(54) Title: METHOD OF TREATING OR PREVENTION OF ATHEROTHROMBOTIC EVENTS IN PATIENTS WITH HIS-
TORY OF MYOCARDIAL INFARCTION

Figure 2-Panel A

Cardiovascular Death, MI, or Stroke
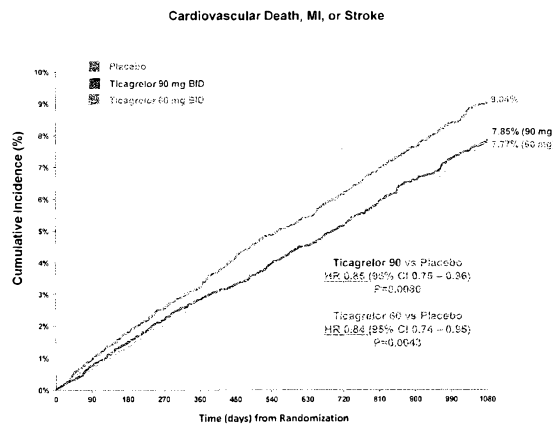
(57) Abstract: The present disclosure relates to methods for reducing the rate of cardiovascular death, myocardial infarction, or
stroke in a patient in recognized need thereof, comprising administering to the patient a pharmaceutical composition comprising 60
mg ticagrelor twice daily.

METHOD OF TREATING OR PREVENTION OF ATHEROTHROMBOTIC EVENTS IN PATIENTS WITH HISTORY OF MYOCARDIAL INFARCTION

[001] This application claims the benefit of priority under 35 U.S.C. § 119 to United States provisional patent application serial numbers 62/108,453, filed January 27, 2015; 62/112,318, filed February 5, 2015; 62/117,871 , filed February 18, 2015; 62/133,224, filed March 13, 2015; 62/133,327, filed March 14, 2015; 62/156,083, filed May 1, 2015; 62/156,823, filed May 4, 2015; and 62/211,635, filed August 28, 2015.

[002] The present disclosure generally relates to methods of treating or preventing antithrombotic events in patients with acute coronary syndrome (ACS) or a history of myocardial infarction (MI). In one aspect, the present disclosure relates to methods for reducing the rate of cardiovascular death, myocardial infarction, or stroke in a patient with a history of myocardial infarction, comprising administering twice daily to the patient a pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier. In another aspect, the present disclosure relates to methods for reducing the rate of cardiovascular death, myocardial infarction, or stroke in a patient with acute coronary syndrome, comprising administering twice daily to the patient a pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier.

[003] Ticagrelor is a direct-acting reversible binding $P2Y_{12}$ receptor antagonist that inhibits platelet activation and aggregation mediated by the $P2Y_{12}$ ADP-receptor. Ticagrelor, a cyclopentyltrizolopyrimidine, is not in the same chemical class as any other available antiplatelet agent. Currently marked antiplatelet agents include the cyclo-oxygenase inhibitor acetylsalicylic acid (also known as ASA or aspirin) and the thienopyridines clopidogrel, ticlopidine, and prasugrel. In addition to acting as a

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P2Y$_{12}$ receptor antagonist, ticagrelor is also known to increase local endogenous

adenosine levels by inhibiting equilibrative nucleoside transporter-1 (ENT-1).

Adenosine is formed locally at sites of hypoxia and tissue damage through

degradation of released adenosine tri- and di-phosphate (ATP and ADP). As

adenosine degradation is essentially restricted to the intracellular space, inhibition of

ENT-1 by ticagrelor prolongs the half-life of adenosine and thereby increases its

local extracellular concentration, providing enhanced local adenosine responses.

Adenosine has been documented to have a number of effects that include:

vasodilation, cardioprotection, platelet inhibition, modulation of inflammation, and

induction of dyspnea, which may contribute to the clinical profile of ticagrelor.

[004] Ticagrelor is also known by its chemical name (1*S*,2*S*,3*R*,5*S*)-3-[7-{[(1*R*,2*S*)-

2-(3,4-difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3*H*-[1,2,3]-triazolo[4,5-

d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol. The empirical formula of

ticagrelor is $C_{23}H_{28}F_2N_6O_4S$, and its molecular weight is 522.57 Da. The chemical

structure of ticagrelor is:
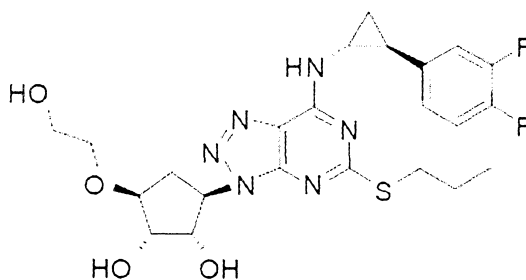
[005] At room temperature, ticagrelor is a crystalline powder with an aqueous

solubility of approximately 10 µg/mL.

[006] Ticagrelor can be taken with or without food. In patients, absorption of

ticagrelor occurs with a median time to reach the peak plasma concentration of

ticagrelor (c$_{max}$) after administration (t$_{max}$) of 1.5 hours with a t$_{max}$ range of 1.0 to 4.0

hours. The formation of the major circulating metabolite AR-C124910XX from ticagrelor occurs with a median t_{max} of 2.5 hours and a range of 1.5 to 5.0 hours. The mean absolute bioavailability of ticagrelor is about 36% (range 30% to 42%). Ingestion of a high-fat meal has no effect on the peak plasma concentration of ticagrelor (c_{max}), but results in a 21% increase in the integral of the concentration-time curve (AUC).

[007] Furthermore, ticagrelor as crushed tablets mixed in water, given orally or administered through a nasogastric tube into the stomach, is bioequivalent to whole tablets (AUC and c_{max} within 80% to 125% for ticagrelor and its major metabolite AR-C124910XX) with a median t_{max} of 1.0 hour (range 1.0 to 4.0 hours) for ticagrelor and 2.0 hours (range 1.0 to 8.0 hours) for AR-C124910XX. The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and AR-C124910XX are extensively bound to human plasma proteins (>99%).

[008] Ticagrelor presents several advantages over other commercially available $P2Y_{12}$ receptor antagonists. For example, ticagrelor is not a prodrug and therefore does not require metabolic activation. In addition, administration of ticagrelor results in a rapid onset of antiplatelet effect (within 2 hours for most patients), low interindividual variability, and reversibility that results in a faster offset of platelet inhibition when compared with thienopyridines such as clopidogrel, ticlopidine, and prasugrel.

[009] The randomized, double blind Platelet Inhibition and Patient Outcomes (PLATO) clinical trial studied ticagrelor 90 mg with aspirin twice daily compared with clopidogrel 75 mg with aspirin once daily in patients presenting across the spectrum of acute coronary syndrome. The results of the PLATO trial showed that ticagrelor reduced ischemic events for up to a year after an acute coronary syndrome. In 2011,

BRILINTA®, which contains ticagrelor, was approved by the US Food and Drug Administration (USFDA) in view of the PLATO clinical trial results.

[0010] Myocardial infarction is a global problem. In the United States alone, the incidence of acute myocardial infarction is approximately 600,000 cases a year, and nearly 8 million people have a history of myocardial infarction. Moreover, patients who have suffered a myocardial infarction are at heightened risk of recurrent ischemic events. The recent APOLLO RWE clinical trial found that approximately one in every five patients who remain event free for 12 months after a myocardial infarction will suffer a recurrent myocardial infarction, stroke or die from a cardiovascular event in the subsequent 36 months. Accordingly, patients with a history of myocardial infarction may derive particular benefit from intensive secondary prevention.

[0011] A key element in the pathobiology of cardiovascular ischemic events is the activated platelet. Correspondingly, antiplatelet therapy is a cornerstone in the prevention of such events. To that end, aspirin reduces ischemic risk in patients presenting with an acute coronary syndrome as well as in long-term secondary prevention. The addition of a $P2Y_{12}$ receptor antagonist to aspirin (referred to as dual anti platelet therapy or DAPT) has previously been shown to further reduce the risk of ischemic events in this population in the first year after an acute coronary syndrome.

[0012] The role of $P2Y_{12}$ receptor antagonists in long-term secondary prevention after myocardial infarction, however, has not been established. Both U.S. and European practice guidelines currently recommend treatment with a $P2Y_{12}$ receptor antagonist for up to one year after a myocardial infarction. One of the preferred $P2Y_{12}$ receptor antagonists in patients with an acute coronary syndrome is ticagrelor,

a reversibly-binding, direct-acting agent that achieves a high degree of platelet

inhibition and has low inter-individual variability. When added to aspirin for up to 1

year in patients with an acute coronary syndrome, ticagrelor 90 mg twice daily

reduced major adverse cardiovascular events including cardiovascular death

compared with clopidogrel 75 mg once daily, with steady accrual of benefit over time.

[0013] Following PLATO, the Prevention of Cardiovascular Events in Patients with

Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of

Aspirin (PEGASUS-TIMI 54) trial (also referred to as the PEGASUS trial or

PEGASUS study herein) was designed to test the hypothesis that long-term therapy

with ticagrelor added to low-dose aspirin will reduce the risk of major adverse

cardiovascular events in stable patients with a history of myocardial infarction.

Aspirin is known to reduce the risk of ischemic events in patients who present with

an acute coronary syndrome and in secondary prevention of myocardial infraction. A

significant majority of patients in the PEGASUS trial were administered a daily

maintenance dose of 75 mg to 150 mg of aspirin, with less than 0.1% of patients

being administered a daily maintenance dose of more or less than 75 mg to 150 mg

of aspirin.

[0014] Bleeding represents an important safety issue for all antiplatelet medications.

Inherent to their pharmacodynamic effects, antiplatelet agents increase the risk of

bleeding. There is a risk of bleeding across all degrees of severity from minimal

nuisance bleeding to life-threatening and fatal bleeding that may occur during long-

term out-of-hospital care or as a result of cardiac and other surgical procedures.

[0015] Moreover, it was previously established that ticagrelor is metabolized by the

liver, and impaired hepatic function can increase risks for bleeding and other adverse

events. Recognizing the balance between ischemic and bleeding risk with

antithrombotic therapy and considering that the intensity of antiplatelet therapy required may differ between the acute and chronic settings, the PEGASUS trial evaluated two intensities of ticagrelor therapy: the 90 mg twice daily dose studied in PLATO as well as a lower dose, 60 mg twice daily, to examine whether lower intensity in the chronic phase of long-term therapy may improve the balance of efficacy and bleeding.

[0016] Prior to the PEGASUS trial, the optimal intensity of platelet inhibition for long-term therapy was unknown. Ticagrelor doses lower than 60 mg bid were also considered for study in the PEGASUS trial, but modelling predicted that, for example, ticagrelor 45 mg bid would not generate a sustained inhibition of platelet aggregation (IPA) level greater than clopidogrel 75 mg bid. Furthermore, modeling predicted that intra-individual variability in IPA would increase with decreasing ticagrelor dose and that individual variability in IPA would be two to three times greater with ticagrelor 45 mg bid compared to ticagrelor 90 mg bid. While modeling suggested that ticagrelor 60 mg bid could generate a sustained IPA level greater than clopidrogel 75 mg bid with acceptable intra-individual variability, the ticagrelor 60 mg bid dosing regimen had not been tested in man prior to the PEGASUS study. The December 13, 2013 USFDA label, as revised, for the BRILINTA® drug refers only to the PLATO study.

[0017] After PLATO, the PEGASUS-TIMI 54 clinical trial (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin) was designed to evaluate whether long-term therapy with ticagrelor in addition to aspirin, in an experimental arm, reduces the risk of major adverse cardiovascular events in stable patients with a history of myocardial infarction in comparison with placebo administered in a placebo comparator arm.

[0018] In a first aspect, disclosed herein is a method comprising, in a randomized, double blind clinical trial, administering, in an experimental arm, to a patient in recognized need of reducing the risk of cardiovascular death, myocardial infarction, or stroke in the patient, an amount of ticagrelor and aspirin effectively reducing the risk of cardiovascular death, myocardial infarction, or stroke, in the patient, the risk in the experimental arm being effectively reduced compared, in a placebo comparator arm, with the reduction of risk in a patient in recognized need of reducing the risk of cardiovascular death, myocardial infarction, or stroke resulting from administering to the patient a placebo and aspirin, wherein the placebo comparator arm is not an active comparator arm, such as clopidogrel with aspirin, which was the active comparator arm of the PLATO study, and further wherein the patients in both the experimental and the placebo comparator arms had a history of myocardial infarction within 12 to 36 months prior to treatment in the experimental and the placebo comparator arms.

[0019] This method was tested and found to be efficacious in the PEGASUS study, a randomized, double blind clinical trial involving over 21,000 patients. Following a comprehensive review of the PEGASUS study results, the USFDA approved a label expansion for the BRILINTA® drug to include administration of ticagrelor 60 mg bid to patients with a history of myocardial infarction. The expanded indication for BRILINTA was approved under USFDA Priority Review, a designation granted to medicines that the USFDA determines to have the potential to provide significant improvements in the treatment, prevention or diagnosis of a disease. The September 2015 USFDA label, as revised, for the BRILINTA® drug refers to both the PLATO and PEGASUS studies.

[0020] In some embodiments of the first aspect, the method also shows a trend toward reduced risk of fatal bleeding in a patient administered ticagrelor in an experimental arm compared to a patient administered placebo in the placebo comparator arm.

[0021] In some embodiments of the first aspect, ticagrelor is administered 90 mg twice daily in the experimental arm. In some embodiments of the first aspect, ticagrelor is administered 60 mg twice daily in the experimental arm.

[0022] In some embodiments of the first aspect, a pharmaceutical composition comprising 90 mg of ticagrelor and a pharmaceutically acceptable carrier is administered twice daily. In some embodiments of the first aspect, a pharmaceutical composition comprising 60 mg of ticagrelor and a pharmaceutically acceptable carrier is administered twice daily in the experimental arm. In some embodiments of the first aspect, the pharmaceutical composition comprising ticagrelor and a pharmaceutically acceptable carrier administered in the experimental arm is a formulation in the form of a tablet administered orally.

[0023] In a second aspect, disclosed herein is a method for reducing the rate of a composite endpoint of cardiovascular death, myocardial infarction, or stroke in a patient in recognized need thereof, comprising administering to the patient twice daily a pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier,

wherein the patient has a history of myocardial infarction at least 12 months prior to the twice daily administration of the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier;

wherein the patient is also administered a daily maintenance dose of aspirin of 75 mg to 150 mg,

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wherein the method results in a statistically significant reduction in the rate of the composite endpoint relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only; and

wherein the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only.

[0024] The efficacy of the disclosed methods of the first and second aspects for reducing the rate of cardiovascular death, myocardial infarction, or stroke was demonstrated by the PEGASUS-TIMI 54 study.

[0025] In some embodiments of the first and second aspects, the daily maintenance dose of aspirin is 75 mg to 100 mg.

[0026] In some embodiments of the first and second aspects, the patient has a history of myocardial infarction at least 12 months prior to the twice daily administration of the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier.

[0027] In some embodiments of the first and second aspects, the patient has a history of myocardial infarction 12 to 36 months prior to the twice daily administration of the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier.

[0028] In some embodiments of the first and second aspects, the patient has a history of myocardial infarction as a result of an acute coronary syndrome. In some further embodiments of the first and second aspects, prior to the administration, the patient was administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier for a portion of 12 months

after the acute coronary syndrome. In some further embodiments of the first and

second aspects, prior to the administration, the patient was administered twice daily

a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically

acceptable carrier for 12 months after the acute coronary syndrome. In still some

further embodiments of the first and second aspects, prior to the administration, the patient was administered a pharmaceutical composition comprising a 180 mg ticagrelor loading dose prior to administration twice daily of a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier for a portion of the 12 months after the acute coronary syndrome.

[0029] In some embodiments of the first and second aspects, no loading dose of ticagrelor is required. In some further embodiments of the first and second aspects, wherein no loading dose of ticagrelor is required, the patient has a history of myocardial infarction at least 12 months prior to the twice daily administration of the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier.

[0030] In some embodiments of the first and second aspects, the method satisfies at least one of the following conditions:

(a)   the method numerically reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(b)   the method results in a relative risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(c)   the method numerically reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(d)   the method results in a statistically significant reduction in the rate of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(e)   the method results in a relative risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke that is statistically significantly less than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(f)   the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of approximately 7.8%;

(g)   the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of 7.8%;

(h)   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(i)   the method results in a numerical reduction in the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(j)   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke that is statistically significantly less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(k)   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of approximately 0.84 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(l)   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of 0.84 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(m)   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(n)   the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(o)   the method reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.27% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(p)   the method reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by 1.27% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

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(q)   the method results in a relative risk reduction of approximately 17% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke from 1 to 360 days relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(r)   the method results in a relative risk reduction of 17% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke from 1 to 360 days relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(s)   the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(t)   the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by 1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(u)   the method reduces the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.3% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only; or

(v)   the method reduces the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke at three years by 1.3% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only.

[0031] In some embodiments of the first and second aspects, the method satisfies at least one of the following conditions:

(a) the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(b) the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(c) the method does not result in a relative risk for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(d) the method does not result in a relative risk for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(e) the method does not result in a relative risk for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(f) the method does not result in a relative risk for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(g) the method results in a numerical increase in the number of TIMI major bleeding events per 100 patient years of less than 0.5 relative to a dosing

regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(h) the method results in a numerical increase in the number of TIMI major bleeding events per 100 patient years of 0.44 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(i) the method does not result in a numerical increase in the number of fatal bleeding events per 100 patient years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(j) the method results in a numerical increase in the number of intracranial hemorrhage events per 100 patient years of 0.05 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(k) the method results in a difference in the Kaplan-Meier rate of fatal bleeding at three years of less than 0.05% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only; or

(l) the method results in a difference in the Kaplan-Meier rate of intracranial hemorrhage at three years of less than 0.20% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only.

[0032] In some embodiments of the first and second aspects, no overall differences in the safety or effectiveness of the method are observed between elderly and younger patients.

[0033] In some other embodiments of the first and second aspects, the relative risk reduction of cardiovascular death, myocardial infarction, or stroke with ticagrelor is similar regardless of renal function. In some embodiments of the first and second aspects, the patient is administered a pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier twice daily for up to 47 months.

[0034] In some embodiments of the first and second aspects, the method is as effective in reducing the rate of cardiovascular death, myocardial infarction, or stroke in the patient as a method wherein the patient is administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg.

[0035] In some embodiments of the first and second aspects, the method reduces the rate of irreversible harm to the patient relative to a method wherein the patient is administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg.

[0036] In some embodiments of the first and second aspects, the method reduces the rate of the composite endpoint of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage, or fatal bleeding relative to a method wherein the patient is administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg.

[0037] In some embodiments of the first and second aspects, the method improves the risk-benefit profile of ticagrelor administered on a background of aspirin. In some further embodiments, the method improves the risk-benefit profile relative to a method wherein the patient is administered twice daily a pharmaceutical composition

comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg.

[0038] In some embodiments of the first and second aspects, the method results in a net clinical benefit relative to a method wherein the patient is administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg.

[0039] In some embodiments of the first and second aspects, the method reduces the rate of the composite endpoint of cardiovascular death, myocardial infarction, stroke, TIMI major bleeding relative to a method wherein the patient is administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg.

[0040] In a third aspect, disclosed herein is a method for reducing the rate of a composite endpoint of cardiovascular death, myocardial infarction, or stroke in a patient in recognized need thereof, comprising administering to the patient twice daily a pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier,

wherein the patient has or had acute coronary syndrome,

wherein the patient is also administered a daily maintenance dose of aspirin of 75 mg to 150 mg, and

wherein the rate of the composite endpoint in the patient is reduced relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only.

[0041] In some embodiments of the third aspect, the patient has acute coronary syndrome.

[0042] In some embodiments of the third aspect, the patient had acute coronary syndrome.

[0043] In some embodiments of the third aspect, the patient has a history of myocardial infarction.

[0044] In some embodiments of the third aspect, the patient has a history of myocardial infarction as a result of acute coronary syndrome.

[0045] In some embodiments of the third aspect, the daily maintenance dose of aspirin is 75 mg to 100 mg.

[0046] In a fourth aspect, disclosed herein is a method for reducing the rate of a composite endpoint of cardiovascular death, myocardial infarction, or stroke in a patient in recognized need thereof, comprising administering to the patient twice daily a pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier,

wherein the patient has history of myocardial infarction or the patient has or had acute coronary syndrome,

wherein the patient is also administered a daily maintenance dose of aspirin of 75 mg to 150 mg, and

wherein the rate of the composite endpoint in the patient is reduced relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only.

[0047] In some embodiments of the fourth aspect, the daily maintenance dose of aspirin is 75 mg to 100 mg.

[0048] In some embodiments of all the aspects, the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier can be taken with or without food.

[0049] In some embodiments of all the aspects, the pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier can be taken with or without food.

[0050] In some embodiments of all the aspects, methods disclosed herein are stopped for five days prior to a surgery that has a major risk of bleeding and resumed as soon as possible after hemostasis is achieved.

[0051] In some embodiments of all the aspects, the pharmaceutical composition is a solid oral dosage form. In some embodiments of all the aspects, a pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as a solid oral dosage form further comprising a filler present in an amount of 20% to 70% by weight, a binder present in an amount of 3% to 6% by weight, a disintegrant present in an amount of 2% to 6% by weight, and a lubricant present in an amount of 0.5% to 1% by weight. In still some further embodiments of all the aspects, the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as a solid oral dosage form further comprising a mixture of mannitol and dibasic calcium phosphate present in an amount of 20% to 70% by weight, hydroxypropyl cellulose present in an amount of 3% to 6% by weight, sodium starch glycolate present in an amount of 2% to 6% by weight, and magnesium stearate present in an amount of 0.5% to 1% by weight.

