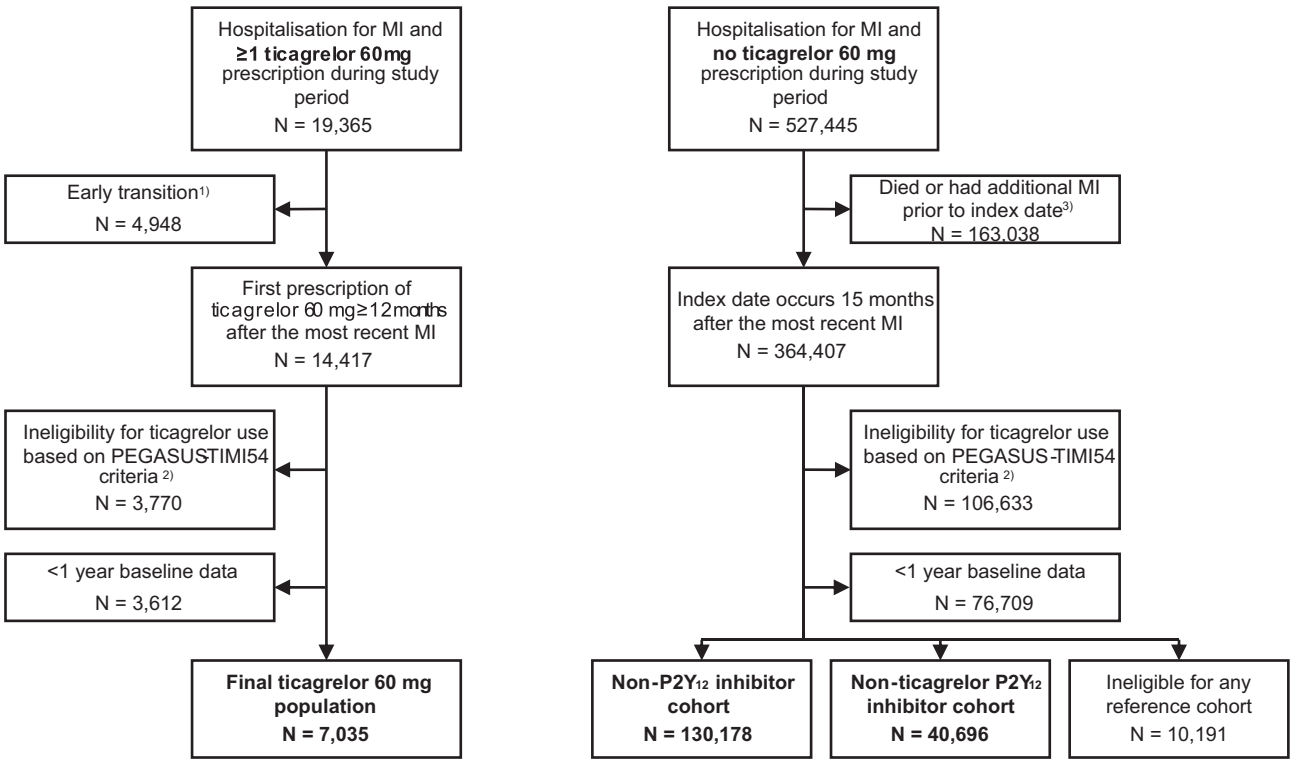


Figure 1 CONSORT diagram.

comorbidities and medical history, 26% had a diagnosis of anaemia recorded and 5.5% had a prior hospitalization for bleeding.

In terms of prior $P2Y_{12}$-inhibitor therapy, 95% of those that received ticagrelor 60 mg had a prior prescription for ticagrelor 90 mg with a median duration of use of 12.4 months [interquartile range (IQR) 10.8–16.4]; 9.6% and 4.6% had previously received clopidogrel and prasugrel, respectively. In terms of concomitant medical therapy at the time of receiving ticagrelor 60 mg, 85% were receiving low-dose aspirin (data only available for European data sources), 78% were receiving lipid-lowering therapy, 66% were receiving beta-blockers, 38% were receiving an angiotensin-converting enzyme (ACE) inhibitor, and 23% an angiotensin receptor blocker (ARB).