[0052] In some further embodiments of all the aspects, the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as a tablet and administered orally.

[0053]   In some embodiments of all the aspects, the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as an orally administered tablet further comprising a filler present in an amount of 20% to 70% by weight, a binder present in an amount of 3% to 6% by weight, a disintegrant present in an amount of 2% to 6% by weight, and a lubricant present in an amount of 0.5% to 1% by weight. In still some further embodiments of all the aspects, the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as an orally administered tablet further comprising a mixture of mannitol and dibasic calcium phosphate present in an amount of 20% to 70% by weight, hydroxypropyl cellulose present in an amount of 3% to 6% by weight, sodium starch glycolate present in an amount of 2% to 6% by weight, and magnesium stearate present in an amount of 0.5% to 1% by weight.

[0054]   In some other embodiments of all the aspects, the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as an orally administered tablet further comprising mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, ferric oxide black and ferric oxide red. In still some other embodiments of all the aspects, the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as an orally administered tablet further comprising mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol 400, ferric oxide black and ferric oxide red.

[0055]   In some embodiments of all the aspects, the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as an orally administered tablet as described in Table 1.

Table 1. Orally Administered Tablet Formulation

Component	Quantity per unit (mg)
Tablet core	
Ticagrelor	60
Mannitol	84
Dibasic calcium phosphate	42
Sodium starch glycolate	6
Hydroxypropyl cellulose	6
Magnesium stearate	2
Tablet coating	
Hydroxypropyl methylcellulose	4.4
Titanium dioxide	2.2
Polyethylene glycol 400	0.4
Ferric oxide black	0.001
Ferric oxide red	0.01

[0056]   In some embodiments of all the aspects, a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as a solid oral dosage form further comprising a filler present in an amount of 20% to 70% by weight, a binder present in an amount of 3% to 6% by weight, a disintegrant present in an amount of 2% to 6% by weight, and a lubricant present in an amount of 0.5% to 1% by weight.

[0057]   In still some further embodiments of all the aspects, the pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as a solid oral dosage form further comprising a mixture of mannitol and dibasic calcium phosphate present in an amount of 20% to 70% by weight, hydroxypropyl cellulose present in an amount of 3% to 6% by weight, sodium starch glycolate present in an amount of 2% to 6% by weight, and magnesium stearate present in an amount of 0.5% to 1% by weight.

[0058] In some further embodiments of all the aspects, the pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as a tablet and administered orally.

[0059] In some embodiments of all the aspects, a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as an orally administered tablet further comprising a filler present in an amount of 20% to 70% by weight, a binder present in an amount of 3% to 6% by weight, a disintegrant present in an amount of 2% to 6% by weight, and a lubricant present in an amount of 0.5% to 1% by weight. In still some further embodiments of all the aspects, the pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as an orally administered tablet further comprising a mixture of mannitol and dibasic calcium phosphate present in an amount of 20% to 70% by weight, hydroxypropyl cellulose present in an amount of 3% to 6% by weight, sodium starch glycolate present in an amount of 2% to 6% by weight, and magnesium stearate present in an amount of 0.5% to 1% by weight.

[0060] In some other embodiments of all the aspects, the pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier is formulated as an orally administered tablet further comprising mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, talc , polyethylene glycol 400, and ferric oxide yellow.

[0061] In some further embodiments of all the aspects, the orally administered tablet comprising 90 mg ticagrelor is round, biconvex, yellow, film-coated tablet marked with a "90" above "T" on one side.

[0062] In some further embodiments of all the aspects, the orally administered tablet comprising 60 mg ticagrelor is round, biconvex, pink, film-coated tablet marked with "60" above "T" on one side.

[0063] In some embodiments of all the aspects, tablets comprising ticagrelor may be crushed, mixed with water and drunk. In some other embodiments of all the aspects, a pharmaceutical composition comprising ticagrelor and a pharmaceutically acceptable carrier may be administered via a nasogastric tube (CH8 or greater).

[0064] In some embodiments of all the aspects, a patient who misses an administration of a pharmaceutical composition comprising ticagrelor and a pharmaceutically acceptable carrier is next administered a pharmaceutical composition comprising ticagrelor and a pharmaceutically acceptable carrier (their next pharmaceutical composition) at its scheduled time.

[0065] The dosage unit forms of the disclosure can be produced by compacting or compressing an admixture or composition, for example, a powder or granules, under pressure to form a stable three-dimensional shape (e.g., a tablet). As used herein, "tablet" includes compressed pharmaceutical dosage unit forms of all shapes and sizes, whether coated or uncoated.

[0066] The expression "dosage unit form" as used herein refers to a physically discrete unit of agent appropriate for the patient to be treated. In general, a compacted mixture has a density greater than that of the mixture prior to compaction. A dosage unit form of the disclosure can have almost any shape including concave and/or convex faces, rounded or angled corners, and a rounded to rectilinear shape. In some embodiments, the compressed dosage forms of the disclosure comprise a rounded tablet having flat faces. The solid pharmaceutical dosage forms of the disclosure can be prepared by any compaction and compression method known by

persons of ordinary skill in the art of forming compressed solid pharmaceutical

dosage forms. In particular embodiments, the pharmaceutical compositions provided

herein may be prepared using conventional methods known to those skilled in the

field of pharmaceutical formulation, as described, e.g., in pertinent textbooks. See,

e.g., Remington: The Science and Practice of Pharmacy, 21st Ed., Lippincott

Williams & Wilkins, Baltimore, Md. (2003); Ansel et al., Pharmaceutical Dosage

Forms And Drug Delivery Systems, 7th Edition, Lippincott Williams & Wilkins, (1999);

The Handbook of Pharmaceutical Excipients, 4th edition, Rowe et al., Eds.,

American Pharmaceuticals Association (2003); Gibson, Pharmaceutical

Preformulation And Formulation, CRC Press (2001), these references are hereby

incorporated herein by reference to the extent they disclose suitable, conventional

methods known to those skilled in the field of pharmaceutical formulation.

[0067]   As described above, the pharmaceutical compositions of the present

disclosure comprise a pharmaceutically acceptable carrier, adjuvant, or vehicle,

which, as used herein, includes any and all suitable solvents, diluents, or other liquid

vehicle, dispersion or suspension aids, surface active agents, isotonic agents,

thickening or emulsifying agents, preservatives, solid binders, lubricants and the like,

as suited to the particular dosage form desired. Remington's Pharmaceutical

Sciences, Sixteenth Edition, E. W. Martin (Mack Publishing Co., Easton, Pa., 1980)

discloses various carriers used in formulating pharmaceutically acceptable

compositions and known techniques for the preparation thereof. Except insofar as

any conventional carrier medium is incompatible with ticagrelor, such as by

producing any undesirable biological effect or otherwise interacting in a deleterious

manner with any other component(s) of the pharmaceutically acceptable composition,

its use is contemplated to be within the scope of this disclosure. Some examples of

materials which can serve as suitable pharmaceutically acceptable carriers include,
but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum
proteins, such as human serum albumin, buffer substances such as phosphates,
glycine, sorbic acid, or potassium sorbate, partial glyceride mixtures of saturated
vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate,
disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride,
zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, polyacrylates,
waxes, polyethylene-polyoxypropylene-block polymers, wool fat, sugars such as
lactose, glucose and sucrose; starches such as corn starch and potato starch;
cellulose and its derivatives such as sodium carboxymethyl cellulose, ethyl cellulose
and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients such as
cocoa butter and suppository waxes; oils such as peanut oil, cottonseed oil;
safflower oil; sesame oil; olive oil; corn oil and soybean oil; glycols, such as
propylene glycol or polyethylene glycol; esters such as ethyl oleate and ethyl laurate;
agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide;
alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol, and
phosphate buffer solutions, as well as other non-toxic compatible lubricants such as
sodium lauryl sulfate and magnesium stearate, as well as coloring agents, releasing
agents, coating agents, sweetening, flavoring and perfuming agents, preservatives
and antioxidants can also be present in the composition, according to the judgment
of the formulator of ordinary skill in the art.

[0068]   In some embodiments, a pharmaceutical composition comprising
ticagrelor and a pharmaceutically acceptable carrier further comprises a filler, a
binder, a disintegrant, and a lubricant. In some embodiments, a filler is selected
from mannitol, sorbitol, dibasic calcium phosphate dihydrate, dibasic calcium

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phosphate anhydrate, and tribasic calcium phosphate, or any mixture thereof. In some embodiments, a binder is selected from hydroxypropyl cellulose, alginic acid, carboxymethylcellulose sodium, copovidone, and methylcellulose, or any mixture thereof. In some embodiments, a disintegrant is selected from sodium starch glycolate, croscarmellose sodium, and crospovidone, or any mixture thereof. In some embodiments, a lubricant is selected from magnesium stearate, stearic acid, palmitic acid, calcium stearate, carnauba wax, hydrogenated vegetable oils, mineral oil, polyethylene glycols, and sodium stearyl fumarate.

[0069]   In some embodiments of all the aspects, a pharmaceutical composition comprising ticagrelor and a pharmaceutically acceptable carrier further comprises a filler present in an amount of 20% to 70% by weight, a binder present in an amount of 3% to 6% by weight, a disintegrant present in an amount of 2% to 6% by weight, and a lubricant present in an amount of 0.5% to 1% by weight.

[0070]   In some embodiments of all the aspects, a pharmaceutical composition comprising ticagrelor and a pharmaceutically acceptable carrier further comprises a mixture of mannitol and dibasic calcium phosphate present in an amount of 20% to 70% by weight, hydroxypropyl cellulose present in an amount of 3% to 6% by weight, sodium starch glycolate present in an amount of 2% to 6% by weight, and magnesium stearate present in an amount of 0.5% to 1% by weight.

BRIEF DESCRIPTION OF FIGURES

[0071]   Figure 1 depicts the trial consort diagram in the PEGASUS-TIMI 54 study.

[0072]   Figure 2 depicts Kaplan-Meier rates of cardiovascular Death, myocardial infarction, and stroke through 3 years in the PEGASUS-TIMI 54 study by treatment allocation (*Panel A*), hazard ratios and rates of the primary endpoint and individual components for each dose as well as both doses pooled (*Panel B*).

[0073]   Figure 3 depicts Kaplan-Meier rates of cardiovascular death, myocardial infarction, and stroke through 3 years in the PEGASUS-TIMI 54 study by treatment allocation.

[0074]   Figure 4 depicts primary efficacy endpoint subgroup analyses of ticagrelor 60 mg bid in the PEGASUS-TIMI 54 trial.

[0075]   Figure 5 depicts primary efficacy endpoint subgroup analyses in the PEGASUS-TIMI 54 trial.

[0076]   Figure 6 depicts primary efficacy endpoint subgroup analyses in the PEGASUS-TIMI 54 trial.

[0077]   Figure 7 depicts primary efficacy endpoint subgroup analyses of ticagrelor 60 mg bid in PEGASUS-TIMI 54 trial.

[0078]   Figure 8 depicts the percentage of patients still on treatment over time in the safety analysis set in the PEGASUS-TIMI 54 trial.

[0079]   Figure 9 depicts TIMI major bleeding - subgroups in the PEGASUS-TIMI 54 study.

[0080]   Figure 10 depicts TIMI major bleeding - subgroups in the PEGASUS-TIMI 54 study.

[0081]   Figure 11 depicts TIMI major bleeding - subgroups in the PEGASUS-TIMI 54 study.

[0082]   Figure 12 depicts a Kaplan-Meier estimate of time to premature permanent discontinuation of study drug due to bleeding based on the safety analysis set.

[0083]   Figure 13 depicts the predicted probability of a cardiovascular death, myocardial infarction, or stroke event and the predicted probability of a TIMI major bleeding event within three years using the final dose-exposure-response models, stratified by treatment arm.

[0084]   Figure 14 depicts the composite endpoint of cardiovascular death, myocardial infarction, and stroke events/no events versus exposure using the final exposure-response analysis data set.

[0085]   Figure 15 depicts TIMI major bleeding events/no events versus exposure using the final exposure-response analysis data set.

[0086]   Figure 16 depicts the distribution of cardiovascular death, myocardial infarction, and stroke event times, stratified by dose.

[0087]   Figure 17 depicts the distribution of TIMI major bleeding event times, stratified by dose.

[0088]   Figure 18 depicts Kaplan-Meier estimates of patients without TIMI Major Bleeding events vs. time, stratified by dose.

[0089]   Figure 19 depicts the events caused or prevented per every 1000 patients treated for 3 years in the PEGASUS-TIMI 54 trial in the ticagrelor 60 mg bid arm for various safety and efficacy endpoints.

[0090]   Figure 20 depicts the events caused or prevented per every 1000 patients treated for 3 years in the PEGASUS-TIMI 54 trial in the ticagrelor 90 mg bid arm for various safety and efficacy endpoints.

[0091]   Figure 21 depicts the Kaplan-Meier rates for the composite endpoint of cardiovascular death, myocardial infarction, or stroke in patients randomized to placebo at 90 days and 3 years by time from $P2Y_{12}$ inhibitor withdrawal.

[0092]   Figure 22 depicts hazard ratios for cardiovascular death, myocardial infarction, or stroke at 3 years by time from $P2Y_{12}$ inhibitor withdrawal to randomization in the PEGASUS-TIMI 54 Study.

[0093]   Figure 23 depicts the Kaplan-Meier rates for cardiovascular death, myocardial infarction, or stroke at 3 years with ticagrelor 90 mg bid twice daily,

ticagrelor 60 mg bid twice daily compared with placebo in patients withdrawn from

$P2Y_{12}$ inhibitor therapy within 30 days (A), between 30 days and 1 year (B), and

more than 1 year of randomization (C).

[0094] Figure 24 depicts the Kaplan-Meier rates for the composite endpoint of

cardiovascular death, myocardial infarction, or stroke at 3 years with ticagrelor doses

pooled (purple) compared with placebo in patients withdrawn from P2Y12 inhibitor

therapy within 30 days of randomization stratified by a qualifying myocardial

infarction, 24 months prior to randomization (left) and $\geqslant$24 months prior to

randomization (right).

[0095] Figure 25 depicts the Kaplan-Meier rates for the composite endpoint of

cardiovascular death, myocardial infarction, or stroke for the first 90 days (left) and

as a landmark from 90 days to 3 years (right) in patients withdrawn from $P2Y_{12}$

inhibition $\leqslant$30 days from randomization by treatment (placebo vs. ticagrelor doses

pooled).

[0096] Figure 26 depicts TIMI major bleeding at 3 years with ticagrelor 90 mg bid

twice daily (red), ticagrelor 60 mg bid twice daily (blue), and both doses pooled

(purple) compared to placebo by time from $P2Y_{12}$ inhibitor withdrawal.

[0097] Figure 27 depicts TIMI major bleeding at 3 years with ticagrelor 90 mg bid

twice daily (red), ticagrelor 60 mg bid twice daily (blue) compared to placebo (green)

in patients withdrawn from $P2Y_{12}$ inhibitor therapy within 30 days.

DEFINITIONS

[0098] As used herein, the following definitions shall apply unless otherwise

indicated.

[0099] As used herein, the term "solid dosage form" generally refers to a

pharmaceutical composition, which when used in an oral mode of administration

include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is mixed with at least one inert, pharmaceutically acceptable carrier, which can also be referenced as an excipient.

[00100]   As used herein, an "excipient" or "a pharmaceutically acceptable carrier" includes functional and non-functional ingredients in a pharmaceutical composition.

[00101]   As used herein, a "disintegrant" is an excipient that hydrates a pharmaceutical composition and aids in tablet dispersion. As used herein, a "diluent" or "filler" is an excipient that adds bulkiness to a pharmaceutical composition.

[00102]   As used herein, a "surfactant" is an excipient that imparts pharmaceutical compositions with enhanced solubility and/or wetability.

[00103]   As used herein, a "binder" is an excipient that imparts a pharmaceutical composition with enhanced cohesion or tensile strength (e.g., hardness).

[00104]   As used herein, a "glidant" is an excipient that imparts a pharmaceutical compositions with enhanced flow properties.

[00105]   As used herein, a "colorant" is an excipient that imparts a pharmaceutical composition with a desired color. Examples of colorants include commercially available pigments such as FD&C Blue # 1 Aluminum Lake, FD&C Blue #2, other FD&C Blue colors, titanium dioxide, iron oxide, and/or combinations thereof. In one embodiment, the pharmaceutical composition provided by the disclosure is purple.

[00106]   As used herein, a "lubricant" is an excipient that is added to pharmaceutical compositions that are pressed into tablets. The lubricant aids in compaction of granules into tablets and ejection of a tablet of a pharmaceutical composition from a die press.

[00107]   As used herein, a "P2Y$_{12}$ receptor antagonist" is an antiplatelet agent

that at least partially inhibits the function of the G-protein coupled receptor P2Y$_{12}$.

Examples of P2Y$_{12}$ receptor antagonists include clopidogrel, prasugrel, ticlopidine,

ticagrelor, cangrelor, and elinogrel.

[00108]   As used herein, an "adenosine diphosphate receptor inhibitor," also

referred to as an "ADP receptor blocker" or "ADP rec. block." is an antiplatelet agent

that at least partially inhibits the function of some or all types of adenosine

diphosphate receptors (i.e., P2Y receptors). "Adenosine diphosphate receptor

inhibitor," "ADP receptor blocker," "ADP rec. block," and "P2Y$_{12}$ receptor antagonist"

are used interchangeably herein.

[00109]   As used herein, "net clinical benefit" or "risk-benefit profile" is the time

from randomization to the first occurrence of any event from the composite of

cardiovascular death, myocardial infarction, stroke or TIMI major bleeding.

[00110]   As used herein, "irreversible harm" is the time from randomization to

first occurrence of any event from the composite of cardiovascular death, myocardial

infarction, stroke, intracranial bleeding or fatal bleeding.

[00111]   As used herein, a "risk factor" is a demographic factor that influences

the underlying risk of an event independently of any drug treatment.

[00112]   As used herein, a "covariate" is a demographic factor that modifies the

effect of drug treatment after the impact of risk factors has already been taken into

account.

[00113]   As used herein, the "absolute risk reduction" is the difference in the risk

of an outcome in a treatment arm in relation to a comparator or placebo arm.

[00114]   As used herein, the "relative risk reduction" is the absolute risk reduction divided by the risk of an outcome (alternatively referred to as the rate of an outcome) in the comparator or placebo arm.

[00115]   As used herein, a "statistically significant reduction in the rate of cardiovascular death, myocardial infarction, or stroke" means the reduction in the rate of cardiovascular death, myocardial infarction, or stroke for the disclosed method relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 to 150 mg only is statistically significant for at least one of the following statistical metrics: relative risk reduction or hazard ratio. Formal statistical testing included the endpoints of cardiovascular death and all-cause mortality, as well as the composite endpoint of cardiovascular death, myocardial infarction, and stroke. The limit for establishing statistical significance in formal statistical testing, accounting for interim analysis and multiple testing of the two doses of ticagrelor, was $p < 0.02598$. All other p-values recited herein for exploratory endpoints should be considered nominal because the p-values are not controlled for multiplicity. In some embodiments, a statistically significant reduction in the rate of cardiovascular death, myocardial infarction, or stroke is characterized by a p-value of less than 0.026 for one of the aforementioned statistical metrics. In some other embodiments, a statistically significant reduction in the rate of cardiovascular death, myocardial infarction, or stroke is characterized by a p-value of less than 0.01 for one of the aforementioned statistical metrics. In some embodiments, a statistically significant reduction in the rate of cardiovascular death, myocardial infarction, or stroke is characterized by a p-value of less than 0.001 for one of the aforementioned statistical metrics.

[00116]   As used herein, a "nominally significant" exploratory endpoint is characterized by a p-value of less than 0.05.

[00117]   As used herein, "Kaplan-Meier rate" or "Kaplan-Meier estimate" refers to the probability of an event or outcome occurring in a given time interval as calculated by the Kaplan-Meier method. More information regarding Kaplan-Meier analysis and survival statistics may be found in Rich, Jason T., et al. "A practical guide to understanding Kaplan-Meier curves." Otolaryngology-Head and Neck Surgery 143.3 (2010): 331-336 and Jager, Kitty J., et al. "The analysis of survival data: the Kaplan–Meier method." Kidney international 74.5 (2008): 560-565.

[00118]   As used herein, "hazard ratio" means the ratio of hazard rates corresponding to a particular event or outcome in an experimental arm relative to a comparator arm. Hazard ratios measure how often a particular event or outcome occurs in an experimental arm compared to how often in occurs in a comparator arm over time. A hazard ratio of one means that there is no difference in event frequency between the experimental arm and the comparator arm. A hazard ratio of greater than one means an event or outcome occurred more frequently in the experimental arm compared to the comparator arm. A hazard ratio of less than one means an event or outcome occurred less frequently in the experimental arm compared to the comparator arm.

[00119]   As used herein, "number needed to treat" (NNT) is the number of patients who must follow a treatment regimen over a specified time in order to achieve the desired treatment outcome or endpoint for one person.

[00120]   As used herein, "number needed to harm" (NTH) is the number of patients who must follow a treatment regimen over a specified time in order to observe an adverse event for one person.

[00121]   As used herein, "cardiovascular death" means sudden cardiac death, death due to acute myocardial infarction, death due to heart failure, death due to a cerebrovascular event, death due to other cardiovascular causes (i.e., pulmonary embolism, aortic disease, cardiovascular intervention), and deaths for which there was no clearly documented non-cardiovascular cause.

[00122]   As used herein, "acute coronary syndrome" refers to a condition where blood supplied to the heart muscle is suddenly stopped, i.e., heart attack or unstable angina. Acute coronary syndromes may entail a sudden and complete blockage of blood flow to the heart or a transient blockage.

[00123]   As used herein, "coronary heart diseases death" (CHD death) means sudden cardiac death, death due to acute myocardial infarction, and the subset of death due to other cardiovascular causes that are secondary to a coronary revascularization procedure.