Relative to patients who received a non-ticagrelor $P2Y_{12}$ inhibitor or no $P2Y_{12}$ inhibitor, those who received ticagrelor 60 mg were more likely to be male, have diabetes mellitus, and have heart failure and other comorbidities, such as chronic obstructive pulmonary disease (COPD) (*Table 1*). In terms of ischaemic risk, they were more likely to have a history of prior MI, before the index event for inclusion, and percutaneous coronary intervention (PCI), and were more likely to have >1 ischaemic risk factor. They were less likely to have atrial fibrillation or chronic kidney disease and were younger. In terms of prior $P2Y_{12}$ inhibitor, patients who received ticagrelor 60 mg were more likely to have been treated with ticagrelor 90 mg and less likely to have been treated with clopidogrel. Those receiving ticagrelor 60 mg were more frequently treated with guideline-directed medical therapies, including aspirin, lipid-lowering therapy, beta-blockers, ACEi or ARB, and proton-pump inhibitors (PPIs). The proportion of patients receiving ticagrelor, a non-ticagrelor $P2Y_{12}$ inhibitor, or no $P2Y_{12}$ inhibitor varied by the number of ischaemic risk factors and ranged from 75% on $P2Y_{12}$ inhibitor with 1 or 2 ischaemic risk factors to 61% in those with 5 or more ischaemic risk factors (*Figure 3*).

Bleeding

There were 45 bleeding events leading to hospitalization in patients receiving ticagrelor 60 mg up to 24 months, with KM rates in the pooled analysis of 0.96% [95% confidence interval (CI): 0.69–1.33] at 12 months and 1.52% (1.09–2.12) at 24 months (*Figure 4*). In the pooled analysis, there was significant heterogeneity at 12 months (I^2 of 60%) driven by two countries (the UK and Germany) with the smallest cohorts and numbers of events. A sensitivity analysis excluding those cohorts provided KM rates of 0.71% (0.48–1.04) at 12 months and 1.33% (0.9–1.97) at 24 months with less heterogeneity (I^2 of 12% at 12 months).

Ischaemic events and mortality

The composite of MI, stroke or all-cause death was evaluated in the 5067 patients in whom death was ascertainable. There were a total of 161 ischaemic events or death, including 148 first and 13 recurrent events. KM rates were 3.33% (95% CI 2.75–4.04) at 12 months and 6.72% (5.62–8.02) at 24 months (*Figure 4*). There was significant heterogeneity at 24 months in the pooled analysis (I^2 of 81.3%; 0% at 12 months) driven by rates in the countries with the smallest populations and lowest number of events (the UK and Germany). In a sensitivity analysis excluding these countries, the rates were 3.14% (2.56–3.85) and 6.16% (5.09–7.47) at 12 and 24 months, respectively (I^2 of 0% at 12 months and 82.6% at 24 months).

Treatment persistence and adherence

Treatment persistence is shown in *Figure 5*. At 12 months from initiation of ticagrelor 60 mg, persistence on therapy ranged from 61.0 to 83.2% by country. At 24 months, rates by country ranged from 31.4 to 71.1%. The percentage of patients who were adherent

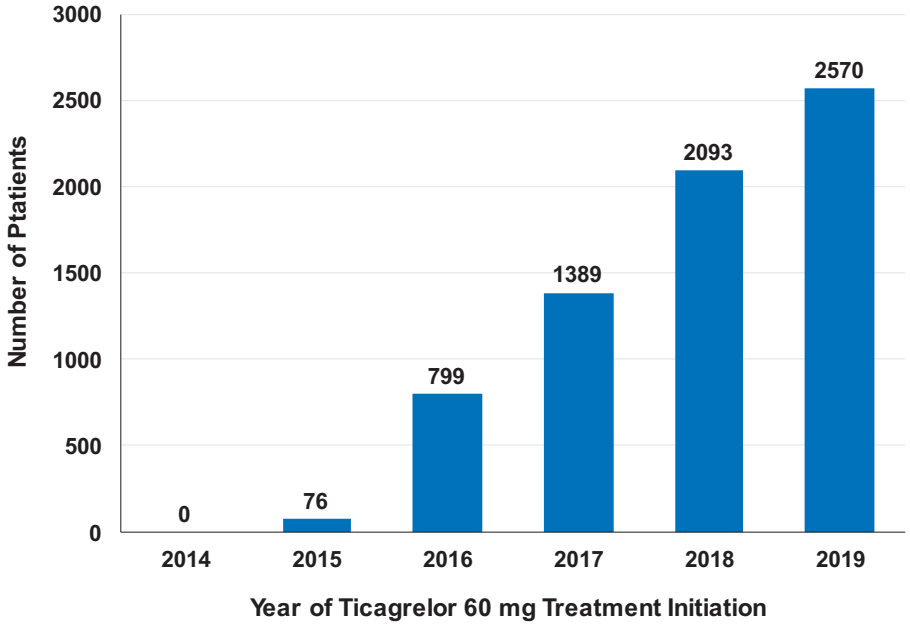


Figure 2 Treatment initiation with ticagrelor 60 mg over time. Data beyond year 2019 was only available from US Optum and MarketClarity, and the 46 patients who had their first ticagrelor 60 mg prescription in 2020 are therefore not displayed in the figure.

to their ticagrelor 60 mg treatment, defined as an MPR ≥80%, within the first 12 months, ranged from 64.8 to 82.7%.

Discussion

The current analysis provides several insights into the use of ticagrelor 60 mg for secondary prevention in patients with prior MI in routine clinical practice. First, the use is increasing but remains overall limited relative to the number of potentially eligible patients. Second, the patients selected to receive ticagrelor 60 mg appeared to be at higher ischaemic risk relative to those that were not; however, bleeding risk factors such as anaemia and prior hospitalization for bleeding were similar between groups, but patients who had atrial fibrillation and/or prior use of clopidogrel were less likely to receive ticagrelor 60 mg. Third, the persistence rates and adherence were high generally for the first 12 months, but there was variability across countries, and the persistence decreased from 12 to 24 months. Finally, the risk of ischaemic events was about three-fold higher than the risk of bleeding events, and the risk of these events approximated those observed in the pivotal randomized trial.

Overall, prescriptions of ticagrelor 60 mg are increasing; however, the use appears low relative to those eligible, including patients at lower bleeding risk and high ischaemic risk. Of note, in the current cohort, approximately 40% of those not receiving ticagrelor 60 mg had atrial fibrillation, and, although not excluded because they were not receiving an anticoagulant, they generally would not be recommended for long-term ticagrelor. The observation that 40% had atrial fibrillation underscores the complexity of treatment in patients with both MI and atrial fibrillation and the underutilization of therapeutic anticoagulation. A large determinant of ticagrelor 60 mg non-use appeared to be clopidogrel use at the qualifying MI. Use of clopidogrel for MI is likely associated with several factors, including socio-economic status, clinician perception of bleeding risk, and the need for anticoagulation. Those who did receive ticagrelor 60 mg were generally consistent in profile with those enrolled in the pivotal trial and were of high ischaemic risk by baseline characteristics.[3] Overall, the underutilization of this and other therapies underscores the need for implementation science to better understand how to improve the provision of care in patients at high risk for atherothrombosis.

Variability in treatment persistence and adherence represent an additional challenge both in practice and in trials.[9] While low adherence is a well-described issue, overall persistence and adherence was high for 12 months and persistence remained high but more variable at 24 months, with most countries reporting treatment persistence in about half of patients at 24 months. This observation underscores the need for additional work to better understand reasons for non-adherence and treatment discontinuation and to support patients through education and shared decision-making to adhere to therapies prescribed for the prevention of severe events. Although the current study is observational, prior registry and trial data consistently show that patients with prior MI remain at heightened ischaemic risk long term; decreased persistence may reflect perceptions of stability in the outpatient setting and a desire to de-escalate the intensity of platelet inhibition. Recent trials have suggested that de-escalation for bleeding risk may effectively be done through aspirin cessation rather than cessation of $P2Y_{12}$ inhibition.[10] These findings have been further expanded to support the efficacy and safety of $P2Y_{12}$-inhibitor monotherapy in patients undergoing complex PCI.[11]

The observation that bleeding and ischaemic risk approximate those observed in the pivotal trial is reassuring, especially noting the three-fold excess in ischaemic risk supporting the overall benefit of antithrombotic therapy (Supplementary material online, *Figure S1*).[3] The event rate for ischaemic events and mortality in ALETHEIA was 3.33% in year 1 and 3.39% in year 2 from initiation, and in PEGASUS-TIMI 54, they were 2.73 and 2.78%, respectively. The higher rates observed in ALETHEIA may be explained by the use of all-cause vs. CV mortality as well as patient characteristics. Bleeding risk was also