[00124]   As used herein, "myocardial infarction" (MI) is diagnosed based on the Universal Myocardial infarction definition published by Thygesen *et al* in 2007. The terms "myocardial infarction", "myocardial infarction," "spontaneous myocardial infarction," and "spontaneous MI" are used interchangeably herein. Myocardial infarction is diagnosed based on a detection of rise and/or fall of cardiac biomarkers, preferably troponin, with at least one value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least one of the following symptoms of myocardial ischemia:

•   ECG changes (ST segment, T waves, or new left bundle branch block) indicative of new ischemia; development of pathologic Q waves on the ECG; imaging evidence of new loss of viable myocardium or new regional wall motion abnormality;

- Sudden unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST- elevation or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood;

- PCI-related Myocardial Infarction: elevation of cardiac biomarkers N3x 99th percentile of the URL within 48 hours after PCI;

- CABG-related Myocardial infarction: Elevation of cardiac biomarkers N5x, 99th percentile of the URL within 72 hours after CABG, plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary occlusion, or imaging evidence of loss of viable myocardium;

- Silent myocardial infarction based on ECG or imaging findings; or

- Pathological findings of an acute myocardial infarction not otherwise meeting above definitions.

[00125]   As used herein, a patient with a "history of myocardial infarction" or a "history of spontaneous myocardial infarction" refers to a patient who has experienced at least one myocardial infarction diagnosed based on the Universal Myocardial infarction definition published by Thygesen *et al* in 2007. For example, as referred to herein, a patient with acute coronary syndrome (ACS) is also considered to be a patient with a history of myocardial infarction.

[00126]   As used herein, "stroke" means an acute episode of neurologic dysfunction attributed to a central nervous system vascular cause.

[00127]   As used herein, "primary ischemic stroke" means an acute episode of focal brain, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue and documented by imaging.

[00128]   As used herein, "primary hemorrhagic stroke" means an acute episode of focal or global brain, spinal, or retinal dysfunction caused by non-traumatic intraparenchy- mal, intraventricular, or subarachnoid hemorrhage as documented by neuroimaging or autopsy.

[00129]   As used herein, "TIMI major bleeding" refers to at least one of: intracranial bleeding; clinically overt signs of hemorrhage associated with a drop in hemoglobin (Hgb) of ⩾5 g/dL (or, when hemoglobin is not available, a fall in hematocrit of ⩾15%); or fatal bleeding (a bleeding event that directly led to death within 7 days).

[00130]   As used herein, "other TIMI major bleeding events" refers to TIMI major bleeding events other than intracranial hemorrhage or fatal bleeding.

[00131]   As used herein, "TIMI minor bleeding" refers to any clinically overt sign of hemorrhage (including imaging) that is associated with a fall in Hgb of 3 to b 5 g/dL (or, when hemoglobin is not available, a fall in hematocrit of 9 to below 15%).

[00132]   As used herein, the "safety analysis set" refers to all patients who received at least 1 dose of randomized ticagrelor or placebo and for whom post-dose data were available were included in the safety population. Any erroneously treated patients (e.g., randomized to ticagrelor but actually given placebo) were to be accounted for in the actual treatment group.

[00133]   As used herein, the "efficacy analysis set," the "intention-to-treat analysis set," and the "full analysis set" refers to all randomized patients, irrespective of their protocol adherence and continued participation in the study. Patients were analyzed according to their randomized study drug irrespective of whether the event occurred before or following discontinuation of study drug.

[00134]   As used herein, "about" or "approximately" means within 20%, such as

within 10% and further such as within 5%, of a given value or range.

[00135]   As used herein, "baseline" refers to "a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 to 150 mg only."

"Baseline" and "a dosing regimen where the patient receives the daily maintenance

dose of aspirin of 75 to 150 mg only" may be used interchangeably herein.

Endpoints in the PEGASUS-TIMI 54 trial (i.e., relative risk reduction for the

composite endpoint of cardiovascular death, myocardial infarction, or stroke) were

evaluated for the two doses of ticagrelor relative to baseline.

Example: PEGASUS-TIMI 54 (PEGASUS)

[00136]   The PEGASUS-TIMI 54 trial (also referred to as the PEGASUS trial or

PEGASUS study herein) was a randomized, double-blind, placebo-controlled

multinational clinical trial that enrolled over 21,000 patients at 1,161 sites in 31

countries. The protocol was approved by the relevant ethics committees at all

participating sites. In the U.S., the PEGASUS trial was assigned a ClinicalTrials.gov

number of NCT01225562. Results from the PEGASUS trial were discussed in

Bonaca, Marc P., et al. "Long-term use of ticagrelor in patients with prior myocardial

infarction." New England Journal of Medicine 372.19 (2015): 1791-1800.

[00137]   Eligible patients had a history of a spontaneous myocardial infarction 1

to 3 years prior to enrollment and one of the following additional high risk features:

age greater than or equal to 65 years; diabetes mellitus requiring medication; a

second prior spontaneous myocardial infarction; multivessel coronary artery disease;

or chronic renal dysfunction defined as an estimated creatinine clearance less than

60 mL/min. Patients were ineligible if there was planned use of a $P2Y_{12}$ receptor

antagonist, dipyridamole, cilostazol, or anticoagulant therapy during the study period

or if they required dialysis, had a bleeding disorder, a history of ischemic stroke, an intracranial bleed, tumor, or vascular abnormality, or a recent gastrointestinal bleed or major surgery. Patients could be randomized regardless of their prior adenosine diphosphate (ADP) receptor blocker therapy or a lapse in therapy.

[00138]   Full eligibility criteria have been previously published (*See* Bonaca MP, Bhatt DL, Braunwald E, *et al.* Design and rationale for the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial infarction 54 (PEGASUS-TIMI 54) trial. *Am Heart J* 2014;167:437,444.e5, hereinafter referred to as *Bonaca*), the portions related to full eligibility criteria of which are incorporated herein by reference. Written informed consent was obtained from all patients. Inclusion/exclusion criteria for the PEGASUS trial are shown in Table 2. Most (89.1%) of the patients enrolled in the PEGASUS trial had received previous treatment with an adenosine diphosphate receptor blocker; most commonly clopidogrel (83.7%), with 4.4% having received prasugrel, 0.5% ticlopidine, and 0.4% ticagrelor (Table 3).

Table 2. Inclusion/Exclusion Criteria for the PEGASUS-TIMI 54 Trial

Inclusion	Exclusion
At least 50 years old Spontaneous MI 1-3 years prior *plus* at least one of the following risk factors: • Age of ≥65 • Diabetes mellitus on medication • A second prior MI • Multivessel CAD (≥50% in 2+ coronary territories) • Chronic renal dysfunction (*non-end stage, est. creat. cl. <60 mL/min*) • Taking ASA 75-150 mg daily Contraception in women of child-bearing potential Provides written informed consent	Planned use of ADP receptor blockers, dipyridamole or cilostazol Planned revascularization (coronary, peripheral, cerebrovascular) Potent inducer/inhibitor/substrate of CYP3A use Chronic anticoagulation Known bleeding diathesis or coagulation disorder Increased risk of bleeding defined as: • A history of intracranial bleed at any time, • A central nervous system tumor or intracranial vascular abnormality (eg, aneurysm, arteriovenous malformation) at any time, • Intracranial or spinal cord surgery within 5 years, or • A gastrointestinal (GI) bleed within the past 6 months, or major surgery within 30 days History of ischemic stroke Patients considered to be at risk of bradycardic events (eg, known sick sinus syndrome or second or third degree atrioventricular [AV] block) unless already treated with a permanent pacemaker Coronary-artery bypass grafting in the last 5 years Known severe liver disease Renal failure requiring dialysis Pregnancy or lactation Life-expectancy <1 year Any condition judged by the investigator to make participation unsafe for the patient Concern for inability to comply with the protocol Prior participation in a trial with ticagrelor (if treated with active ticagrelor) Involvement in planning or conduct of the study Participation in another clinical study with an investigational product during the prior 30 days

Table 3. Previous treatment with ADP receptor blocker any time prior to randomization (full analysis set)

Previous treatment	Number (%) of patients			
	Ticagrelor 90 mg bd N=7050	Ticagrelor 60 mg bd N=7045	Placebo N=7067	Total N=21162
Patients previously treated with ADP receptor blocker	6271 (89.0%)	6289 (89.3%)	6285 (88.9%)	18845 (89.1%)
Clopidogrel	5922 (84.0%)	5915 (84.0%)	5878 (83.2%)	17715 (83.7%)
Prasugrel	287 (4.1%)	317 (4.5%)	325 (4.6%)	929 (4.4%)
Ticlodipine	34 (0.5%)	35 (0.5%)	38 (0.5%)	107 (0.5%)
Ticagrelor	31 (0.4%)	26 (0.4%)	38 (0.5%)	95 (0.4%)
Missing	4 (0.1%)	1 (0.0%)	5 (0.1%)	10 (0.0%)
Time from last dose to randomisation				
Ongoing at randomisation, prior to study drug[a]	4 (0.1%)	6 (0.1%)	10 (0.1%)	20 (0.1%)
After first dose of study drug[b]	14 (0.2%)	23 (0.3%)	12 (0.2%)	49 (0.2%)
0-7 days	1826 (25.9%)	1816 (25.8%)	1828 (25.9%)	5470 (25.8%)
8-90 days	1243 (17.6%)	1257 (17.8%)	1243 (17.6%)	3743 (17.7%)
3-12 months	1498 (21.2%)	1520 (21.6%)	1540 (21.8%)	4558 (21.5%)
>12 months	1676 (23.8%)	1661 (23.6%)	1645 (23.3%)	4982 (23.5%)
Unknown	10 (0.1%)	6 (0.1%)	7 (0.1%)	23 (0.1%)
Reason stopped				
Treating physician recommendation	5901 (83.7%)	5897 (83.7%)	5899 (83.5%)	17697 (83.6%)
Patient preference	325 (4.6%)	345 (4.9%)	346 (4.9%)	1016 (4.8%)
Bleeding	9 (0.1%)	9 (0.1%)	9 (0.1%)	27 (0.1%)
Non-bleeding adverse reaction or symptom	9 (0.1%)	7 (0.1%)	7 (0.1%)	23 (0.1%)
Other	6 (0.1%)	3 (0.0%)	4 (0.1%)	13 (0.1%)
Missing	21 (0.3%)	28 (0.4%)	20 (0.3%)	69 (0.3%)

Source: CSR Table 11.1.3.11.1

Treatment with ADP receptor blocker at any time prior to randomisation.

[a]   Treatment with open label ADP receptor blocker continued on or after day of randomisation, but stopped prior to first dose of study drug

[b]   Treatment with open label ADP receptor blocker continued after the first dose of study drug (protocol violation)

ADP Adenosine diphosphate; bd Twice daily; N Number of patients in treatment group

[00139]   Eligible patients were randomized in a 1:1:1 ratio to receive ticagrelor

90 mg orally twice daily, ticagrelor 60 mg orally twice daily, or placebo.

Randomization was performed using a central computerized telephone or web based

system, and allocation was double-blind. The mean time from qualifying myocardial

infarction to randomization in the study was 21.8 months, and the majority of patients

(60.7%) had a qualifying myocardial infarction one to two years prior to

randomization.

[00140]   A modified study treatment option (blinded double dummy ticagrelor or

clopidogrel) was provided to investigators for use if a patient developed an indication

for $P2Y_{12}$ receptor blockade as previously published (*See Bonaca*). The modified

treatment option was used by less than 4% of patients during the study. Patients

undergoing elective major non-cardiovascular procedures were advised to stop study

treatment 5 days prior to the procedure and resume it when deemed appropriate by

the treating physician. The protocol also defined discontinuation criteria for

temporary interruption and permanent discontinuation from treatment with ticagrelor

(Table 4).

[00141]   All patients enrolled in the PEGASUS trial were instructed to take open

label aspirin at a dose of 75 to 150 mg daily. Because the study population was

stable, no loading dose of ticagrelor was administered.

[00142]   The primary efficacy endpoint was the composite of cardiovascular

death, myocardial infarction, or stroke. Secondary endpoints were cardiovascular

death and all-cause mortality. The analysis of secondary endpoints proceeded in a

hierarchical fashion, starting with cardiovascular death and then death from any

cause. Additional endpoints listed below were evaluated on an exploratory basis.

Exploratory efficacy endpoints included substituting coronary heart disease death for

cardiovascular death, and the additional end points of urgent coronary

revascularization, unstable angina, and transient ischemic attack. The primary safety

endpoint was TIMI major bleeding. Other safety endpoints included intracranial

hemorrhage (ICH) and fatal bleeding. Definitions of the endpoints have been

previously published (See Bonaca). A central clinical events committee whose

members were unaware of the treatment assignments adjudicated all efficacy

endpoints and bleeding episodes.

Table 4. Protocol-defined discontinuation criteria

Temporary interruption of study drug	Permanent discontinuation from treatment with study drug

• Severe thrombocytopenia (platelet count <50,000/:L). Patients could restart study drug once severe thrombocytopenia resolved.
 • Major surgery (for elective minor surgery or other invasive procedures, study drug could be continued or interrupted temporarily at the Investigator's discretion)
 • Major bleeding
 • Development of a reversible bleeding diathesis or coagulation disorder
 • Need for treatment with prohibited concomitant medications
 • Development of significant conduction system disease (eg sick sinus syndrome or second or third degree atrioventricular [AV] block) until treated with a pacemaker
 • Severe hepatic impairment
	The Investigator could decide to permanently discontinue study drug, in consultation with the TIMI Hotline, for the following safety-related reasons:
	 • Incorrectly enrolled patient in whom the eligibility criteria violation would put the patient at undue risk
	 • Development of a condition that would subject the patient to undue risk:
	   − Ischaemic stroke or intracranial bleeding of any kind; intracranial or spinal cord surgery; discovery of a CNS tumour or intracranial vascular abnormality (eg, aneurysm, arteriovenous malformation)
	   − Development of chronic bleeding diathesis or coagulation disorder
	   − Renal failure requiring dialysis
	   − Pregnancy
	   − Development of significant conduction system disease (eg, sick sinus syndrome or second or third degree AV block) not treated with a permanent pacemaker
	 • AE considered to be related to study drug, for which the Investigator felt continued treatment would put the patient at undue risk.
	 • Severe non-compliance with protocol.

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[00143]   A total of 1360 primary endpoint events would be required to provide approximately 90% power to detect a 20% relative risk reduction with the 90 mg twice daily dose and approximately 83% power to detect a 19% relative risk reduction with the 60 mg twice daily dose when each dose was compared individually with placebo. The primary efficacy analysis was conducted on an intention-to-treat basis, with each of the two doses individually compared to placebo, as a time to event analysis from randomization to the first occurrence of any element of the primary composite endpoint: cardiovascular death, myocardial infarction, or stroke. Analysis of secondary endpoints proceeded in a hierarchical fashion, starting with CV death. An exploratory analysis of both doses combined compared with placebo was prespecified.

[00144]   Safety analyses included all randomized patients who received at least one dose of study drug and for whom post-dose data were available. Patients were censored at the first of the pre-specified Common Study End Date, withdrawal of consent, or the last clinical event assessment. Safety was analyzed as on-treatment including all events occurring after first dose and within 7 days after the last dose of study drug. To control overall type I error, alpha was apportioned to each ticagrelor dose-placebo comparison (using a correlation of 0.5 between the test statistics) and a Haybittle-Peto approach was employed to take into account an interim analysis of efficacy that was performed by the Independent Data Monitoring Committee, resulting in a significance level of 0.026 being indicative of statistical significance for the final analyses. Event rates are expressed as Kaplan-Meier estimates of cumulative incidence. Hazard ratios and 95% confidence intervals were generated using a Cox proportional hazards model and all reported P values are two-sided. Because clinical trials are conducted under widely varying conditions, adverse

reaction rates observed in clinical trials cannot be directly compared to rates in the

clinical trials of another drug and may not reflect the rates observed in practice.

[00145]   A total of 21,162 patients were randomized between October 2010 and

April 2013. Trial sample size determination was made with the assumptions of a 3.5%

per year event rate for the primary endpoint in the placebo group based on prior

studies in similar populations and a target relative risk reduction for the ticagrelor 90

mg bid arm of 20% and approximately 19% for the ticagrelor 60 mg bid dose

compared with placebo arm. Baseline characteristics of the patients were well

balanced between the experimental and comparator placebo treatment arms (Tables

5 and 6).

Table 5. Baseline Characteristics of All Patients in the PEGASUS-TIMI 54 Trial

Demographic	% Patients
<65 years	45%
Diabetes	32%
Multivessel disease	59%
History of >1 MI	17%
Chronic non-end stage renal disease	19%
Stent	80%
Prior P2Y12 platelet inhibitor therapy	89%
Lipid lowering therapy	94%

Table 6. Baseline Characteristics of the Patients by Treatment Group

Characteristic	Ticagrelor 90 mg bid N=7050 n (%)	Ticagrelor 60 mg bid N=7045 n (%)	Placebo N=7067 n (%)
Demographics			
Age – yr, mean (SD)	65.4 (8.4)	65.2 (8.4)	65.4 (8.3)
Female	1682 (23.9)	1661 (23.6)	1717 (24.3)
Caucasian*	6126 (86.9)	6077 (86.3)	6124 (86.7)
Weight – kg, mean (SD)	82 (16.7)	82 (17.0)	82 (16.6)
Clinical Characteristics			
Hypertension	5462 (77.5)	5461 (77.5)	5484 (77.6)
Hypercholesterolemia	5410 (76.7)	5380 (76.4)	5451 (77.1)
Current smoker	1187 (16.8)	1206 (17.1)	1143 (16.2)
Diabetes mellitus	2241 (31.8)	2308 (32.8)	2257 (31.9)
Multivessel coronary disease	4155 (58.9)	4190 (59.5)	4213 (59.6)
History of PCI	5852 (83.0)	5879 (83.5)	2837 (82.6)
History of more than 1 prior MI	1143 (16.2)	1168 (16.6)	1188 (16.8)
Peripheral artery disease	371 (5.3)	368 (5.2)	404 (5.7)
Creatinine clearance <60 mL/min	428 (6.1)	403 (5.7)	423 (6.0)
Qualifying Event			
Years from MI – median (IQR)	1.7 (1 – 2)	1.7 (1 – 2)	1.7 (1 – 2)
STEMI	3763 (53.4)	3757 (53.4)	3809 (54.0)
NSTEMI	2898 (41.1)	2842 (40.4)	2743 (40.3)
MI type unknown	382 (5.4)	436 (6.2)	405 (5.7)
Medications at enrollment			

Aspirin (any dose)	6846 (97.1)	6847 (97.2)	6865 (97.1)
Statin	6532 (92.5)	6491 (92.1)	6582 (93.1)
Beta-blocker	5809 (82.4)	5787 (82.1)	5870 (83.1)
ACEI or ARB	5709 (81.0)	5637 (80.0)	5703 (80.7)
Geographic region/country			
Asia and Australia	793 (11.2%)	788 (11.2%)	788 (11.2%)
Europe and South Africa	4128 (58.6%)	4146 (58.9%)	4154 (58.8%)
North America	1307 (18.5%)	1297 (18.4%)	1303 (18.4%)
South America	822 (11.7%)	814 (11.6%)	822 (11.6%)
USA	866 (12.3%)	863 (12.2%)	872 (12.3%)

*Self-reported

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

[00146]   The mean (SD) age was 65 (8) years, nearly one quarter of patients were female, and close to one third had diabetes mellitus. Patients were predominantly Caucasian (87%), and 99.8% of patients received prior aspirin therapy. The safety population was predominantly Caucasian (86.7%). 12.1% of patients enrolled in PEGASUS were Hispanic or Latino, and Black (1.7%), Asians (10.7%), and other (0.9%) races also participated in the study. The median time from the qualifying myocardial infarction to randomization was 1.7 years (IQR 1.0-2.0) with 54% of the qualifying events being ST-segment-elevation myocardial infarction. The majority of the patients had a history of percutaneous coronary intervention (PCI) (83%) and multivessel coronary artery disease (59%). In regards to additional pre-defined atherothrombotic risk factors, 54.4% of the patients were aged ≥65 years, 28.5% had diabetes mellitus requiring medication, 16.5% had a history of a second prior presumed spontaneous MI (≥1 year prior to randomization), 59.3% had a

history of angiographic evidence of multivessel CAD, and 5.9% had chronic non-end

stage renal dysfunction (as reported by the investigator). 47.8% of the patients had

more than one risk factor for atherothrombosis, and 14.6% had three or more risk

factors. The randomized treatment groups were balanced with regard to these pre-

defined atherothrombotic risk factors.

[00147]   Patients were well treated according to current guidelines (Table 7)

(*see* Fihn SD, Gardin JM, Abrams J, et al. 2012

"ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and

management of patients with stable ischemic heart disease: a report of the American

College of Cardiology Foundation/American Heart Association task force on practice

guidelines, and the American College of Physicians, American Association for

Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for

Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons."

Circulation 2012;126:e354-471, and Task Force Members, Montalescot G, Sechtem

U, et al. "2013 ESC guidelines on the management of stable coronary artery disease:

the Task Force on the management of stable coronary artery disease of the

European Society of Cardiology." *Eur Heart J* 2013;34:2949-3003).

[00148]   Nearly all patients (95.7%) received aspirin at a dose between 75 mg

and 100 mg. Few patients (2.7%) took more than 100 mg of aspirin, and very few

patients (<0.1%, N = 97) took more or less than the daily maintenance dose of 75 to

150 mg of aspirin mandated in the PEGASUS-TIMI 54 study protocol. As expected,

due to prescription practices in the United States and elsewhere, doses of 75 to 81

mg and 100 mg of aspirin dominated (48.9% and 48.3%, respectively). Maintenance

doses of aspirin above 100 mg were shown to reduce the effectiveness of ticagrelor

for patients with acute coronary syndrome in the PLATO trial.

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[00149]   20,942 patients (99.0%) received at least one dose of study drug. The

proportion of patients in each arm who prematurely discontinued treatment over the

duration of the trial was 32.0%, 28.7%, and 21.4% in ticagrelor 90 mg, ticagrelor 60

mg, and placebo arms, respectively (P<0.001 for each dose versus placebo). Of

patients on study drug, compliance (defined as taking ≥80% of pills administered

while on treatment) was 79%, 80%, and 82% in ticagrelor 90 mg, ticagrelor 60 mg,

and placebo arms, respectively.

[00150]   The median duration of follow up was 33 months (IQR 28 – 37)

resulting in 55,266 patient years of follow-up. Ascertainment of the primary endpoint

was complete for 98.8% of potential patient years of follow up. Details of patient

disposition are described in Figure 1.Both doses of ticagrelor in the experimental arm

significantly reduced the primary endpoint of cardiovascular death, myocardial

infarction, or stroke compared to placebo with Kaplan-Meier rates at 3 years of 7.85%

in the ticagrelor 90 mg arm, 7.77% in the ticagrelor 60 mg arm, and 9.04% in the

placebo arm (HR for ticagrelor 90 mg vs placebo 0.85, 95% CI 0.75 – 0.96,

P=0.0080; HR for ticagrelor 60 mg vs placebo 0.84, 95% CI 0.74 – 0.95, P=0.0043)

(Figure 2A, Figure 3). Each of the primary endpoint components of cardiovascular

death, myocardial infarction, and stroke contributed to the reduction in the primary

composite endpoint. Based on intention-to-treat data (i.e., regardless of study drug

discontinuation), if 10,000 patients were started on treatment with ticagrelor versus

placebo, 40 and 42 ischemic events would be prevented with ticagrelor 90 mg bid

and ticagrelor 60 mg bid, respectively. The effect of ticagrelor on each of the

components of the primary endpoint was highly consistent (Figure 2B). Similarly,

there was a numerical reduction in the rate of the composite of coronary heart

disease death, myocardial infarction, or stroke for both ticagrelor doses compared

with placebo (18% RRR, HR 0.82 (95% CI 0.72, 0.93), p=0.0016 for 90 mg bid and

17% RRR, HR 0.83 (95% CI 0.73, 0.94), p=0.0033 for ticagrelor 60 mg bid). In

addition, there was a numerical reduction in the rate of coronary stent thrombosis for

both ticagrelor doses compared with placebo (36% RRR, HR 0.64 (95% CI 0.41,

1.00), p=0.0499 for ticagrelor 90 mg bid, and 18% RRR, HR 0.82 (95% CI 0.54,

1.23), p=0.3328 for ticagrelor 60 mg bid). Analysis of time to first stent thrombosis

for each treatment group is shown in Table 7. There was a trend with ticagrelor

toward a numerical reduction in the rate of cardiovascular death alone, but the effect

was not statistically significant. The difference in the rate of death from any cause

was not statistically significant for either dose of ticagrelor compared to placebo

(Table 8). The frequency of death (including bleeding) was 4.8% (n=333), 4.2%

(n=290), and 4.7% (n=329) for the ticagrelor 90 mg bid, ticagrelor 60 mg bid, and

placebo arms, respectively. When bleeding events were excluded, the frequency of

death was 4.4% (n=304), 3.9% (n=274), and 4.4% (n=309) for ticagrelor 90 mg bid,

ticagrelor 60 mg bid, and placebo arms, respectively. Of note, PEGASUS was

powered to detect changes in the primary composite endpoint of CV death, MI or

stroke only. The study was not powered to detect changes in cardiovascular death

or total mortality. P-values recited in Table 8 except for the cardiovascular death

endpoint, all-cause mortality endpoint, and primary composite endpoint of

cardiovascular death, myocardial infarction, or stroke were not controlled for

multiplicity and should be considered as nominal. Other prespecified efficacy

endpoints including hospitalization for unstable angina and transient ischemic attack

were infrequent in all arms (≤1% at 3 years) and are shown in Tables 9 and 10.

There were no significant differences in the rates of urgent revascularization,

hospitalization for unstable angina, or transient ischemic attack with either ticagrelor

dose compared to placebo (Table 9).

Table 7 . Analysis of Time to First Stent Thrombosis (Full Analysis Set)

Characteristic	Ticagrelor 90 mg bd N = 7050				Ticagrelor 60 mg bd N = 7045				Placebo N= 7067	
	Patients (%) with events	KM %	HR (95 % CI)	p-value	Patients (%) with events	KM %	HR (95 % CI)	p-value	Patients (%) with events	KM %
Patients with a history of coronary stent implantation or receiving a stent during the study	5651				5695				5661	
Stent thrombosis	32 (0.6%)	0.6%	0.64 (0.41 , 1.00)	0.0499	41 (0.7%)	0.8%	0.82 (0.54 , 1.23)	0.3328	50 (0.9%)	0.9%

Hazard ratios and p-values are calculated separately for each ticagrelor dose vs placebo from Cox proportional hazards model with treatment group as the only explanatory variable.
Kaplan-Meier percentage calculated at 36 months.
For patients with stent thrombosis attributed to a stent implanted before randomization, time is calculated from the date of randomization.
For patients with stent thrombosis attributed to a stent implanted after randomization, time is calculated from the date of stent implantation.
If a patient had more than 1 stent and the stent thrombosis could not be attributed to a specific stent, then it is assumed to have occurred in the most recent stent.
bd Twice daily; CI Confidence interval; HR Hazard ratio; KM Kaplan-Meier; N Number of patients in treatment group

Table 8. Efficacy Endpoints

Endpoint	Ticagrelor 90 mg bid (N=7050) n (%)	Ticagrelor 60 mg bid (N=7045) n (%)	Placebo (N=7067) n (%)	Ticagrelor 90 mg bid vs Placebo HR (95% CI) p-value	Ticagrelor 60 mg bid vs Placebo HR (95% CI) p-value
Cardiovascular Death, Myocardial infarction, or Stroke	493 (7.85)	487 (7.77)	578 (9.04)	0.85 (0.75 – 0.96) P=0.0080	0.84 (0.74 – 0.95) P=0.0043
Coronary Heart Disease Death, Myocardial infarction, or Stroke	438 (6.99)	445 (7.09)	535 (8.33)	0.82 (0.72 – 0.93) P=0.0016	0.83 (0.73 – 0.94) P=0.0033
Cardiovascular Death or Myocardial infarction	424 (6.79)	422 (6.77)	497 (7.81)	0.85 (0.75 – 0.97) P=0.014	0.85 (0.74 – 0.96) P=0.012
Coronary Heart Disease Death or Myocardial infarction	350 (5.59)	360 (5.57)	429 (6.68)	0.81 (0.71 – 0.94) P=0.0041	0.84 (0.73 – 0.96) P=0.013
Cardiovascular Death	182 (2.94)	174 (2.86)	210 (3.39)	0.87 (0.71 – 1.06) P=0.15	0.83 (0.68 – 1.01) P=0.067
Coronary Heart Disease Death	97 (1.53)	106 (1.72)	132 (2.08)	0.73 (0.56 – 0.95) P=0.021	0.80 (0.62 – 1.04) P=0.093
Myocardial infarction	275 (4.40)	285 (4.53)	338 (5.25)	0.81 (0.69 – 0.95) P=0.010	0.84 (0.72 – 0.98) P=0.031
All Stroke	100 (1.61)	91 (1.47)	122 (1.94)	0.82 (0.63 – 1.07) P=0.14	0.75 (0.57 – 0.98) P=0.034
Ischemic Stroke	88 (1.41)	78 (1.28)	103 (1.65)	0.85 (0.64 – 1.14) P=0.28	0.76 (0.56 – 1.02) P=0.063
Death from any cause	326 (5.15)	289 (4.69)	326 (5.16)	1.00 (0.86-1.16) P=0.99	0.89 (0.76 – 1.04) P=0.14

Rates are presented as 3-year Kaplan-Meier estimates

Table 9. Other Efficacy Endpoints

Endpoint	Ticagrelor 90 mg bid (N=7050)	Ticagrelor 60 mg bid (N=7045)	Placebo (N=7067)	Ticagrelor 90 mg bid vs Placebo	Ticagrelor 60 mg bid vs Placebo
	n (%)	n (%)	n (%)	HR (95% CI) p-value	HR (95% CI) p-value
Hospitalization for Unstable Angina	33 (0.50)	39 (0.61)	37 (0.57)	0.89 (0.56 – 1.43) 0.63	1.05 (0.67 – 1.65) 0.82
Urgent Coronary Revascularization for Unstable Angina	74 (1.16)	62 (0.95)	76 (1.13)	0.97 (0.71 – 1.34) 0.87	0.82 (0.58 – 1.14) 0.24
Transient Ischemic Attack	17 (0.27)	17 (0.27)	17 (0.29)	1.00 (0.51 – 1.96) P=1.00	1.00 (0.51 – 1.96) P=1.00

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Table 10. Incidences of the Primary Composite Endpoint, Primary Composite Endpoint Components, and Secondary Endpoints in the PEGASUS-TIMI 54 Trial

	Ticagrelor 60 mg bid (N=7045)		Placebo (N=7067)		HR (95% CI)	p-value
	n (patients with event)	KM%	n (patients with event)	KM%		
Time to first CV death, MI, or stroke*	487	7.8	578	9.0	0.84 (0.74, 0.95)	0.0043
CV Death[a]	116		128			
Myocardial infarction[a]	283		336			
Stroke[a]	88		114			
Subjects with events at any time						
CV Death[b]**	174	2.9	210	3.4	0.83 (0.68, 1.01)	
Myocardial infarction[b]	285	4.5	338	5.2	0.84 (0.72, 0.98)	
Stroke[b]	91	1.5	122	1.9	0.75 (0.57, 0.98)	
All-cause mortality**	289	4.7	326	5.2	0.89 (0.76, 1.04)	

60 mg BID

CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; KM = Kaplan-Meier percentage calculated at 36 months; MI = Myocardial infarction; N = Number of patients; *Primary endpoint; **Secondary endpoints.
a For the components, the first-occurring component of the composite is included.
b The number of first events for the components CV Death, MI and Stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

[00151] There was no apparent heterogeneity in the efficacy of ticagrelor at either dose on the rate of the primary composite endpoint across major subgroups including age, sex, index myocardial infarction type, time from qualifying myocardial infarction, diabetes, aspirin dose, history of percutaneous intervention, and region of randomization (Figure 4). Additional subgroups are shown in Figures 5, 6, and 7, and efficacy data for ticagrelor stratified by aspirin dose is shown in Table 11.

Table 11. Efficacy Endpoint of Cardiovascular Death, Myocardial Infarction, or Stroke, Stratified by Post-Randomization Aspirin Dose

Aspirin Dose Post-Randomization		Ticagrelor 90 mg bid N = 7050 n (%)	Ticagrelor 60 mg bid N = 7045 n (%)	Placebo N=7067 n (%)
≤ 100 mg	n	6851	6850	6881
	Patients with events	474 (6.9%)	466 (6.8%)	555 (8.1%)
	KM %	7.89%	7.6%	8.9%
	HR (95% CI)	0.85 (0.75, 0.96)	0.84 (0.74, 0.95)	
	p-value	0.0110	0.0046	
> 100 mg	n	198	191	185
	Patients with events	19 (9.6%)	21 (11.0%)	23 (12.4%)
	KM %	9.8%	12.1%	13.7%
	HR (95% CI)	0.76 (0.42, 1.40)	0.89 (0.49, 1.60)	
	p-value	0.3849	0.6889	

[00152] The absolute risk reductions for the treatment arms (ticagrelor plus aspirin) vs. aspirin alone at three years were 1.27% in the ticagrelor 60 mg bid arm and 1.19% in the 90 mg bid arm. The relative risk reduction (RRR) for the composite endpoint of cardiovascular disease, myocardial infarction, or stroke from 1 to 360 days (17% RRR) and from 361 days and onwards (16% RRR) were similar for the ticagrelor 60 mg bid arm compared to placebo. In addition, the hazard ratio for the composite endpoint of cardiovascular disease, myocardial infarction, or stroke from 1 to 360 days (0.83) and from 361 days and onwards (0.84) were similar for the ticagrelor 60 mg bid arm relative

to the placebo arm (Table 12). The superior treatment effect of ticagrelor was consistent throughout the study as evidenced by the Kaplan-Meier plot of cardiovascular death, myocardial infarction, and stroke through 3 years (Figure 2A, Figure 3), where the curves for the ticagrelor arms started to separate from the curve for the placebo arm following randomization and continued to separate throughout the study.

[00153] Patients in the ticagrelor 60 mg bid arm received study drug for up to 48 months (Figure 8). For the ticagrelor 90 mg bid, ticagrelor 60 mg bid, and placebo arms, mean total duration of exposure to study drug (first dose to last dose) was 23.9, 25.3, and 27.3 months, respectively; median total duration of exposure was 28.3, 29.4, and 30.4 months, respectively. The higher proportion of patients prematurely permanently discontinued from study drug in both the ticagrelor arms relative to the placebo arm resulted in lower mean and median total duration of exposure in the ticagrelor arms. The superior treatment effect of ticagrelor over time suggests that it may be appropriate to continue treatment with ticagrelor as long as the patient remains at high risk of an atherothrombotic event.

[00154] The primary safety endpoint of TIMI major bleeding was higher with both doses of ticagrelor compared to placebo, with rates at 3 years of 2.60% in the ticagrelor 90 mg bid arm, 2.30% in the ticagrelor 60 mg bid arm, and 1.06% in the placebo arm (HR for ticagrelor 90 BID vs placebo 2.69, 95% CI 1.96 – 3.70, p<0.001; HR for ticagrelor 60 BID vs placebo 2.32, 95% CI 1.68 – 3.21, p<0.001, Table 14) with no apparent heterogeneity among major subgroups (Figures 9-11).

Table 12. Landmark analysis of primary clinical endpoint (full analysis set)

Characteristic	Time Interval		Ticagrelor 90mg bd	Ticagrelor 60mg bd	Placebo
Composite of CV Death/MI/Stroke	1-360 days	n	7050	7045	7067
		Patients with events	198 (2.8%)	189 (2.7%)	227 (3.2%)
		KM% at 12 months	2.8%	2.7%	3.2%
		Hazard Ratio (95% CI)	0.87 (0.72, 1.06)	0.83 (0.69, 1.01)	
	361 days or more	n[a]	6768	6783	6760
		Patients with events	295 (4.4%)	298 (4.4%)	351 (5.2%)
		KM% at 24 months[b]	2.4%	2.7%	3.0%
		KM% at 36 months[b]	5.2%	5.2%	6.0%
		Hazard Ratio (95% CI)	0.84 (0.72, 0.98)	0.84 (0.72, 0.98)	

Source: CSR Table 11.2.4.5

[a] Only patients who are event-free in the first period (days 1-360) are included in the second period (day 361 and onwards).

[b] Cumulative percentage from day 1 to 360 days after randomisation, and from day 361 to day 720 and 1080 respectively.

Hazard ratios are calculated separately for each ticagrelor dose vs placebo from Cox proportional hazards model with treatment group as the only explanatory variable

CI Confidence interval; HR Hazard ratio; KM Kaplan-Meier; n Number of patients in category or analysis; N Number of patients in treatment group

Table 13. Cumulative Exposure Over Time (Safety Analysis Set)

Time on Study Drug[a]	Number(%) of patients		
	Ticagrelor 90 mg bd (N=6988)	Ticagrelor 60 mg bd (N=6958)	Placebo (N=6996)
0 days	6988 (100%)	6958 (100%)	6996 (100%)
1 day	6988 (100%)	6958 (100%)	6996 (100%)
30 days	6434 (92.1%)	6527 (93.8%)	6799 (97.2%)
4 months	5899 (84.4%)	6110 (87.8%)	6505 (93.0%)
8 months	5476 (78.4%)	5705 (82.0%)	6204 (88.7%)
12 months	5203 (74.5%)	5481 (78.8%)	5992 (85.6%)
18 months	4842 (69.3%)	5126 (73.7%)	5643 (80.7%)
24 months	4291 (61.4%)	4505 (64.7%)	4996 (71.4%)
30 months	3142 (45.0%)	3328 (47.8%)	3653 (52.2%)
36 months	1445 (20.7%)	1620 (23.3%)	1716 (24.5%)
42 months	216 (3.1%)	222 (3.2%)	270 (3.9%)

Source: CSR Table 11.3.1.2.2
[a]   Number of patients on treatment at the start of the interval.
Percentages are based on the total numbers of patients in the treatment group (N).
This table is based on total duration from first dose date to last dose date.
bd Twice daily

[00155]   The rate of fatal bleeding or non-fatal intracranial hemorrhage was not

notably different, i.e., had very small differences, between treatment arms (Table 14).

The number of fatal bleeding events was low, corresponding to Kaplan-Meier rates at

36 months of 0.1% (n = 6), 0.3% (n = 11), and 0.3% (n = 12) for the ticagrelor 90 mg bid,

ticagrelor 60 mg bid, and placebo arms, respectively. Similarly, there were few

incidences of intracranial hemorrhage, corresponding to Kaplan-Meier rates at 36

months of 0.6% (n = 29), 0.6% (n = 28), and 0.5% (n = 23) for the ticagrelor 90 mg bid,

ticagrelor 60 mg bid, and placebo arms, respectively. The TIMI minor bleeding and

bleeding leading to transfusion was similarly increased with ticagrelor versus placebo

(Table 3). The rates of bleeding leading to transfusion were 2.4% for ticagrelor 90 mg,

2.1% for ticagrelor 60 mg and 0.7% for placebo (P<0.001 for each dose versus placebo).

[00156]   "Other TIMI major bleeding," while important due to their potential to cause

morbidity and increased care requirements, are manageable clinically and do not cause

irreversible harm.

[00157]   Premature treatment discontinuation for bleeding was higher with both

doses of ticagrelor compared to placebo at 7.8% for ticagrelor 90 mg bid, 6.2% for

ticagrelor 60% bid, and 1.5% for placebo (Table 14). Figure 12 shows a Kaplan-Meier

estimate of time to premature permanent discontinuation of study drug due to bleeding

based on the safety analysis set. Overall outcome of bleeding events in the PEGASUS-

TIMI 54 trial are shown in Table 15.

[00158]   However, the ticagrelor arms showed a trend toward reduced fatal

bleeding rate compared to the placebo arm, with 6 and 11 fatal bleeding incidents in the

90 mg and 60 mg ticagrelor arms, respectively, versus 12 fatal bleeding incidents in the

placebo arm. In particular, the ratio of fatal bleeding events over TIMI major bleeding events in each ticagrelor experimental arm (6/127, i.e., about 1/21, for 90 mg arm and 11/115, i..e, about 1/10, for 60 mg arm) is much less than that in the placebo comparator arm (12/54, i.e., 1/4.5). Overall, absolute bleeding rates are in line with what has been observed in other long-term dual antiplatelet therapy trials.

[00159]   Dyspnea was more frequent with both doses of ticagrelor, with 3-year event rates of 18.9% in patients in the ticagrelor 90 mg bid arm, 15.8% in patients in the ticagrelor 60 mg bid arm, and 6.4% in patients in the placebo arm (P<0.001 for each dose versus placebo, Table 3). The median duration of resolved dyspnea adverse events was 22, 31, and 49 days in the ticagrelor 90 mg bid arm, ticagrelor 60 mg bid arm, and placebo arm, respectively. The frequency of dyspnea and the median duration of resolved dyspnea adverse events were numerically lower for patients in the ticagrelor 60 mg bid arm relative to the ticagrelor 90 mg bid arm. The majority of dyspneic episodes with either dose of ticagrelor were characterized as either mild (57%) or moderate (38%) in severity, and dyspnea as a serious adverse event in patients on ticagrelor was infrequent (3-year rate 0.3%). Regardless of treatment group, the majority of patients with dyspnea adverse events had only one episode. The rates of dyspnea leading to study drug discontinuation were 6.5% with ticagrelor 90 mg bid, 4.3% with ticagrelor 60 mg bid, and 0.7% with placebo (P<0.001 for each dose versus placebo, Table 3). In a substudy of PLATO in which 199 subjects underwent pulmonary function testing irrespective of whether they reported dyspnea, there was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

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Table 14. Safety and Tolerability Endpoints

End Point	Ticagrelor 90 mg bid (N=6988) n (%)	Ticagrelor 60 mg bid (N=6958) n (%)	Placebo (N=6996) n (%)	Ticagrelor 90 mg bid vs Placebo HR (95% CI) p-value	Ticagrelor 60 mg bid vs Placebo HR (95% CI) p-value
Bleeding					
TIMI Major	127 (2.60)	115 (2.30)	54 (1.06)	2.69 (1.96 – 3.70) P<0.001	2.32 (1.68 – 3.21) P<0.001
TIMI Minor	66 (1.31)	55 (1.18)	18 (0.36)	4.15 (2.47 – 7.00) P<0.001	3.31 (1.94 – 5.63) P<0.001
Bleeding requiring transfusion	122 (2.40)	105 (2.10)	37 (0.70)	3.75 (2.59 – 5.42) P<0.001	3.08 (2.12 – 4.48) P<0.002
Leading to study drug discontinuation	454 (7.80)	355 (6.2)	88 (1.5)	5.67 (4.51 – 7.12) P<0.001	4.31 (3.41 – 5.45) P<0.001
Fatal bleeding or non-fatal intracranial hemorrhage	33 (0.71)	32 (0.63)	30 (0.60)	1.20 (0.73 – 1.97) p=0.47	1.22 (0.74 – 2.01) p=0.43
Intracranial Hemorrhage	29 (0.56)	28 (0.61)	23 (0.47)	1.44 (0.83 – 2.49) P=0.19	1.33 (0.77 – 2.31) P=0.31
Fatal Bleeding	6 (0.11)	11 (0.25)	12 (0.26)	0.58 (0.22 – 1.54) P=0.27	1.00 (0.44 – 2.27) P=1.00
Other Adverse Events					
Dyspnea					
AE	1204 (17.22)	986 (14.17)	382 (5.46)	3.55 (3.17 – 3.99) P<0.001	2.82 (2.50 – 3.17) P<0.001
Leading to study drug discontinuation	430 (6.2)	296 (4.3)	51 (0.7)	8.89 (6.65 – 11.88) P<0.001	6.35 (4.84 – 8.12) P<0.001
SAE	22 (0.3)	22 (0.3)	8 (0.1)	3.02 (1.34 – 6.78) p=0.0075	2.91 (1.30 – 6.54) p=0.0097
Renal adverse event	166 (2.4)	173 (2.5)	161 (2.3)		
Bradyarrhythmia adverse event	105 (1.5)	121 (1.7)	105 (1.5)		
Gout adverse event	99 (1.4)	97 (1.4)	70 (1.0)		

Rates are presented as 3-year Kaplan-Meier estimates

Table 15. Bleeding Events

	Ticagrelor 60 mg bid (N=6958)		Placebo (N=6996)	
	n (%) patients with event	Events / 100 pt yrs	n (%) patients with event	Events / 100 pt yrs
TIMI Major	115 (1.7)	0.78	54 (0.8)	0.34
Fatal	11 (0.2)	0.08	12 (0.2)	0.08
Intracranial hemorrhage	28 (0.4)	0.19	23 (0.3)	0.14
TIMI Major or Minor	168 (2.4)	1.15	72 (1.0)	0.45

[00160]   There were no notable differences in the rates of renal, hepatic,

bradyarrythmic, or gout adverse events, and no liver or kidney related issues were

identified during the PEGASUS trial (Table 14). Frequencies of pre-defined

bradyarrhythmic AEs were similar across treatment groups. PLATO and PEGASUS

excluded patients at increased risk of bradycardic events (e.g., patients who have sick

sinus syndrome, 2nd or 3rd degree AV block, or bradycardic-related syncope and not

protected with a pacemaker). An assessment of adverse events possibly related to

bradyarrhythmia showed that dizziness, hypotension and syncope were more frequently

reported in the ticagrelor 90 mg bid and ticagrelor 60 mg bid arms compared with the

placebo arms. In the PEGASUS trial, syncope was reported by 1.2% and 0.9% of

patients on 60 mg ticagrelor bid and placebo, respectively.