Table 1 Baseline characteristics by prescribed treatment

	Ticagrelor 60 mg, *N* = 7035	Non-ticagrelor $P2Y_{12}$ inhibitor, *N* = 40 696	No $P2Y_{12}$ inhibitor, *N* = 130 178
Age, median (IQR)	67 (61.2–72.8)	68.4 (60.6–75.1)	68.8 (60–77)
Female, *n* (%)	2041 (29)	13 942 (34.3)	46 929 (36.0)
Hypertension, *n* (%)	6183 (87.9)	40 373 (99.2)	124 482 (95.6)
Hypercholesterolaemia, *n* (%)	7026 (99.9)	14 531 (35.7)	41 816 (32.1)
Diabetes mellitus, *n* (%)	2304 (32.8)	5482 (13.5)	13 423 (10.3)
Chronic kidney disease, *n* (%)	1141 (16.2)	11 610 (28.5)	23 491 (18.0)
COPD/asthma, *n* (%)	2638 (37.5)	13 297 (32.7)	33 011 (25.4)
Heart failure, *n* (%)	2054 (29.2)	6806 (16.7)	20 521 (15.8)
Atrial fibrillation, *n* (%)	755 (10.7)	16 453 (40.4)	48 057 (36.9)
Peripheral artery disease, *n* (%)	1678 (23.9)	36 843 (90.5)	102 075 (78.4)
Prior MI, *n* (%)	830 (11.8)	2574 (6.3)	8140 (6.3)
History of PCI, *n* (%)	5994 (85.2%)	31 029 (76.2)	77 409 (59.5)
Ischaemic risk factors[a], *n* (%)			
1	1566 (22.3)	9835 (24.2)	33 910 (26)
2	2527 (35.9)	12 855 (31.6)	49 680 (38.2)
3	1765 (25.1)	9832 (24.2)	29 020 (22.3)
4	837 (11.9)	5707 (14)	13 232 (10.2)
≥5	285 (4.1)	2467 (6.1)	4305 (3.3)
Iron deficiency anaemia, *n* (%)	1860 (26.4)	13 541 (33.3)	37 640 (28.9)
Hospitalization for bleeding, *n* (%)	385 (5.5)	1783 (4.4)	5833 (4.5)
Prior ticagrelor 90 mg, *n* (%)	6665 (94.7)	6566 (16.1)	50 715 (39.0)
Prior clopidogrel, *n* (%)	674 (9.6)	36 051 (88.6)	35 904 (27.6)
Prior prasugrel, *n* (%)	322 (4.6)	5813 (14.3)	6689 (5.1)
Aspirin, *n* (%)[b]	1891 (85.0)	5578 (60.7)	50 335 (63.8)
Lipid lowering therapy, *n* (%)	5508 (78.3)	27 788 (68.3)	74 226 (57.0)
Beta-blocker, *n* (%)	4645 (66.0)	23 901 (58.7)	66 512 (51.1)
ACEi, *n* (%)	2695 (38.3)	13 922 (34.2)	40 609 (31.2)
ARB, *n* (%)	1583 (22.5)	7371 (18.1)	23 025 (17.7)
PPI, *n* (%)	2241 (31.9)	10 935 (26.9)	36 395 (28)

[a]Age ≥65, chronic kidney disease, diabetes, second prior MI, <2 years from qualifying MI to index date or <1 year from most recent ticagrelor 90 prescription to index date, and PAD.
[b]Data available from European data sources only.

similar with rates of 0.96 and 0.56% in year 1 and 2, respectively, in ALETHEIA compared with rates of 0.86% per year in PEGASUS-TIMI 54, although the bleeding definition in ALETHEIA was broader. It is notable that the observed bleeding rate was not higher in ALETHEIA (0.96% at 12 months) given that a significant proportion of those receiving ticagrelor 60 mg had a prior history of bleeding requiring hospitalization (5.5%) or anaemia (26.4%), both important risk factors for bleeding.[12] Overall, these data suggest that, in the cohort selected for analysis, clinicians are appropriately selecting patients for long-term ticagrelor on the basis of their clinical assessment of bleeding risk; however, the current analysis suggests that such therapy may be underutilized, particularly in those with high ischaemic risk and without high bleeding risk who potentially may derive reduced cardiovascular mortality risk.[13]