[00161]   In addition, a reversible increase in serum uric acid levels consistent with

previous findings was observed during the PEGASUS trial. In the PLATO trial, serum

uric acid levels increased approximately 0.6 mg/dL from baseline for patients

administered ticagrelor 90 mg bid compared to an approximately 0.2 mg/dL increase

from baseline for patients administered clopidogrel. The difference in serum uric acid

levels observed during the PLATO trial disappeared within 30 days of discontinuing

treatment. Moreover, reports of gout did not differ between treatment groups in PLATO

(0.6% in each group). During the PEGASUS trial, it was observed that serum uric acid

levels increased approximately 0.2 mg/dL from baseline for patients administered

ticagrelor 60 mg bid. No elevation in serum uric acid levels was observed in the

placebo arm. Gout occurred more commonly in patients in the experimental arm (1.5%)

than in the placebo arm (1.1%), and there were no reports of urate nephropathy.

Hypotension occurred more commonly in patients in the ticagrelor 60 mg bid (0.66

events/100 patient (pt) years) and ticagrelor 90 mg bid (0.66 events/100 pt years) arms

relative to the placebo arm (0.45 events/100 pt years).

[00162]   In the PEGASUS trial, mean serum uric acid concentrations decreased

after treatment was stopped. Furthermore, in the PEGASUS-TIMI 54 trial, serum

creatinine concentration increased by >50% in approximately 4% of patients

administered 60 mg ticareglor bid, which was comparable to the increase observed in

patients in the placebo arm. There was no evidence that the increase in serum

creatinine in the ticagrelor treatment groups is related to renal impairment. In addition,

the frequency of renal related adverse events was similar for ticagrelor and aspirin

alone regardless of age and baseline renal function. Rates of adverse events and

serious adverse events are listed in Table 16. Rates of adverse events that occurred in

the PEGASUS trial at rates of 3% or more are shown in Table 17.

Table 16. Adverse Events

Adverse Event	Ticagrelor 90 mg bid (N=6988)	Ticagrelor 60 mg bid (N=6958)	Placebo (N=6996)
	n (%)	n (%)	n (%)
Any adverse event	5327 (76.2)	5268 (75.7)	4837 (69.1)
Leading to discontinuation of study drug	1306 (18.7)	1117 (16.1)	596 (8.5)
Leading to death	161 (2.3)	149 (2.1)	203 (2.9)
Any serious adverse event	1514 (21.7)	1499 (21.5)	1511 (21.6)
Leading to discontinuation of study drug	256 (3.7)	255 (3.7)	211 (3.0)
Non-Cardiovascular death	142 (2.0)	113 (1.6)	111 (1.6)
Death	326 (4.6)	289 (4.1)	326 (4.6)

Nb, mortality data analyzed in the intention-to-treat population.

Table 17. Non-hemorrhagic Adverse Reactions Reported in >3.0% of Patients

	Ticagrelor 60 mg bid (N=6958)	Placebo (N=6996)
Dyspnea	14.2	5.5
Dizziness	4.5	4.1
Diarrhea	3.3	2.5

[00163]   Patients who have had a myocardial infarction remain at heightened risk of ischemic events over the long-term. Results of the PEGASUS clinical trial showed that the addition of the $P2Y_{12}$ receptor antagonist ticagrelor to low-dose aspirin in such patients reduces the risk of cardiovascular death, myocardial infarction or stroke significantly. The benefit of ticagrelor was consistent, among major clinical subgroups, and by region, consistent among the individual fatal and non-fatal components of the primary endpoint and continued to accrue over time.

[00164]   The results of the PEGASUS clinical trial were used to develop an exposure response model for the ticagrelor 60 mg bid, ticagrelor 90 mg bid, and placebo arms. The influence of risk factors (RFs) associated with the composite

endpoint of cardiovascular death, myocardial infarction, and stroke and the safety

endpoint of TIMI major bleeding were evaluated using an RF model developed for the

placebo data. The RF model was then used on all treatment groups to evaluate the

hazard associated with each risk factor in patients treated with ticagrelor 60 mg bid or

ticagrelor 90 mg bid. Risk factors included in the analysis were age, serum creatinine,

body mass index, diabetes mellitus, hypertension, peripheral artery disease, history of

more than one prior MI, qualifying STEMI event, history of unstable angina pectoris,

dose of aspirin, race, gender, smoker status, ethnicity, coronary artery bypass grafting

(CABG) during study, PCI during study, previous spontaneous bleeding requiring

hospitalization, and left ventricular disease.

[00165]   In addition, potential dose-exposure-response relationships between

plasma exposure of ticagrelor and the composite endpoint of cardiovascular death,

myocardial infarction, and stroke and the safety endpoint of TIMI major bleeding, as well

as potential covariate effects on the dose-exposure-response relationships, were

investigated using exposure response modelling. Figure 13 shows the predicted

probability of a cardiovascular death, myocardial infarction, or stroke event and the

predicted probability of a TIMI major bleeding event within three years using the final

dose-exposure-response models, stratified by treatment arm. The average predicted

probability of event in the placebo, ticagrelor 60 mg bid, ticagrelor 90 mg bid arms, were:

8.47%, 6.82% and 6.74% for cardiovascular death, myocardial infarction, or stroke

events and 1.02%, 2.46% and 2.65% for TIMI major bleeding events. Figure 14 depicts

the composite endpoint of cardiovascular death, myocardial infarction, and stroke

events/no events versus exposure using the final exposure-response analysis data set,

and Figure 15 depicts TIMI major bleeding events/no events versus exposure using the final exposure-response analysis data set.

[00166]   The cardiovascular death, myocardial infarction, or stroke events on treatment data generated in the PEGASUS-TIMI 54 clinical trial was also described by a parametric time-to-event model.. Figure 16 shows the distribution of cardiovascular death, myocardial infarction, and stroke event times, stratified by dose. The baseline hazard slightly decreased with time described by a Weibull distribution. A proportional hazards model was assumed when describing the influence of RFs and drug exposure.

[00167]   The exposure response model developed from the PEGASUS study data demonstrated a similar and consistent benefit of ticagrelor across subgroups, with eight risk factors identified to increase the risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke in the placebo arm: age (hazard ratio (HR) of 1.03 per year above 65 years); serum creatinine (HR of 1.01 per μmol/L above 87 μmol/L); history of unstable angina pectoris (HR of 1.41); diabetes mellitus (HR of 1.58); peripheral artery disease (HR of 1.51); more than one previous MI (HR of 2.04); Hispanic/Latino ethnicity (HR of 1.33); and current smoker (HR of 1.43). No subgroup, apart from Japanese ethnicity, was statistically identified to be more or less sensitive to ticagrelor exposure after accounting for risk factors.

[00168]   Based on the results of the exposure response model, there was a lower risk of event in Japanese patients compared to the overall population (e.g. a HR of 0.29 for a Japanese patient with a median exposure in the 60 mg group (606 nM) compared to placebo and a HR of 0.83 for a non-Japanese patient with median exposure in the 60 mg group (606 nM) compared to placebo). The observed lower risk of event in

Japanese patients may be due to a lower underlying risk, Japanese patients being more

sensitive to ticagrelor exposure or a combination of both. However, there was limited

data (20 events in 901 patients) in the Japanese population.

[00169]   The estimated exposure-response relationship was flat, indicating close to

maximum response. The average concentration of ticagrelor at steady state ($c_{ss,av}$)

exposure was a slightly stronger predictor of event over the studied exposure range

compared to a pooled general ticagrelor treatment effect for 60 and 90 mg doses.

[00170]   The TIMI major bleeding on treatment data in the PEGASUS-TIMI 54

clinical trial was further described by a parametric time-to-event model. Figure 17

shows the distribution of TIMI major bleeding event times, stratified by dose. The

baseline hazard was constant over time described by an Exponential distribution. A

proportional hazards model was assumed when describing the influence of risk factors

and drug exposure. Only two risk factors were identified for TIMI major bleeding: age

(increased risk with increasing age with a HR of 1.04 per year above 65 years) and

coronary artery bypass grafting (CABG) (temporary effect up to 7 days after procedure

with a HR of 575).

[00171]   Patients treated with ticagrelor 60 mg bid and ticagrelor 90 mg bid in the

PEGASUS trial exhibited a higher incidence of TIMI major bleeding compared to

placebo patients, consistent with the safety profile of other commercially available $P2Y_{12}$

receptor antagonists. The risk of event was described to increase with increasing drug

exposure (ticagrelor $c_{ss,av}$) by a log-linear exposure-response relationship. The

estimated relative risk increase versus placebo after 36 months was 142% and 160%

for ticagrelor 60 and 90 mg bid, respectively, and the increased risk of TIMI major

bleeding with ticagrelor exposure was similar and consistent across subgroups. Figure 18 shows Kaplan-Meier estimates of patients without TIMI Major Bleeding events vs. time, stratified by dose. No subgroup was statistically identified to be more or less sensitive to ticagrelor exposure after accounting for risk factors.

[00172] Age was the only risk factor that was identified in both the final CV death/myocardial infarction/stroke model as well as in the final TIMI major bleeding model. However, the average risk of CV death, myocardial infarction, or stroke was reduced for patients in the ticagrelor 60 mg bid and ticagrelor 90 mg bid arms relative to the placebo arm for all compared age groups (Table 18). The absolute risk reduction for the composite endpoint of cardiovascular death, myocardial infarction, and stroke at three years with ticagrelor 60 mg bid compared to placebo was higher in patients greater than 75 years of age than in patients less than 65 years of age (2.15% vs 1.38%). However, the absolute risk increase for TIMI major bleeding at three years with ticagrelor (60 mg) compared to placebo was also higher in patients greater than 75 years of age than in patients less than 65 years of age (2.38% vs 1.05%).

Table 18. Predicted (observed) average risk at 3 years versus age group for cardiovascular death, myocardial infarction, and stroke events and TIMI major bleeding events

Treatment Group	Age < 65 years		Age 65-75 years		Age > 75 years	
	CV Event*	Bleed**	CV Event*	Bleed**	CV Event*	Bleed**
Placebo	7.30% (8.5%)	0.75% (0.82%)	8.68% (7.83%)	1.13% (1.04%)	12.06% (14.1%)	1.62% (1.7%)
Ticagrelor 60 mg bid	5.92% (6.31%)	1.80% (1.52%)	6.93% (7.06%)	2.75% (2.88%)	9.91% (9.37%)	4.00% (4.25%)
Ticagrelor 90 mg bid	5.80% (5.77%)	1.93% (2.29%)	6.98% (6.8%)	2.94% (2.46%)	9.31% (13.2%)	4.24% (5.76%)

* CV Event: CV death, MI, or stroke
** Bleed: TIMI major bleeding

[00173]   Patients administered ticagrelor 60 mg bid experienced a net clinical

benefit (time from randomization to first occurrence of any event from the composite of

cardiovascular death, myocardial infarction, stroke, or TIMI major bleeding) in the

PEGASUS-TIMI 54 trial, with a relative risk reduction of 5% relative to the placebo arm

(Table 19). In addition, risk reduction for irreversible harm (time from randomization to

first occurrence of any event from the composite of cardiovascular death, myocardial

infarction (MI), stroke, intracranial hemorrhage (ICH), or fatal bleeding) was

demonstrated for patients administered ticagrelor 60 mg bid and patients administered

90 mg bid compared to the placebo arm. A relative risk reduction for irreversible harm

of 12% and 14% was demonstrated for ticagrelor 90 mg bid and ticagrelor 60 mg bid

relative to the placebo arm in the PEGASUS trial. Figure 19 and 20 depict the events

per every 1000 patients treated for 3 years in the PEGASUS trial in the ticagrelor 60 mg

bid and ticagrelor 90 mg bid arms, respectively.

Table 19. Net Clinical Benefit and Irreversible Harm

Characteristic	Ticagrelor 90 mg bid vs. placebo (N = 6988)			Ticagrelor 60 mg bid vs. placebo (N =6958)		
	RRR (%)	HR (95% CI)	P-value	RRR (%)	HR (95% CI)	P-value
Net clinical benefit*	0	1.00 (0.90-1.22)	0.9563	5	0.95 (0.85-1.06)	0.3412
Irreversible harm**	12	0.88 (0.78-0.99)	0.0372	14	0.86 (0.77-0.97)	0.0160

* Net clinical benefit is a composite endpoint of CV death, MI, stroke, or TIMI major bleeding
** Irreversible harm is a composite endpoint of CV death, MI, stroke, ICH, or fatal bleeding

[00174]   Irreversible harm analysis focused on events with the most severe

consequences and excluded "other TIMI major bleeding events." As used herein, "other

TIMI major bleeding events" refers to TIMI major bleeding events other than intracranial

hemorrhage or fatal bleeding. While "other TIMI major bleeding events" are clinically important because they cause morbidity and requirement for care, the events are still manageable clinically and do not cause irreversible harm. Excluding "other TIMI major bleeding events" from the benefit-risk evaluation is consistent with the approach previously used by the Food and Drug Administration for other drugs. Based on intention-to-treat data (i.e., regardless of study drug discontinuation), if 10,000 patients were started on treatment with ticagrelor versus placebo, 41 and 31 TIMI major bleeding events per year would be prevented with ticagrelor 90 mg bid and ticagrelor 60 mg bid, respectively.

[00175] An absolute risk reduction was observed for ticagrelor 90 mg bid and ticagrelor 60 mg bid relative to placebo for: the primary composite endpoint of CV death, MI, or stroke; and the individual endpoints CV death, MI, and stroke (Table 20). Accordingly, when the benefits are weighed against the risks for events of irreversible harm, a favorable benefit-risk balance is demonstrated for both ticagrelor 90 mg bid and ticagrelor 60 mg bid compared to placebo.

Table 20. Absolute Risk Reduction (ARR), Absolute Risk Increase (ARI) and Number Needed to Treat (NNT) or Harm (NNH)

	Ticagrelor 90 mg bid		Ticagrelor 60 mg bid	
Efficacy endpoint	*ARR (%)*	*NNT*	*ARR (%)*	*NNT*
CV death, MI, or stroke	1.19	84	1.27	79
CV death	0.45	222	0.53	189
MI	0.85	118	0.72	139
Stroke	0.33	303	0.47	213
Safety endpoint	*ARI (%)*	*NNH*	*ARI (%)*	*NNH*
TIMI major bleeding	1.54	65	1.24	81
ICH	0.09	1111	0.14	714
Fatal bleeding	-0.15	n/a	-0.01	n/a

[00176]   There has been much uncertainty regarding the duration of dual antiplatelet therapy required in patients with coronary disease. For patients with a history of spontaneous myocardial infarction, observations from other studies have suggested a benefit to a longer duration of more intensive antiplatelet therapy. For example, in landmark analyses from trials of the three principal $P2Y_{12}$ receptor antagonists (clopidogrel, prasugrel, and ticagrelor) in patients presenting with acute coronary syndromes, there appeared to be continued accrual of clinical benefit with $P2Y_{12}$ receptor blockade in the months beyond the immediate period following the acute coronary syndrome.

[00177]   Similarly, in the subgroup of patients with prior myocardial infarction from a trial of a protease-activated platelet receptor antagonist, there appeared to be continued accrual of clinical benefit beyond the first year of therapy. Of note, though, a dedicated trial of long-term prevention with clopidogrel on a background of aspirin in a broad patient population with atherosclerotic disease or risk factors did not show a statistically significant benefit. A subsequent analysis specifically examining the subset of patients with prior myocardial infarction did suggest a reduction in ischemic risk, but this was post hoc and current practice guidelines continue to recommend stopping $P2Y_{12}$ receptor antagonists 1 year after a myocardial infarction.

[00178]   Further contributing to uncertainty about the effectiveness of prolonged dual antiplatelet therapy, a series of randomized trials have not shown a benefit to prolonged dual antiplatelet therapy following percutaneous coronary intervention (PCI) (including after ACS). However, these studies were relatively small and enrolled relatively low risk patients.

[00179]   Patients in PEGASUS-TIMI 54 were further categorized by time from last

P2Y$_{12}$ inhibitor (days: $\leq$30 days, 31-360, >360). In the placebo arm, patients who more

recently stopped P2Y$_{12}$ inhibitor therapy had a greater number of risk factors but still

had a higher risk of MACE after multivariable adjustment [$\leq$30 days, hazard ratio

(HR)$_{adj}$ 1.47, 95% confidence interval (CI) 1.12-1.93, P = 0.005; 30 days - 1 year, HR$_{adj}$

1.28, 95% CI 0.98-1.67, P = 0.073) compared with those who stopped >1 year prior (P-

trend = 0.0097) (Figure 21). The benefit of ticagrelor depended on the time from last

dose, with HRs (95% CI) for ticagrelor (pooled doses) vs. placebo of 0.73 (0.61-0.87),

0.86 (0.71-1.04), and 1.01 (0.80-1.27), respectively, by category (P-trend for interaction

< 0.001) (Figure 22). Figure 23 shows the Kaplan-Meier curve for cardiovascular death,

myocardial infarction, or stroke at 3 years with ticagrelor 90 mg bid twice daily, ticagrelor

60 mg bid twice daily compared with placebo in patients withdrawn from P2Y12 inhibitor

therapy within 30 days, between 30 days and 1 year, and more than 1 year of

randomization. The benefit in those $\leq$ 30 days of stopping was similar regardless of

time from MI (<2 years, HR 0.73, 95% CI 0.60-0.89 vs. $\geq$ 2 years, HR 0.71, 95% CI

0.50-1.00) (Figure 24).

Table 21. Efficacy of ticagrelor (doses pooled) vs. placebo for reduction of CVD, MI, or Stroke by time from P2Y2$_{12}$ inhibitor withdrawal – restricted to N=17,885 patients with no history of MI or PCI within one year of randomization.

	Hazard Ratio	p-value	p-trend across groups
0-30 day	0.73 (95% CI 0.60 – 0.87)	0.0005	0.0009
>30 to 1 year	0.84 (95% CI 0.70 – 1.02)	0.0853	
> 1 year	1.01 (95% CI 0.80 – 1.28)	0.9249	

[00180]   Patients enrolled in the PEGASUS study who began or recommenced

treatment with ticagrelor (60 mg and 90 mg pooled) within 30 days following withdrawal

of dual antiplatelet therapy experienced a 27% reduction in the risk of developing a

subsequent atherothrombotic event (2.2% absolute reduction). Patients enrolled in the

PEGASUS study who began or recommenced treatment with ticagrelor (60 mg and 90

mg pooled) between 31 days and one year following withdrawal of dual antiplatelet

therapy experienced a 14% reduction in the risk of developing a subsequent

atherothrombotic event (1.1% absolute reduction). Patients who began or

recommenced treatment with ticagrelor more than one year after withdrawal of previous

dual antiplatelet therapy event did not experience a reduction in the risk of developing a

subsequent atherothrombotic event. Accordingly, the reduction in the risk of

cardiovascular death, myocardial infarction, or stroke in stable patients with prior

myocardial infarction is greatest in those who have more recently stopped $P2Y_{12}$

therapy, with hazard ratios of 0.75, 0.82, and 1.06 respectively for patients in the 60 mg

ticagrelor bid arm.

[00181]   In the subgroup of patients who began or recommenced treatment with

ticagrelor (60 mg and 90 mg pooled) within 30 days following withdrawal of dual

antiplatelet therapy, the reduction in the risk of cardiovascular death, myocardial

infarction, or stroke was similar regardless of whether the patient's qualifying myocardial

infarction was less than 2 years prior to randomization (HR 0.73, 95% CI 0.60–0.89) or

2 years or more (HR 0.71, 95% CI 0.50–1.00). The benefit of ticagrelor (doses pooled)

was notable both in the first 90 days after randomization, with an HR of 0.54 (95% CI

0.34–0.86), and also beyond 90 days (HR 0.76, 95% CI 0.63–0.92) for both doses

pooled (Figure 25). Similar effect sizes were seen for the individual components of the primary endpoint, with HRs for pooled ticagrelor doses vs. placebo for cardiovascular death of 0.78 (95% CI 0.57–1.07), for myocardial infarction of 0.72 (95% CI 0.58–0.90), and for stroke of 0.64 (95% CI 0.43–0.95).

[00182] Baseline characteristics for patients by timing from last dose of $P2Y_{12}$ inhibitor in the PEGASUS trial were similar between groups for most characteristics (Table 22). However, patients who had discontinued their $P2Y_{12}$ inhibitor within the past 30 days were, temporally closer to their most recent myocardial infarction (median 16 vs. 19 vs. 29 months, P < 0.001). They also more frequently had diabetes, multivessel coronary artery disease (CAD), and prior PCI, and were more likely to be randomized in North America.

[00183] Of note, patients in the placebo arm who had discontinued their $P2Y_{12}$ inhibitor within the past 30 days were at higher risk for cardiovascular death, myocardial infarction, or stroke (9.91% at 3 years) when compared with those who had discontinued 30 days to 1 year prior (8.70%) and those who stopped more than 1 year before randomization (6.91%, P-trend 0.0097). On the other hand, TIMI major bleeding in patients randomized to placebo was similar across time bins from $P2Y_{12}$ inhibitor withdrawal with 3 year rates in those less than 30 days, 30 days to 1 year, and more than 1 year of 0.7, 1.2, and 0.9%, respectively. After adjusting for baseline differences, the hazard ratio for TIMI major bleeding was 0.51 (95% CI 0.20–1.33, P = 0.17) for patients stopping less than 30 days and 0.69 (0.29 - 1.66, P = 0.41) for those stopping 30 days to 1 year both compared with those stopping 0.1 year from randomization (P-trend across groups 0.18).

Table 22. Baseline characteristics, stratified by time from P2Y$_{12}$ inhibitor withdrawal

Variable	≤ 30 Days			>30 Days to 1 Year			> 1 Year		
	90 mg	60 mg	Placebo	90 mg	60 mg	Placebo	90 mg	60 mg	Placebo
N	2397	2383	2401	2142	2178	2181	1706	1697	1676
Demographics									
Age, median(IQR)	65 (58,71)	65 (57,71)	65 (58,71)	65 (59,71)	65 (59,71)	65 (60,71)	66 (59,71)	66 (59,71)	66 (59,71)
Female (%)	22	21	22	22	23	25	25	23	21
Caucasian* (%)	82	82	82	91	90	90	90	92	92
BMI, median (IQR)	28 (25,31)	28 (25,31)	28 (25,31)	28 (25,31)	28 (25,31)	28 (25,31)	28 (25,31)	28 (25,31)	28 (26,31)
Clinical Characteristics									
Hypertension (%)	77	79	78	77	75	75	75	77	77
Hyperlipidemia (%)	81	80	81	77	75	76	76	78	79
Current smoker (%)	16	19	17	17	17	16	18	17	17
Diabetes mellitus (%)	33	34	33	29	31	30	31	31	31
Multivessel CAD (%)	67	69	68	61	60	59	57	57	59
History of PCI (%)	92	93	91	87	88	86	88	86	86
History of >1 MI (%)	15	16	17	16	16	16	16	16	17
**eGFR <60 ml/min(%)	22	22	23	23	21	22	24	22	24
Region									
Western Europe (%)	23	24	23	34	34	35	39	37	37
Eastern Europe (%)	25	25	25	31	31	30	28	30	31
North America (%)	29	27	28	16	16	16	14	13	13
South America (%)	6	7	7	12	12	13	12	14	11
Asia/Pacific (%)	17	17	17	8	8	7	8	7	7
Qualifying Event									
Months from MI – M (IQR)	16 (13,24)	16 (13,24)	16 (13,24)	18 (15,23)	19 (15,23)	19 (15,23)	28 (25,32)	29 (25,33)	29 (25,33)
STEMI	55	54	56	54	55	55	55	56	56
NSTEMI	41	42	41	43	42	41	42	40	40
MI type unknown	4	5	4	4	3	4	4	5	4

*Self Reported
**The estimated glomerular filtration rate was calculated with the use of the Modification of Diet in Renal Disease equation.

[00184]   The benefit of ticagrelor for long-term secondary prevention in patients

with prior MI and at least one additional risk factor appeared more marked in patients

continuing on or re-starting after only a brief interruption of $P2Y_{12}$ inhibition, when

compared with patients who had proved themselves stable more than 2 years from their

MI and off $P2Y_{12}$ inhibitor therapy for more than a year. The increase in bleeding events

with ticagrelor was similar regardless of this time interval. For clinicians considering a

strategy of prolonged $P2Y_{12}$ inhibitor therapy in high-risk patients, these data suggest

greater benefit in the continuation of such therapy without interruption after MI, rather

than re-initiating such therapy in patients who have remained stable for an extended

period. Table 23 shows outcomes at 36 months by time from $P2Y_{12}$ withdrawal to

randomization.

Table 23. Outcomes at 3 years by time from P2Y$_{12}$ inhibitor withdrawal to randomization

Timing from P2Y$_{12}$ inhibitor withdrawal	Endpoint	Placebo (n = 6258) n (%)	Ticagrelor pooled (n = 12 503) n (%)	Ticagrelor 90 mg bid (n = 6245) n (%)	Ticagrelor 60 mg bid (n = 6258) n (%)	HR (95% CI) P-value — Ticagrelor pooled vs. placebo	Ticagrelor 90 mg bid vs. placebo	Ticagrelor 60 mg bid vs. placebo
≤30 days	*Efficacy*							
	CV death, myocardial infarction, stroke	213 (9.9)	313 (7.7)	152 (7.4)	161 (8.0)	0.73 (0.61-0.87) 0.0003	0.70 (0.57-0.87) 0.0009	0.75 (0.61-0.92) 0.0064
	CV death	64 (3)	100 (2.5)	53 (2.5)	47 (2.4)	0.78 (0.57-1.07) 0.13	0.83 (0.58-1.19) 0.31	0.74 (0.51-1.08) 0.12
	Cor. heart dis. death	36 (1.8)	52 (1.3)	24 (1.1)	28 (1.5)	0.72 (0.47-1.11) 0.14	0.67 (0.40-1.12) 0.12	0.78 (0.48-1.28) 0.33
	Myocardial infarction	134 (6.2)	195 (4.9)	90 (4.6)	105 (5.2)	0.72 (0.58-0.90) 0.0038	0.67 (0.51-0.87)(0 .0028	0.78 (0.61-1.01) 0.061
	Stroke	44 (2.1)	56 (1.4)	28 (1.3)	28 (1.5)	0.64 (0.43-0.95) 0.025	0.64 (0.4-1.02) 0.061	0.64 (0.4-1.03) 0.064
	Safety							
	TIMI Major Bleeding	14 (0.7)	86 (2.5)	43 (2.4)	43 (2.6)	3.36 (1.91-5.92) <0.0001	3.44 (1.88-6.28) <0.001	3.3 (1.8-6.03) 0.0001
	TIMI Major or Minor Bleeding	21 (1.1)	134 (4.0)	67 (3.8)	67 (4.1)	3.50 (2.21-5.54) <0.0001	3.57 (2.19-.83) <0.0001	3.43 (2.1-5.60) <0.0001
	Intracranial bleeding	7 (0.4)	23 (0.7)	13 (0.7)	10 (0.8)	1.79 (0.77-4.18) 0.18	2.07 (0.82-5.18) 0.12	1.53 (0.58-4.03) 0.39

Timing from P2Y$_{12}$ inhibitor withdrawal	Endpoint	Placebo (n = 6258) n (%)	Ticagrelor pooled (n = 12 503) n (%)	Ticagrelor 90 mg bid (n = 6245) n (%)	Ticagrelor 60 mg bid (n = 6258) n (%)	HR (95% CI) P-value		
						Ticagrelor pooled vs. placebo	Ticagrelor 90 mg bid vs. placebo	Ticagrelor 60 mg bid vs. placebo
	Fatal bleeding	2 (0.1)	8 (0.3)	4 (0.2)	4 (0.4)	2.2 (0.47-13.34) 0.32	2.25 (0.41-12.28) 0.35	2.15 (0.4-11.76) 0.3
	All-cause mortality	106 (4.9)	192 (4.7)	108 (5.1)	84 (4.3)	0.91 (0.72-1.15) 0.43	1.02 (0.78-1.33) 0.90	0.80 (0.60-1.06) 0.12
> 30 days to ≤1 year	*Efficacy*							
	CV death, myocardial infarction, stroke	171 (8.7)	293 (7.6)	152 (8.1)	141 (7.2)	0.86 (0.71-1.04) 0.11	0.90 (0.72-1.12) 0.35	0.82 (0.65-1.02) 0.08
	CV death	59 (3.1)	90 (2.5)	49 (2.8)	41 (2.2)	0.76 (0.55-1.06) 0.10	0.84 (0.57-1.22) 0.35	0.69 (0.46-1.02) 0.065
	Cor. heart dis. death	37 (1.8)	52 (1.4)	26 (1.4)	26 (1.4)	0.70 (0.46-1.07) 0.099	0.71 (0.43-1.17) 0.18	0.70 (0.42-1.15) 0.16
	Myocardial infarction	103 (5.2)	174 (4.4)	83 (4.2)	91 (4.6)	0.85 (0.66-1.08) 0.19	0.82 (0.61-1.09) 0.17	0.88 (0.66-1.16) 0.37
	Stroke	34 (1.9)	62 (1.7)	34 (1.9)	28 (1.4)	0.91 (0.6-1.39) 0.68	1.02 (0.63-1.64) 0.93	0.82 (0.49-1.35) 0.42
	Safety							
	TIMI Major Bleeding	16 (1.2)	82 (2.7)	39 (2.8)	43 (2.7)	2.89 (1.69-4.94) 0.0001	2.85 (1.59-5.1) 0.0004	2.94 (1.66-5.22) 0.0002
	TIMI Major or Minor Bleeding	21 (1.6)	116 (3.8)	57 (3.9)	59 (3.8)	3.11 (1.96-4.96) <0.0001	3.17 (1.92-5.23) <0.0001	3.07 (1.86-5.05) <0.0001

Timing from P2Y$_{12}$ inhibitor withdrawal	Endpoint	Placebo (n = 6258) n (%)	Ticagrelor pooled (n = 12 503) n (%)	Ticagrelor 90 mg bid (n = 6245) n (%)	Ticagrelor 60 mg bid (n = 6258) n (%)	HR (95% CI) P-value		
						Ticagrelor pooled vs. placebo	Ticagrelor 90 mg bid vs. placebo	Ticagrelor 60 mg bid vs. placebo
	Intracranial bleeding	5 (0.4)	16 (0.5)	7 (0.5)	9 (0.6)	1.81 (0.66-4.95) 0.25	1.63 (0.52-5.14) 0.40	1.97 (0.66-5.88) 0.22
	Fatal bleeding	5 (0.5)	5 (0.2)	1 (0.1)	4 (0.3)	0.57 (0.16-1.97) 0.37	0.24 (0.03-204) 0.19	0.87 (0.23-3.25) 0.84
	All-cause mortality	91 (4.9)	161 (4.3)	91 (4.8)	70 (3.8)	0.88 (0.68-1.14) 0.34	1.01 (0.75-1.35) 0.96	0.76 (0.56-1.04) 0.086
> 1 year	*Efficacy*							
	CV death, myocardial infarction, stroke	103 (6.9	209 (6.6)	100 (6.3)	109 (6.9)	1.01 (0.80-1.27) 0.96	0.96 (0.73-1.26) 0.75	1.05 (0.81-1.38) 0.70
	CV death	31 (2.2)	81 (2.6)	36 (2.3)	45 (2.8)	1.3 (0.86-1.97) 0.22	1.15 (0.71-1.86) 0.57	1.45 (0.92-2.29) 0.11
	Cor. heart dis. death	23 (1.6)	40 (1.2)	18 (1.1)	22 (1.2)	0.86 (0.52-1.44) 0.58	0.77 (0.42-1.43) 0.42	0.96 (0.53-1.71) 0.88
	Myocardial infarction	67 (4.4)	121 (3.9)	57 (3.6)	64 (4.1)	0.9 (0.66-1.21) 0.47	0.84 (0.59-1.19) 0.33	0.95 (0.68-1.34) 0.78
	Stroke	21 (1.4)	44 (1.3)	24 (1.5)	20 (1.2)	1.04 (0.62-1.75) 0.88	1.13 (0.63-2.03) 0.69	0.95 (0.51-1.75) 0.87
	Safety							
	TIMI Major Bleeding	12 (0.9)	57 (2.4)	34 (3)	23 (1.9)	2.67 (1.43-4.98) 0.0020	3.28 (1.7-6.33) 0.0004	2.1 (1.05-4.22) 0.037
	TIMI Major or	16 (1.2)	84 (3.5)	53 (4.4)	31 (2.3)	2.94	3.82	2.11

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Timing from P2Y$_{12}$ inhibitor withdrawal	Endpoint	Placebo (n = 6258) n (%)	Ticagrelor pooled (n = 12 503) n (%)	Ticagrelor 90 mg bid (n = 6245) n (%)	Ticagrelor 60 mg bid (n = 6258) n (%)	HR (95% CI) P-value Ticagrelor pooled vs. placebo	Ticagrelor 90 mg bid vs. placebo	Ticagrelor 60 mg bid vs. placebo
	Minor Bleeding					(1.72-5.02) <0.0001	(2.18-6.68) <0.0001	(1.16-3.87) 0.015
	Intracranial bleeding	5 (0.4)	13 (0.6)	6 (0.5)	7 (0.6)	1.48 (0.53-4.14) 0.46	1.42 (0.43-4.64) 0.57	1.56 (0.49-4.9) 0.45
	Fatal bleeding	1 (0)	1 (0)	0 (0)	1 (0.1)	0.57 (0.04-9.11) 0.69	na	1.11 (0.07-17.7) 0.94
	All-cause mortality	55 (3.8)	147 (4.6)	73 (4.7)	74 (4.6)	1.32 (0.97-1.80) 0.076	1.31 (0.92-1.86) 0.13	1.34 (0.94-1.9) 0.10

[00185]   The results of PEGASUS-TIMI 54 now provide a prospectively defined evidence base affirming the hypothesis that long-term, more intensive platelet inhibition with ticagrelor reduces ischemic events in patients with prior spontaneous myocardial infarction.

[00186]   Addressing a related but distinct question, the recently reported DAPT trial demonstrated a reduction in non-fatal ischemic events with continuation of dual antiplatelet therapy with a $P2Y_{12}$ receptor blocker on a background of aspirin for more than 12 months after coronary stenting. Of note, patients in DAPT were restricted to those without a bleeding complication in the prior 12 months and they were randomized immediately after the end of this period to continuation or withdrawal of therapy. Therefore, the trial selected a subset of patients who had recently tolerated $P2Y_{12}$ receptor blockade, which would tend to minimize their bleeding complications. Moreover, an increase in major adverse cardiovascular events was observed soon after discontinuation of $P2Y_{12}$ receptor blockade. (See Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371:2155-66.) This observation suggests that the clinical benefit observed in the PEGASUS trial, in which patients were further removed from their index event and from dual antiplatelet therapy, may underestimate the benefit that would be achieved in continuing ticagrelor without interruption in patients who had successfully completed a one-year course after their myocardial infarction.

[00187]   Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal bleeding. Ticagrelor at both doses increased bleeding including TIMI major bleeding, bleeding leading to transfusion and bleeding leading to study drug

discontinuation. However, rates of the most severe bleeding events of intracranial hemorrhage and fatal bleeding were low over the three years of follow up and similar between the ticagrelor and placebo arms. Bleeding with ticagrelor did not differ in any of the major subgroups evaluated. However, it is important to note that the study protocol excluded patients with a recent bleed, prior stroke, or the need for oral anticoagulant therapy, and therefore the safety of long-term ticagrelor observed should not be generalized to other populations at higher risk of bleeding. Both doses of ticagrelor also caused dyspnea which occurred early after treatment initiation and contributed to higher rates of treatment discontinuation compared to placebo. The rates of drug discontinuation because of dyspnea seen with ticagrelor in this trial were higher than those seen in PLATO. However, that trial enrolled patients with acute coronary syndromes in whom transient dyspnea is frequently associated with their acute illness, in contrast to the stable patients in whom the onset of dyspnea may be surprising and hence more likely to lead to discontinuation.

[00188]   Dyspnea would likely not manifest in patients already tolerating ticagrelor in whom one decides to continue treatment beyond one year after their myocardial infarction. Moreover, rates of drug discontinuation in PEGASUS were similar to those observed in other long-term secondary prevention studies, and most of the difference in discontinuation rates between the ticagrelor and placebo arms accumulated soon after randomization. Consequently, in clinical practice, if a patient was tolerating ticagrelor for 12 months after their myocardial infarction, continuing ticagrelor beyond 12 months would not be expected to trigger a new episode of dyspnea or further increase the risk of bleeding events.

[00189] The two doses of ticagrelor that were studied achieved a similar magnitude of efficacy in the intention-to-treat analysis. However, the rates of bleeding and dyspnea were numerically lower with ticagrelor 60 mg twice daily compared to ticagrelor 90 mg twice daily, resulting in a lower rate of treatment discontinuation and better tolerability for the 60 mg dose. Thus, in general, the 60 mg dose may offer a more attractive benefit-risk and tolerability profile. It should also be noted that both doses were studied on a background of low-dose aspirin, which is recommended for patients with stable ischemic heart disease.

[00190] The addition of ticagrelor 90 mg twice daily or 60 mg twice daily to low-dose aspirin reduced the risk of cardiovascular death, myocardial infarction, or stroke in patients with a myocardial infarction 1 to 3 years earlier. Ticagrelor increased TIMI major bleeding but did not significantly increase intracranial hemorrhage. Ticagrelor showed at least a trend of reducing fatal bleeding. Coupled with the established benefit of ticagrelor in the setting of an acute coronary syndrome, and taking into account the benefit-risk profile, these data support consideration of continuing ticagrelor beyond 1 year in patients with myocardial infarction who are at high risk of cardiovascular events and without major risk factors for bleeding. Taken together, the PLATO and PEGASUS-TIMI 54 clinical trials provide consistent evidence of the benefit ticagrelor can bring to patients with coronary artery disease in acute and chronic secondary prevention.

Example 2: Ticagrelor 60 mg twice-daily provides effective platelet inhibition in patients with prior myocardial infarction (MI) – the PEGASUS-TIMI 54 platelet function substudy

[00191]   The PEGASUS-TIMI 54 trial studied 2 doses of ticagrelor, 90 mg orally

twice daily (bid) and 60 mg bid, for long term prevention of ischaemic events in patients

with prior MI. As shown in Example 1, compared to placebo, both doses reduced the

risk of cardiovascular death, myocardial infarction, or stroke in patients who had a

myocardial infarction 12 to 36 months earlier. The pharmacokinetics (PK) and

pharmacodynamics of the 60 mg bid dose had not previously been studied. This

substudy was aimed to characterize PK and platelet inhibition with ticagrelor 60 mg bid

vs 90 mg bid. 180 patients who had received >4 weeks of study medication had blood

sampling in the morning pre-maintenance dose and again 2h post-dose. All patients

were receiving aspirin. Plasma levels of ticagrelor and an active metabolite (AR-

C124910XX) were determined. Well-known VerifyNow® P2Y12 assay and light

transmittance aggregometry (LTA; ADP 20uM) were performed. Groups were

compared using Kruskal-Wallis test with significance attached to $P < 0.01$ to allow for

multiple group comparisons. Demographic characteristics at the time of randomization

were generally well-matched between the groups (Table 23).

Table 23. Demographic Characteristics

	Placebo (N=64)	Ticagrelor 60 mg bid (N = 58)	Ticagrelor 90 mg bid (N =58)	All groups (N = 180)
Age mean (SD), years	64.2 (6.6)	63.3 (6.6)	64.2 (6.9)	63.9 (6.7)
Body weight, kg, median (IQR)	86 (74.9-98)	86 (76-99.8)	81 (71-94)	85 (74-98.5)
Female sex (%)	21.9%	8.6%	17.2%	16.1%

[00192]   Ticagrelor demonstrates dose proportional pharmacokinetics, which were

similar in patients and healthy volunteers. The results showed that plasma ticagrelor

levels were approximately 1/3 lower with 60 mg vs 90 mg (post dose: 448 vs 717 ng/mL;

P<0.001). Both doses achieved high levels of platelet inhibition pre and post dose, with slightly more variability with 60 mg (Table 24). High platelet reactivity assessed by VerifyNow® (PRU >208) was rare with 60 mg pre-dose (3.5%) and absent post dose. Platelet reactivity pre- and post-dose as measured by LTA was numerically but not significantly lower with 90 mg than 60 mg. In addition, ticagrelor did not significantly affect measures of aspirin response: there were no differences in a VerifyNow Aspirin assay results between the placebo group and either ticagrelor group and no differences in serum thromboxane B2 levels.

[00193] Ticagrelor 60 mg bid achieved high levels of peak and trough platelet inhibition in nearly all patients, with similar consistency of effect compared to 90 mg bid. These results help to explain the efficacy of the lower ticagrelor dose in the PEGASUS-TIMI 54 study.