There are several limitations to this analysis. First, a significant proportion of patients were excluded from the ticagrelor group due to early use of the 60 mg dose (prior to 12 months from their qualifying MI) and due to exclusion criteria, and generalizability should be interpreted in the context of this limitation. Therefore, observations in all patients receiving ticagrelor 60 mg in routine clinical practice may differ. Second, some data sets were relatively small with small numbers of events likely leading to unreliable event risk estimates. Sensitivity analyses excluding these smaller data sets, however, yielded similar findings. Third, the ability to ascertain CV mortality was limited and even all-cause mortality was not available in some data sets. The use of all-cause mortality, instead of CV mortality, may inflate event rates relative to randomized trials with very high quality event ascertainment and adjudication. Although comparisons of outcomes between the groups (ticagrelor, non-ticagrelor $P2Y_{12}$ inhibitor, and no $P2Y_{12}$ inhibitor) would be of potential interest, limitations in the available data sets did not enable adjustment to a degree that would enable adequate control of confounders or modelling around what factors predicted continuation vs. discontinuation. The absence of robust documentation around causes of discontinuation (e.g. routine codes for dyspnoea) limited the ability to better understand reasons for difference in persistence. Additionally, due to the low number of events particularly in individual countries, the ability to conduct additional stratified analyses was limited. Finally, due to the absence

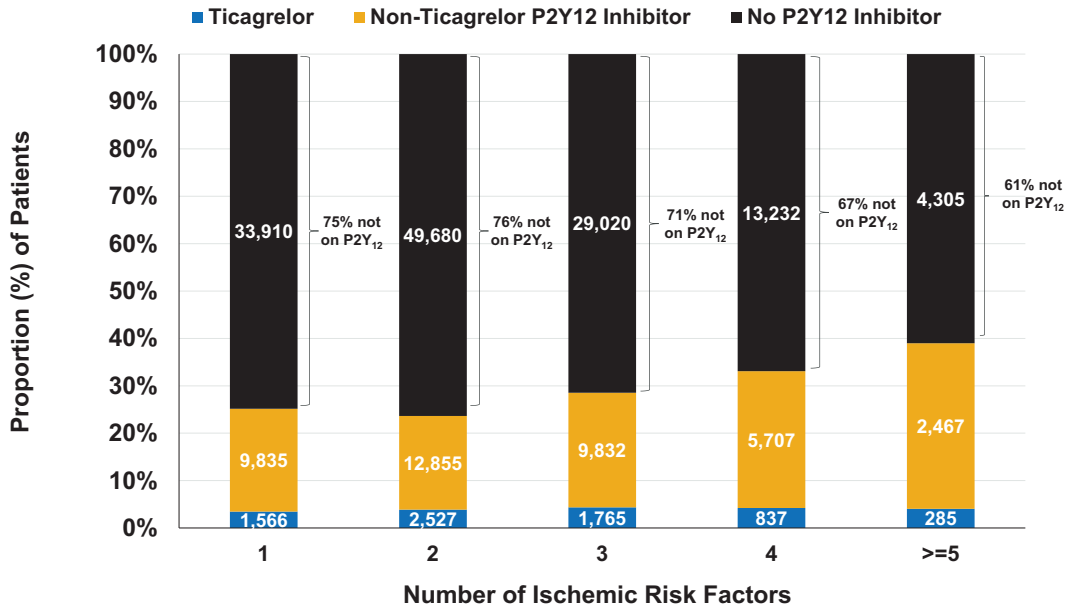


Figure 3 Proportion of patients receiving ticagrelor, non-ticagrelor $P2Y_{12}$ inhibitors, or no $P2Y_{12}$ inhibitors by number of ischaemic risk factors.