Table 24. Platelet Reactivity

	Placebo	Ticagrelor 60 mg	p value 60mg vs placebo	Ticagrelor 90mg	p value 90mg vs placebo	p value 90mg vs 60mg
	N=64	N=58		N=58		
VerifyNow® PRU Pre dose	265 (41)	59 (63)	< 0.001	47 (43)	< 0.001	0.34
VerifyNow® PRU Post dose	267 (40)	29 (39)	< 0.001	20 (19)	< 0.001	0.73
VerifyNow® % inhibition Pre dose	3 (5)	78 (20)	< 0.001	83 (14)	< 0.001	0.34
VerifyNow® % inhibition Post dose	4 (6)	90 (13)	< 0.001	92 (8)	< 0.001	0.59
LTA Max response Pre dose	73 (10)	39 (12)	< 0.001	36 (14)	< 0.001	0.18
LTA Max response Post dose	73 (9)	33 (12)	< 0.001	29 (11)	< 0.001	0.053

Data are mean (SD). Max response: maximum % aggregation response.

OTHER EMBODIMENTS

[00194] Should the meaning of the terms in any of the portions of the patents or publications incorporated by reference conflict with the meaning of the terms used in this disclosure, the meaning of the terms in this disclosure controls.In one aspect, the present disclosure provides a method for reducing the rate of cardiovascular death, myocardial infarction, or stroke in a patient in recognized need thereof, comprising administering to the patient a pharmaceutical composition comprising 60 mg ticagrelor twice daily, wherein the patient is also administered a daily maintenance dose of aspirin of 75 to 150 mg, and further wherein the rate of cardiovascular death, myocardial infarction, or stroke in the patient is reduced relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 to 150 mg only.

[00195] In some embodiments, the daily maintenance dose of aspirin is 75 mg to 100 mg.

[00196] In some embodiments, the daily maintenance dose of aspirin is 75 mg to 81 mg.

[00197] In some embodiments, the daily maintenance dose of aspirin is 100 mg.

[00198] In some embodiments, the patient has a history of myocardial infarction.

[00199] In some embodiments, the patient has a history of myocardial infarction as a result of a ST-segment-elevation myocardial infarction.

[00200] In some embodiments, the patient has a history of myocardial infarction at least 12 months prior to the twice daily administration of the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier.

[00201]   In some embodiments, the patient has a history of myocardial infarction

12 to 36 months prior to the twice daily administration of the pharmaceutical

composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier.

[00202]   In some embodiments, the patient has a coronary stent.

[00203]   In some embodiments, the patient is also administered a lipid lowering

therapy.

[00204]   In some embodiments, the patient is also administered at least one

medication selected from a statin, beta-blocker, ACEI, or ARB.

[00205]   In some embodiments, the patient satisfies the inclusion criteria for the

PEGASUS-TIMI 54 study listed in Table 2.

[00206]   In some embodiments, the patient is at least 50 years old. In some

further embodiments, the patient is at least 65 years old.

[00207]   In some embodiments, the patient has diabetes mellitus requiring

medication.

[00208]   In some embodiments, the patient has a history of angiographic

evidence of a multivessel CAD.

[00209]   In some embodiments, the patient has chronic non-end stage renal

dysfunction.

[00210]   In some embodiments, the patient has more than one risk factor

atherothrombosis. In some further embodiments, the patient has three or more risk

factors for atherothrombosis.

[00211]   In some embodiments, the patient is Caucasian.

[00212]   In some embodiments, the patient is Japanese. In some further

embodiments, the patient is Japanese and the methods results in a hazard ratio for

time to first composite endpoint of cardiovascular death, myocardial infarction, or

stroke of 0.29 relative to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only.

[00213]   In some embodiments, the patient has hypertension.

[00214]   In some embodiments, the patient has hypercholesterolemia.

[00215]   In some embodiments, the patient is a current smoker.

[00216]   In some embodiments, the patient has a history of more than one prior

myocardial infarction.

[00217]   In some embodiments, the patient has peripheral artery disease.

[00218]   In some embodiments, the patient has a history of percutaneous

coronary intervention (PCI).

[00219]   In some embodiments, the patient has a creatinine clearance of less

than 60 mL/min.

[00220]   In some embodiments, the patient does not meet any of the exclusion

criteria for the PEGASUS-TIMI 54 study listed in Table 2.

[00221]   In some embodiments, the patient is not taking dipyridamole or

cilostazol.

[00222]   In some embodiments, the patient is not taking a potent inducer,

inhibitor, or substrate of CYP3A.

[00223]   In some embodiments, the patient does not have chronic

anticoagulation.

[00224]   In some embodiments, the patient does not have a known bleeding

diathesis or coagulation disorder.

[00225]   In some embodiments, the patient is not at increased risk of bleeding

due to:

•   A history of intracranial bleed at any time,

- A central nervous system tumor or intracranial vascular

- abnormality (eg, aneurysm, arteriovenous malformation) at any time,

- Intracranial or spinal cord surgery within 5 years, or

- A gastrointestinal (GI) bleed within the past 6 months, or major surgery within

30 days

[00226]   In some embodiments, the patient does not have a history of ischemic

stroke.

[00227]   In some embodiments, the patient is not considered to be at risk of

bradycardic events.

[00228]   In some embodiments, the patient is considered to be at risk of

bradycardic events but is treated with a permanent pacemaker.

[00229]   In some embodiments, the patient has not undergone coronary-artery

bypass grafting in the last 5 years.

[00230]   In some embodiments, the patient does not have known severe liver

disease.

[00231]   In some embodiments, the patient has a life expectancy of at least one

year.

[00232]   In some embodiments, the patient has a history of myocardial infarction

as a result of an acute coronary syndrome. In some further embodiments, prior to

the administration, the patient was administered twice daily a pharmaceutical

composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier

for a portion of 12 months after the acute coronary syndrome. In some further

embodiments, prior to the administration, the patient was administered twice daily a

pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically

acceptable carrier for 12 months after the acute coronary syndrome. In still some

further embodiments, prior to the administration, the patient was administered a

pharmaceutical composition comprising a 180 mg ticagrelor loading dose prior to

administration twice daily of a pharmaceutical composition comprising 90 mg

ticagrelor and a pharmaceutically acceptable carrier for a portion of the 12 months

after the acute coronary syndrome.

[00233]   In some embodiments, the patient was previous treated with an ADP

receptor blocker. In some further embodiments, the patient was previous treated

with an ADP receptor blocker selected from clopidogrel, prasugrel, ticlodipine, or

ticagrelor.

[00234]   In some embodiments, the patient's last dose of ADP receptor blocker

occurred less than 7 days prior to administration. In some embodiments, the

patient's last dose of ADP receptor blocker occurred 8 to 90 days prior to

administration. In some embodiments, the patient's last dose of ADP receptor

blocker occurred within 30 days prior to administration. In some embodiments, the

patient's last dose of ADP receptor blocker occurred 3 to 12 months prior to

administration. In some embodiments, the patient's last dose of ADP receptor

blocker occurred more than 12 months prior to administration.

[00235]   In some embodiments, the primary efficacy endpoint in a patient

subgroup is consistent with the primary efficacy subgroup analyses shown in Figures

4-7.

[00236]   In some embodiments, TIMI major bleeding in a patient subgroup is

consistent with the TIMI major bleeding subgroup analyses shown in Figures 9-11.

[00237]   In some embodiments, safety and tolerability endpoints are consistent

with the data shown in Table 14.

[00238]   In some embodiments, bleeding events are consistent with the data

shown in Table 15.

[00239]   In some embodiments, adverse events occur at rates consistent with

those disclosed in Tables 16 and 17.

[00240]   In some embodiments, the average risk at three years for patients less

than 65 years of age is consistent with the data shown in Table 18.

[00241]   In some embodiments, the average risk at three years for patients 65

to 75 years of age is consistent with the data shown in Table 18.

[00242]   In some embodiments, the average risk at three years for patients over

75 years of age is consistent with the data shown in Table 18.

[00243]   In some embodiments, the Kaplan-Meier rate of patients without TIMI

Major Bleeding events vs. time is consistent with the curves shown in Figure 18.

[00244]   In some embodiments, the safety and efficacy outcomes at 3 years by

time from P2Y$_{12}$ inhibitor withdrawal to randomization are consistent with the data

shown in Table 22.

[00245]   In some embodiments, the method results in platelet reactivity

consistent with the data shown in Table 24.

[00246]   In some embodiments, the method satisfies at least one of the

following efficacy endpoints:

1. the method numerically reduces the rate of the composite endpoint of

   cardiovascular death, myocardial infarction, or stroke relative to a dosing

   regimen where the patient receives the daily maintenance dose of aspirin of

   75 mg to 150 mg only;

2. the method numerically reduces the absolute risk of the composite endpoint of

   cardiovascular death, myocardial infarction, or stroke relative to a dosing

regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only;

3. the method results in a relative risk of the composite endpoint of

cardiovascular death, myocardial infarction, or stroke of less than one relative

to a dosing regimen where the patient receives the daily maintenance dose of

aspirin of 75 mg to 150 mg only;

4. the method numerically reduces the Kaplan-Meier rate for the composite

endpoint of cardiovascular death, myocardial infarction, or stroke compared to

a dosing regimen where the patient receives the daily maintenance dose of

aspirin of 75 mg to 150 mg only;

5. the method results in a statistically significant reduction in the rate of the

composite endpoint of cardiovascular death, myocardial infarction, or stroke

relative to a dosing regimen where the patient receives the daily maintenance

dose of aspirin of 75 mg to 150 mg only;

6. the method results in a relative risk of the composite endpoint of

cardiovascular death, myocardial infarction, or stroke that is statistically

significantly less than one relative to a dosing regimen where the patient

receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

7. the method results in a Kaplan-Meier rate for the composite endpoint of

cardiovascular death, myocardial infarction, or stroke at three years of

approximately 7.8%;

8. the method results in a Kaplan-Meier rate for the composite endpoint of

cardiovascular death, myocardial infarction, or stroke at three years of 7.8%;

9. the method results in a Kaplan-Meier rate for the composite endpoint of

cardiovascular death, myocardial infarction, or stroke at three years of 7.77%;

10. the method results in a hazard ratio for the composite endpoint of
cardiovascular death, myocardial infarction, or stroke of less than 1 relative to
a dosing regimen where the patient receives the daily maintenance dose of
aspirin of 75 mg to 150 mg only;

11. the method results in a hazard ratio for time to first composite endpoint of
cardiovascular death, myocardial infarction, or stroke that is statistically
significantly less than 1 relative to a dosing regimen where the patient
receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

12. the method results in a numerical reduction in the percentage of patients with
composite endpoint of cardiovascular death, myocardial infarction, or stroke
events relative to a dosing regimen where the patient receives the daily
maintenance dose of aspirin of 75 mg to 150 mg only;

13. the method results in a hazard ratio for time to first composite endpoint of
cardiovascular death, myocardial infarction, or stroke at three years of
approximately 0.84 relative to a dosing regimen where the patient receives
the daily maintenance dose of aspirin of 75 mg to 150 mg only;

14. the method results in a hazard ratio for time to first composite endpoint of
cardiovascular death, myocardial infarction, or stroke at three years of 0.84
relative to a dosing regimen where the patient receives the daily maintenance
dose of aspirin of 75 mg to 150 mg only;

15. the method results in a hazard ratio for time to first composite endpoint of
cardiovascular death, myocardial infarction, or stroke at three years of 0.74 to
0.95 relative to a dosing regimen where the patient receives the daily
maintenance dose of aspirin of 75 mg to 150 mg only;

16. the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

17. the method reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.27% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

18. the method reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by 1.27% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

19. the method results in an approximately 17% relative risk reduction for the composite endpoint of cardiovascular death, myocardial infarction, or stroke from 1 to 360 days relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

20. the method results in 17% relative risk reduction for the composite endpoint of cardiovascular death, myocardial infarction, or stroke from 1 to 360 days relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

21. the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

22. the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by 1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

23. the method reduces the percentage of patients with composite endpoint of cardiovascular death, myocardial infarction, or stroke events at three years by approximately 1.3% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

24. the method reduces the percentage of patients with composite endpoint of cardiovascular death, myocardial infarction, or stroke events at three years by 1.3% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

25. the method numerically reduces the absolute risk of at least one of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

26. the method results in a relative risk of less than one for at least one of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

27. the method numerically reduces the Kaplan-Meier rate for at least one of cardiovascular death, myocardial infarction, or stroke compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

28. the method results in a relative risk for time to first cardiovascular death event of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

29. the method results in a hazard ratio for time to first cardiovascular death event of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

30. the method results in a numerical reduction in the percentage of patients with a cardiovascular death event relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

31. the method results in a Kaplan-Meier rate for cardiovascular death at three years of approximately 2.9%;

32. the method results in a Kaplan-Meier rate for cardiovascular death at three years of 2.9%;

33. the method reduces the Kaplan-Meier rate for cardiovascular death at three years by approximately 0.5% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

34. the method reduces the Kaplan-Meier rate for cardiovascular death at three years by 0.5% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

35. the method results in a hazard ratio for time to first cardiovascular death event at three years of approximately 0.83 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

36. the method results in a hazard ratio for time to first cardiovascular death event at three years of 0.83 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

37. the method results in a hazard ratio for time to first cardiovascular death event at three years of 0.68 to 1.01 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

38. the method results in a 95% confidence interval for the hazard ratio for time to first cardiovascular death event at three years of 0.68 to 1.01 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

39. the method results in a hazard ratio for time to first myocardial infarction event of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

40. the method results in a relative risk for time to first myocardial infarction event of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

41. the method results in a numerical reduction in the percentage of patients with a myocardial infarction event relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

42. the method results in a reduction in the percentage of patients with a myocardial infarction event relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

43. the method results in a hazard ratio for time to first myocardial infarction event at three years of approximately 0.84 relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

44. the method results in a hazard ratio for time to first myocardial infarction event at three years of 0.84 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

45. the method results in a hazard ratio for time to first myocardial infarction event at three years of 0.72 to 0.98 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

46. the method results in a 95% confidence interval for the hazard ratio for time to first myocardial infarction event at three years of 0.72 to 0.98 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

47. the method results in a Kaplan-Meier rate for myocardial infarction at three years of approximately 4.5%;

48. the method results in a Kaplan-Meier rate for myocardial infarction at three years of 4.5%;

49. the method reduces the Kaplan-Meier rate for myocardial infarction at three years by approximately 0.7% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

50. the method reduces the Kaplan-Meier rate for myocardial infarction at three years by 0.7% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

51. the method results in a hazard ratio for time to first stroke event of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

52. the method results in a relative risk for time to first stroke event of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

53. the method results in a numerical reduction in the percentage of patients with a stroke event relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

54. the method results in a hazard ratio for time to first stroke event at three years of approximately 0.75 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

55. the method results in a hazard ratio for time to first stroke event at three years of 0.75 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

56. the method results in a hazard ratio for time to first stroke event at three years of 0.57 to 0.98 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

57. the method results in a 95% confidence interval for the hazard ratio for time to first stroke event at three years of 0.57 to 0.98 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

58. the method results in a Kaplan-Meier rate for stroke at three years of approximately 1.5%;

59. the method results in a Kaplan-Meier rate for stroke at three years of 1.5%;

60. the method reduces the Kaplan-Meier rate for stroke at three years by approximately 0.5% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

61. the method reduces the Kaplan-Meier rate for stroke at three years by 0.5% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

62. the method results in a hazard ratio for time to first ischemic stroke event of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

63. the method results in a relative risk for time to first ischemic stroke event of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

64. the method results in a numerical reduction in the percentage of patients with an ischemic stroke event relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

65. the method results in a hazard ratio for time to first ischemic stroke event at three years of approximately 0.76 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

66. the method results in a hazard ratio for time to first ischemic stroke event at three years of 0.76 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

67. the method results in a hazard ratio for time to first ischemic stroke event at three years of 0.56 to 1.02 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

68. the method results in a 95% confidence interval for the hazard ratio for time to first ischemic stroke event at three years of 0.56 to 1.02 relative to a dosing

regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

69. the method results in a Kaplan-Meier rate for ischemic stroke at three years of approximately 1.3%;

70. the method results in a Kaplan-Meier rate for ischemic stroke at three years of 1.3%;

71. the method reduces the Kaplan-Meier rate for ischemic stroke at three years by approximately 0.4% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

72. the method reduces the Kaplan-Meier rate for ischemic stroke at three years by 0.4% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

73. the method results in a hazard ratio for time to first coronary heart disease death event of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

74. the method results in a relative risk for time to first coronary heart disease death event of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

75. the method results in a numerical reduction in the percentage of patients with a coronary heart disease death event relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

76. the method results in a hazard ratio for time to first coronary heart disease death event at three years of approximately 0.80 relative to a dosing regimen

where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

77. the method results in a hazard ratio for time to first coronary heart disease death event at three years of 0.80 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

78. the method results in a hazard ratio for time to first coronary heart disease death event at three years of 0.62 to 1.04 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

79. the method results in a 95% confidence interval for the hazard ratio for time to first coronary heart disease death event of at three years 0.62 to 1.04 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

80. the method results in a Kaplan-Meier rate for coronary heart disease death at three years of approximately 1.7%;

81. the method results in a Kaplan-Meier rate for coronary heart disease death at three years of 1.7%;

82. the method reduces the Kaplan-Meier rate for ischemic stroke at three years by approximately 0.4% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

83. the method reduces the Kaplan-Meier rate for ischemic stroke at three years by 0.4% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

84. the method numerically reduces the rate of the composite endpoint of coronary heart disease death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

85. the method numerically reduces the absolute risk of the composite endpoint of coronary heart disease death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

86. the method results in a relative risk of the composite endpoint of coronary heart disease death, myocardial infarction, or stroke of less than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

87. the method numerically reduces the Kaplan-Meier rate for the composite endpoint of coronary heart disease death, myocardial infarction, or stroke compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only.

88. the method results in a relative risk reduction for the composite endpoint of coronary heart disease death, myocardial infarction, or stroke at three years of approximately 17%;

89. the method results in a relative risk reduction for the composite endpoint of coronary heart disease death, myocardial infarction, or stroke at three years of 17%;

90. the method results in a hazard ratio for time to first composite endpoint of coronary heart disease death, myocardial infarction, or stroke of less than 1

relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

91. the method results in a numerical reduction in the percentage of patients with composite endpoint of coronary heart disease death, myocardial infarction, or stroke events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

92. the method results in a hazard ratio for time to first composite endpoint of coronary heart disease death, myocardial infarction, or stroke at three years of approximately 0.83 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

93. the method results in a hazard ratio for time to first composite endpoint of coronary heart disease death, myocardial infarction, or stroke at three years of 0.83 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

94. the method results in a hazard ratio for time to first composite endpoint of coronary heart disease death, myocardial infarction, or stroke at three years of 0.73 to 0.94 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

95. the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of coronary heart disease death, myocardial infarction, or stroke at three years of 0.73 to 0.94 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

96. the method results in a Kaplan-Meier rate for the composite endpoint of coronary heart disease death, myocardial infarction, or stroke at three years of approximately 7.1%;

97. the method results in a Kaplan-Meier rate for the composite endpoint of coronary heart disease death, myocardial infarction, or stroke at three years of 7.1%;

98. the method reduces the Kaplan-Meier rate for the composite endpoint of coronary heart disease death, myocardial infarction, or stroke at three years by approximately 1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

99. the method reduces the Kaplan-Meier rate for the composite endpoint of coronary heart disease death, myocardial infarction, or stroke at three years by 1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

100. the method numerically reduces the rate of the composite endpoint of coronary heart disease death or myocardial infarction relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

101. the method numerically reduces the absolute risk of the composite endpoint of coronary heart disease death or myocardial infarction relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

102. the method results in a relative risk of the composite endpoint of coronary heart disease death or myocardial infarction of less than one relative

to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

103. the method numerically reduces the Kaplan-Meier rate for the composite endpoint of coronary heart disease death or myocardial infarction compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

104. the method results in a hazard ratio for time to first composite endpoint of coronary heart disease death or myocardial infarction of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

105. the method results in a numerical reduction in the percentage of patients with composite endpoint of coronary heart disease death or myocardial infarction events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

106. the method results in a hazard ratio for time to first composite endpoint of coronary heart disease death or myocardial infarction at three years of approximately 0.84 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

107. the method results in a hazard ratio for time to first composite endpoint of coronary heart disease death or myocardial infarction at three years of 0.84 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

108. the method results in a hazard ratio for time to first composite endpoint of coronary heart disease death or myocardial infarction at three years of 0.73

to 0.96 relative to a dosing regimen where the patient receives the daily
maintenance dose of aspirin of 75 mg to 150 mg only;

109.   the method results in a 95% confidence interval for the hazard ratio for
time to first composite endpoint of coronary heart disease death or myocardial
infarction at three years of 0.73 to 0.96 relative to a dosing regimen where the
patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg
only;

110.   the method results in a Kaplan-Meier rate for the composite endpoint of
coronary heart disease death or myocardial infarction at three years of
approximately 5.6%;

111.   the method results in a Kaplan-Meier rate for the composite endpoint of
coronary heart disease death or myocardial infarction at three years of 5.6%;

112.   the method reduces the Kaplan-Meier rate for the composite endpoint
of coronary heart disease death or myocardial infarction at three years by 1.1%
compared to a dosing regimen where the patient receives the daily
maintenance dose of aspirin of 75 mg to 150 mg only;

113.   the method reduces the Kaplan-Meier rate for the composite endpoint
of coronary heart disease death or myocardial infarction at three years by
approximately 1.1% compared to a dosing regimen where the patient receives
the daily maintenance dose of aspirin of 75 mg to 150 mg only;

114.   the method numerically reduces the rate of the composite endpoint of
cardiovascular death or myocardial infarction relative to a dosing regimen
where the patient receives the daily maintenance dose of aspirin of 75 mg to
150 mg only;

115.   the method numerically reduces the absolute risk of the composite

endpoint of cardiovascular death or myocardial infarction relative to a dosing

regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only;

116.   the method results in a relative risk of the composite endpoint of

cardiovascular death or myocardial infarction of less than one relative to a

dosing regimen where the patient receives the daily maintenance dose of

aspirin of 75 mg to 150 mg only;

117.   the method numerically reduces the Kaplan-Meier rate for the

composite endpoint of cardiovascular death or myocardial infarction

compared to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only;

118.   the method results in a hazard ratio for time to first composite endpoint

of cardiovascular death or myocardial infarction of less than 1 relative to a

dosing regimen where the patient receives the daily maintenance dose of

aspirin of 75 mg to 150 mg only;

119.   the method results in a numerical reduction in the percentage of

patients with composite endpoint of cardiovascular death or myocardial

infarction events relative to a dosing regimen where the patient receives the

daily maintenance dose of aspirin of 75 mg to 150 mg only;

120.   the method results in a hazard ratio for time to first composite endpoint

of cardiovascular death or myocardial infarction at three years of

approximately 0.85 relative to a dosing regimen where the patient receives

the daily maintenance dose of aspirin of 75 mg to 150 mg only;

121. the method results in a hazard ratio for time to first composite endpoint of cardiovascular death or myocardial infarction at three years of 0.85 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

122. the method results in a hazard ratio for time to first composite endpoint of cardiovascular death or myocardial infarction at three years of 0.74 to 0.96 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

123. the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death or myocardial infarction at three years of 0.74 to 0.96 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

124. the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death or myocardial infarction at three years of approximately 6.8%;

125. the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death or myocardial infarction at three years of 6.8%;

126. the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death or myocardial infarction at three years by approximately 1.0% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

127. the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death or myocardial infarction at three years by 1.0%

compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

128.   the method numerically reduces the rate of death from any cause relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

129.   the method numerically reduces the Kaplan-Meier rate for death from any cause compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

130.   the method results in a hazard ratio for time to first death from any cause of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

131.   the method results in a relative risk for time to first death from any cause of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

132.   the method results in a numerical reduction in the percentage of patients with death from any cause events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

133.   the method results in a hazard ratio for time to first death from any cause at three years of approximately 0.89 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

134.   the method results in a hazard ratio for time to first death from any cause at three years of 0.89 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

135.   the method results in a hazard ratio for time to first death from any

cause at three years of 0.76 to 1.04 relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

136.   the method results in a 95% confidence interval for the hazard ratio for

time to first death from any cause at three years of 0.76 to 1.04 relative to a

dosing regimen where the patient receives the daily maintenance dose of

aspirin of 75 mg to 150 mg only.