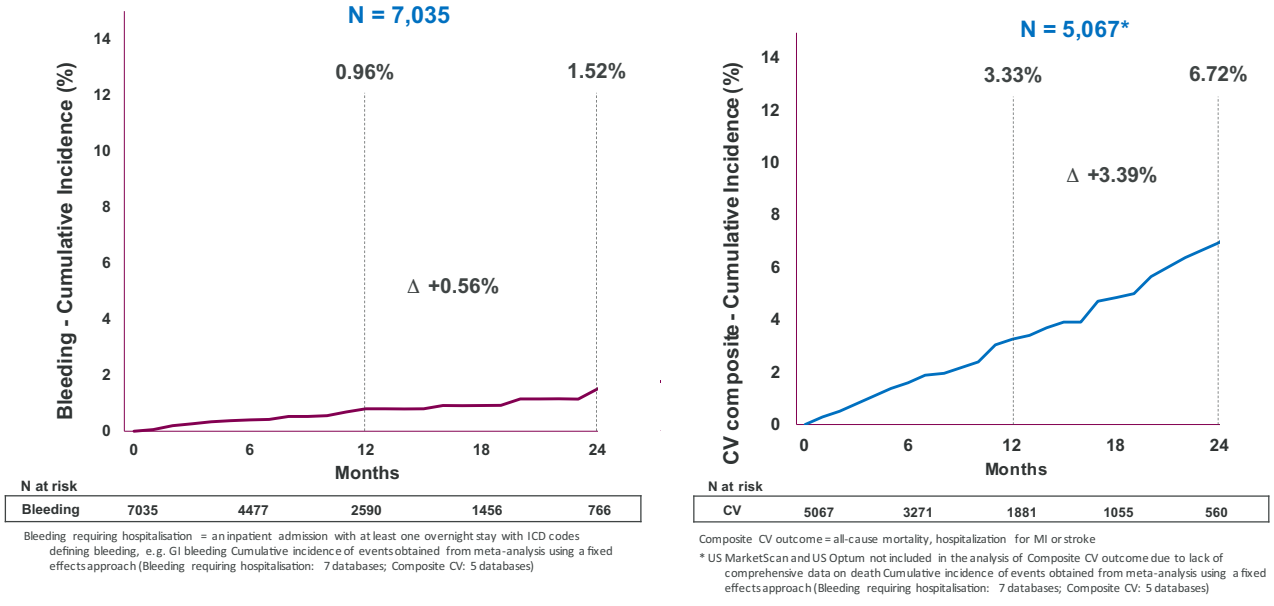
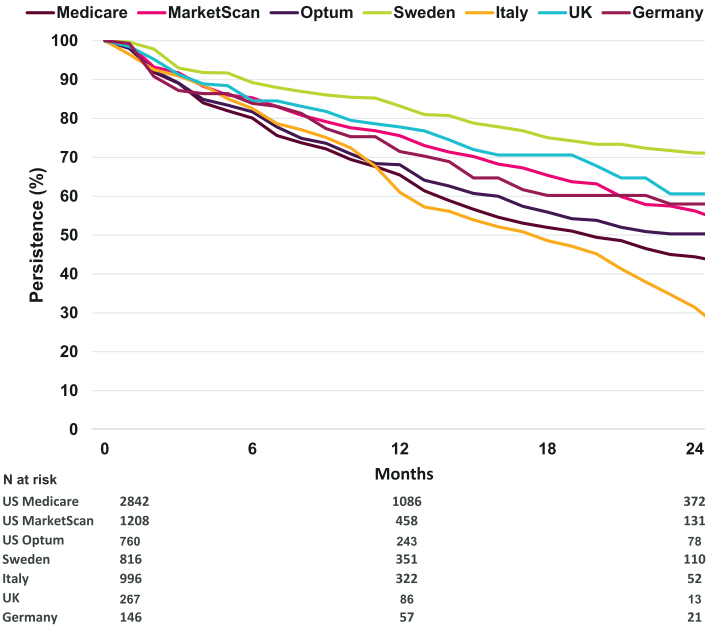


Figure 4 Outcomes in patients receiving ticagrelor 60 mg. The CV composite of MI, stroke or all-cause death was evaluated in the 5067 patients in whom death was ascertainable.

of robust ascertainment of key characteristics such as lab values and transfusions, broader definitions of bleeding typically used in randomized trials could not be examined. One such characteristic was aspirin where outpatient over-the-counter use was not ascertained and may explain in part the proportion of patients not receiving aspirin with a $P2Y_{12}$ inhibitor.

Conclusions

Use of long-term ticagrelor 60 mg after MI is increasing but appears underutilized overall. The risks of ischaemic events and bleeding in patients receiving this therapy are consistent with those observed in the pivotal clinical trials. Underutilization and diminishing persistence



	Persistence % (95% CI)	
	12 months	24 months
US Medicare	65.4 (63.4-67.4)	44.4 (41.9-46.9)
US MarketScan	75.6 (72.6-78.3)	56.2 (51.6-60.5)
US Optum	68.1 (64.0-71.9)	50.3 (44.9-55.5)
Sweden	83.2 (80.0-85.9)	71.1 (66.2-75.4)
Italy	61.0 (57.2-65.1)	31.4 (26.1-37.8)
UK	77.8 (70.8-83.2)	60.6 (46.9-71.9)
Germany	71.5 (62.1-79.0)	58.0 (46.7-67.8)

CI: confidence interval

Discontinuation defined as end of last prescription plus 7 days, switch to another $P2Y_{12}$ inhibitor or anticoagulant, or death, whichever occurred first

Figure 5 Persistence of ticagrelor 60 mg use.

and adherence over time underscore the need for implementation science and strategies to improve adherence in patients at high risk of atherothrombosis.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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