137.   the method results in a Kaplan-Meier rate for death from any cause at

three years of approximately 4.7%;

138.   the method results in a Kaplan-Meier rate for death from any cause at

three years of 4.7%;

139.   the method reduces the Kaplan-Meier rate for death from any cause at

three years by approximately 0.5% compared to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

the method reduces the Kaplan-Meier rate for death from any cause at three

years by 0.5% compared to a dosing regimen where the patient receives the

daily maintenance dose of aspirin of 75 mg to 150 mg only;

140.   the method numerically reduces the rate of urgent coronary

revascularization for unstable angina from any cause relative to a dosing

regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only;

141.   the method numerically reduces the Kaplan-Meier rate for urgent

coronary revascularization for unstable angina compared to a dosing regimen

where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

142. the method results in a hazard ratio for time to first urgent coronary revascularization for unstable angina of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

143. the method results in a numerical reduction in the percentage of patients with urgent coronary revascularization for unstable angina events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

144. the method results in a hazard ratio for time to first urgent coronary revascularization for unstable angina at three years of approximately 0.82 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

145. the method results in a hazard ratio for time to first urgent coronary revascularization for unstable angina at three years of 0.82 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

146. the method results in a hazard ratio for time to first urgent coronary revascularization for unstable angina at three years of 0.58 to 1.14 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

147. the method results in a 95% confidence interval for the hazard ratio for time to first urgent coronary revascularization for unstable angina at three

years of 0.58 to 1.14 relative to a dosing regimen where the patient receives

the daily maintenance dose of aspirin of 75 mg to 150 mg only;

148. the method numerically reduces the rate of coronary stent thrombosis

from any cause relative to a dosing regimen where the patient receives the

daily maintenance dose of aspirin of 75 mg to 150 mg only;

149. the method numerically reduces the Kaplan-Meier rate for coronary

stent thrombosis compared to a dosing regimen where the patient receives

the daily maintenance dose of aspirin of 75 mg to 150 mg only;

150. the method results in a hazard ratio for time to first coronary stent

thrombosis of less than 1 relative to a dosing regimen where the patient

receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

151. the method results in a numerical reduction in the percentage of

patients with coronary stent thrombosis events relative to a dosing regimen

where the patient receives the daily maintenance dose of aspirin of 75 mg to

150 mg only;

152. the method results in a hazard ratio for time to first coronary stent

thrombosis at three years of approximately 0.82 relative to a dosing regimen

where the patient receives the daily maintenance dose of aspirin of 75 mg to

150 mg only;

153. the method results in a hazard ratio for time to first coronary stent

thrombosis at three years of 0.82 relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

154. the method results in a hazard ratio for time to first coronary stent

thrombosis at three years of 0.54 to 1.23 relative to a dosing regimen where

the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

155. the method results in a 95% confidence interval for the hazard ratio for

time to first coronary stent thrombosis at three years of 0.54 to 1.23 relative to

a dosing regimen where the patient receives the daily maintenance dose of

aspirin of 75 mg to 150 mg only;

156. the method results in a relative risk of coronary stent thrombosis of less

than one relative to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only;

157. the method results in a relative risk reduction of approximately 18% for

coronary stent thrombosis at three years relative to a dosing regimen where

the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

158. the method results in a relative risk reduction of 18% for coronary stent

thrombosis at three years relative to a dosing regimen where the patient

receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

159. the method numerically reduces the rate of the composite endpoint of

cardiovascular death, myocardial infarction, or stroke relative to a dosing

regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only in a subgroup shown in Figures 4-7, excluding

subgroups wherein the hazard ratio for time to first composite endpoint of

cardiovascular death, myocardial infarction, or stroke shown in Figures 4-7 is

greater than 1 relative to a dosing regimen where the patient receives the

daily maintenance dose of aspirin of 75 mg to 150 mg only;

160.   the method results in a hazard ratio for time to first composite endpoint

of cardiovascular death, myocardial infarction, or stroke of less than 1 relative

to a dosing regimen where the patient receives the daily maintenance dose of

aspirin of 75 mg to 150 mg only for a subgroup shown in Figures 4-7 to have

an average hazard ratio less than 1;

161.   the method results in a numerical reduction in the percentage of

patients with composite endpoint of cardiovascular death, myocardial

infarction, or stroke events relative to a dosing regimen where the patient

receives the daily maintenance dose of aspirin of 75 mg to 150 mg only for a

subgroup shown in Figures 4-7 to have an average hazard ratio less than 1;

162.   the method results in a hazard ratio for time to first composite endpoint

of cardiovascular death, myocardial infarction, or stroke as shown in Figures

4-7 relative to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only for a subgroup shown in

Figures 4-7;

163.   the method results in a 95% confidence interval for the hazard ratio for

time to first composite endpoint of cardiovascular death, myocardial infarction,

or stroke as shown in Figures 4-7 relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only for a subgroup shown in Figures 4-7;

164.   the method results in an absolute risk reduction for the composite

endpoint of cardiovascular death, myocardial infarction, and stroke at three

years of approximately 2.15%, wherein the patient is more than 75 years of

age;

165.   the method results in an absolute risk reduction for the composite

endpoint of cardiovascular death, myocardial infarction, and stroke at three

years of 2.15%, wherein the patient is more than 75 years of age;

166.   the method results in an absolute risk reduction for the composite

endpoint of cardiovascular death, myocardial infarction, and stroke at three

years of approximately 1.38%, wherein the patient is less than 65 years of

age;

167.   the method results in an absolute risk reduction for the composite

endpoint of cardiovascular death, myocardial infarction, and stroke at three

years of 1.38%, wherein the patient is less than 65 years of age;

168.   the method numerically reduces the rate of the composite endpoint of

cardiovascular death, myocardial infarction, stroke, or TIMI major bleeding

relative to a dosing regimen where the patient receives the daily maintenance

dose of aspirin of 75 mg to 150 mg only;

169.   the method numerically reduces the absolute risk of the composite

endpoint of cardiovascular death, myocardial infarction, stroke, or TIMI major

bleeding relative to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only;

170.   the method numerically reduces the relative risk of the composite

endpoint of cardiovascular death, myocardial infarction, stroke, or TIMI major

bleeding compared to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only;

171.   the method results in a hazard ratio for time to first composite endpoint

of cardiovascular death, myocardial infarction, stroke, or TIMI major bleeding

of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

172. the method results in a numerical reduction in the percentage of patients with the composite endpoint of cardiovascular death, myocardial infarction, stroke, or TIMI major bleeding events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

173. the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, stroke, or TIMI major bleeding at three years of approximately 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

174. the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, stroke, or TIMI major bleeding at three years of 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

175. the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, stroke, or TIMI major bleeding at three years of 0.85 to 1.06 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

176. the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, stroke, or TIMI major bleeding at three years of 0.85 to 1.06 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

177.   the method results in a relative risk reduction of approximately 5% for

the composite endpoint of cardiovascular death, myocardial infarction, stroke,

or TIMI major bleeding at three years relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

178.   the method results in a relative risk reduction of 5% for the composite

endpoint of cardiovascular death, myocardial infarction, stroke, or TIMI major

bleeding at three years relative to a dosing regimen where the patient

receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

179.   the method numerically reduces the rate of the composite endpoint of

cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage,

or fatal bleeding relative to a dosing regimen where the patient receives the

daily maintenance dose of aspirin of 75 mg to 150 mg only;

180.   the method numerically reduces the absolute risk of the composite

endpoint of cardiovascular death, myocardial infarction, stroke, intracranial

hemorrhage, or fatal bleeding relative to a dosing regimen where the patient

receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

181.   the method results in a relative risk of the composite endpoint of

cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage,

or fatal bleeding of less than one relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

182.   the method results in a hazard ratio for time to first composite endpoint

of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage,

or fatal bleeding of less than 1 relative to a dosing regimen where the patient

receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

183.   the method results in a numerical reduction in the percentage of

patients with the composite endpoint of cardiovascular death, myocardial

infarction, stroke, intracranial hemorrhage, or fatal bleeding events relative to

a dosing regimen where the patient receives the daily maintenance dose of

aspirin of 75 mg to 150 mg only;

184.   the method results in a hazard ratio for time to first composite endpoint

of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage,

or fatal bleeding of less than one relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

185.   the method results in a hazard ratio for time to first composite endpoint

of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage,

or fatal bleeding at three years of approximately 0.86 relative to a dosing

regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only;

186.   the method results in a hazard ratio for time to first composite endpoint

of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage,

or fatal bleeding at three years of 0.86 relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

187.   the method results in a hazard ratio for time to first composite endpoint

of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage,

or fatal bleeding at three years of 0.77 to 0.97 relative to a dosing regimen

where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

188.   the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage, or fatal bleeding at three years of 0.77 to 0.97 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

189.   the method results in a relative risk reduction of approximately 14% for the composite endpoint of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage, or fatal bleeding at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

190.   the method results in a relative risk reduction of 14% for the composite endpoint of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage, or fatal bleeding at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

191.   the method results in an absolute risk reduction of approximately 1.27% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

192.   the method results in an absolute risk reduction of 1.27% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

193.   the method results in an absolute risk reduction of approximately 0.53%

for cardiovascular death at three years relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

194.   the method results in an absolute risk reduction of 0.53% for

cardiovascular death at three years relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

195.   the method results in an absolute risk reduction of approximately 0.72%

for myocardial infarction at three years relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

196.   the method results in an absolute risk reduction of 0.72% for

myocardial infarction at three years relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

197.   the method results in an absolute risk reduction of approximately 0.47%

for myocardial infarction at three years relative to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

198.   the method results in an absolute risk reduction of 0.47% for

myocardial infarction relative at three years to a dosing regimen where the

patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg

only;

199.　　the method results in a composite endpoint of cardiovascular death, myocardial infarction, or stroke number needed to treat of approximately 79 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

200.　　the method results in a composite endpoint of cardiovascular death, myocardial infarction, or stroke number needed to treat of 79 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

201.　　the method results in a cardiovascular death number needed to treat of approximately 189 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

202.　　the method results in a cardiovascular death number needed to treat of 189 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

203.　　the method results in a myocardial infarction number needed to treat of approximately 139 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

204.　　the method results in a myocardial infarction number needed to treat of 139 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

205.　　the method results in a stroke number needed to treat of approximately 213 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

206.   the method results in a stroke number needed to treat of 213 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

207.   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke event of less than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

208.   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke event at three years of approximately 0.75 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

209.   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke event at three years of 0.75 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

210.   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke event at three years of 0.61 to 0.92 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the

patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

211.   the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke event at three years of 0.61 to 0.92 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

212.   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke event at three years of less than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 30 days to 1 year prior to administration;

213.   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke event at three years of approximately 0.82 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 30 days to 1 year prior to administration;

214.   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke event at three years of 0.82 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient

stopped a previous $P2Y_{12}$ inhibitor therapy 30 days to 1 year prior to administration;

215.   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke event at three years of 0.65 to 1.02 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to 1 year prior to administration;

216.   the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke event at three years of 0.65 to 1.02 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to 1 year prior to administration;

217.   the method results in a relative risk reduction of 27% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

218.   the method results in a relative risk reduction of approximately 27% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the

patient stopped a previous P2Y$_{12}$ inhibitor therapy within 30 days prior to administration;

219.   the method results in an absolute risk reduction of approximately 2.2% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous P2Y$_{12}$ inhibitor therapy within 30 days prior to administration;

220.   the method results in an absolute risk reduction of 2.2% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous P2Y$_{12}$ inhibitor therapy within 30 days prior to administration;

221.   the method results in a relative risk reduction of approximately 14% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous P2Y$_{12}$ inhibitor therapy 31 days to one year prior to administration;

222.   the method results in a relative risk reduction of 14% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient

stopped a previous P2Y$_{12}$ inhibitor therapy 31 days to one year prior to

administration;

223.   the method results in an absolute risk reduction of approximately 1.1%

for the composite endpoint of cardiovascular death, myocardial infarction, or

stroke at three years relative to a dosing regimen where the patient receives

the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the

patient stopped a previous P2Y$_{12}$ inhibitor therapy 31 days to one year prior to

administration;

224.   the method results in an absolute risk reduction of 1.1% for the

composite endpoint of cardiovascular death, myocardial infarction, or stroke at

three years relative to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient

stopped a previous P2Y$_{12}$ inhibitor therapy 31 days to one year prior to

administration;

225.   the method numerically reduces the rate of the composite endpoint of

cardiovascular death, myocardial infarction, or stroke relative to a dosing

regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only, wherein the patient stopped a previous P2Y$_{12}$ inhibitor

therapy within 30 days prior to administration;

226.   the method numerically reduces the absolute risk of the composite

endpoint of cardiovascular death, myocardial infarction, or stroke relative to a

dosing regimen where the patient receives the daily maintenance dose of

aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous P2Y$_{12}$

inhibitor therapy within 30 days prior to administration;

227.   the method results in a relative risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

228.   the method numerically reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

229.   the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of approximately 8.0%, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

230.   the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of 8.0%, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

231.   the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to administration;

232. the method results in a numerical reduction in the percentage of
patients with composite endpoint of cardiovascular death, myocardial
infarction, or stroke events relative to a dosing regimen where the patient
receives the daily maintenance dose of aspirin of 75 mg to 150 mg only,
wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days
prior to administration;

233. the method reduces the Kaplan-Meier rate for the composite endpoint
of cardiovascular death, myocardial infarction, or stroke at three years by
approximately 1.9% compared to a dosing regimen where the patient receives
the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the
patient stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to
administration;

234. the method reduces the Kaplan-Meier rate for the composite endpoint
of cardiovascular death, myocardial infarction, or stroke at three years by 1.9%
compared to a dosing regimen where the patient receives the daily
maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient
stopped a previous $P2Y_{12}$ inhibitor therapy within 30 days prior to
administration;

235. the method numerically reduces the rate of the composite endpoint of
cardiovascular death, myocardial infarction, or stroke relative to a dosing
regimen where the patient receives the daily maintenance dose of aspirin of
75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor
therapy 31 days to one year prior to administration;

236. the method numerically reduces the absolute risk of the composite
endpoint of cardiovascular death, myocardial infarction, or stroke relative to a

dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to one year prior to administration;

237. the method results in a relative risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than one to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to one year prior to administration;

238. the method numerically reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to one year prior to administration;

239. the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of approximately 8.1%, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to one year prior to administration;

240. the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of 8.1%, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to one year prior to administration;

241. the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of

aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to one year prior to administration;

242. the method results in a numerical reduction in the percentage of patients with composite endpoint of cardiovascular death, myocardial infarction, or stroke events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to one year prior to administration;

243. the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 0.6% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to one year prior to administration;

244. the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by 0.6% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only, wherein the patient stopped a previous $P2Y_{12}$ inhibitor therapy 31 days to one year prior to administration;

245. the method results in a numerical reduction in the rate of all-cause mortality compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

246. the method is as effective in reducing the rate for the composite end point of cardiovascular death, myocardial infarction, or stroke in the patient as

a method wherein the patient is administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg;

247.   the method reduces the rate of irreversible harm to the patient relative to a method wherein the patient is administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg;

248.   the method reduces the rate of the composite endpoint of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage, or fatal bleeding relative to a method wherein the patient is administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg;

249.   the method numerically reduces the rate of the composite endpoint of cardiovascular death, myocardial infarction, stroke, intracranial hemorrhage, or fatal bleeding relative to a method wherein the patient is administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg;

250.   the method improves the risk-benefit profile relative to a method wherein the patient is administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier and a daily maintenance dose of aspirin of 75 to 100 mg; or

251.   the method improves the risk-benefit profile of ticagrelor administered on a background of aspirin.

[00247]   In some embodiments, the method satisfies at least one of the following safety endpoints:

1. the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

2. the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

3. the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

4. the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

5. the method results in a numerical increase in the number of TIMI major bleeding events per 100 patient years of less than 0.5 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

6. the method results in a numerical increase in the number of TIMI major bleeding events per 100 patient years of approximately 0.44 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

7. the method results in a numerical increase in the number of TIMI major bleeding events per 100 patient years of 0.44 relative to a dosing regimen

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where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

8. the method does not result in a numerical increase in the number of fatal bleeding events per 100 patient years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

9. the method results in a numerical increase in the number of intracranial hemorrhage events per 100 patient years of approximately 0.05 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

10. the method results in a numerical increase in the number of intracranial hemorrhage events per 100 patient years of 0.05 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

11. the method results in a difference in the Kaplan-Meier rate of fatal bleeding at three years of less than 0.05% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

12. the method results in a difference in the Kaplan-Meier rate of intracranial hemorrhage at three years of less than 0.1% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

13. the method results in a Kaplan-Meier rate for fatal bleeding at three years of approximately 0.3%;

14. the method results in a Kaplan-Meier rate for fatal bleeding at three years of 0.3%;

15. the method results in a numerical decrease in the ratio of fatal bleeding
    events over TIMI major bleeding events relative to a dosing regimen where
    the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg
    only;

16. the method results in a numerical decrease in the ratio of fatal bleeding
    events over TIMI major bleeding events relative to a dosing regimen where
    the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg
    only;

17. the method results in a decrease in the ratio of fatal bleeding events over TIMI
    major bleeding events relative to a dosing regimen where the patient receives
    the daily maintenance dose of aspirin of 75 mg to 150 mg only;

18. the method results in a decrease in the ratio of fatal bleeding events over TIMI
    major bleeding events relative to a dosing regimen where the patient receives
    the daily maintenance dose of aspirin of 75 mg to 150 mg only;

19. the method results in a numerical decrease of approximately 0.13 in the ratio
    of fatal bleeding events over TIMI major bleeding events relative to a dosing
    regimen where the patient receives the daily maintenance dose of aspirin of
    75 mg to 150 mg only;

20. the method results in a numerical decrease of 0.13 in the ratio of fatal
    bleeding events over TIMI major bleeding events relative to a dosing regimen
    where the patient receives the daily maintenance dose of aspirin of 75 mg to
    150 mg only;

21. the method results in a 3-year dyspnea event rate of approximately 15.8%;

22. the method results in a 3-year dyspnea event rate of 15.8%;

23. the method results in a numerical decrease in median duration of resolved dyspnea adverse events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

24. the method results in a decrease in the median duration of resolved dyspnea adverse events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

25. the method results in a numerical decrease of approximately 18 days in the median duration of resolved dyspnea adverse events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

26. the method results in a numerical decrease of 18 days in the median duration of resolved dyspnea adverse events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

27. the method results in a numerical decrease in median duration of resolved dyspnea adverse events relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

28. the method does not result in a decrease in pulmonary function after one month;

29. the method does not result in a decrease in pulmonary function after at least six months;

30. the method does not result in a hazard ratio greater than one for renal adverse events at 3 years relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

31. the method does not result in a hazard ratio that is nominally significantly greater than one for renal adverse events at 3 years relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

32. the method does not result in a hazard ratio greater than one for gout adverse events at 3 years relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

33. the method does not result in a hazard ratio that is nominally significantly greater than one for gout adverse events at 3 years relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

34. the method does not result in a hazard ratio greater than one for bradyarrhythmia adverse events at 3 years relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

35. the method does not result in a hazard ratio that is nominally significantly greater than one for bradyarrhythmia adverse events at 3 years relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

36. the method results in syncope in approximately 0.9% of patients;

37. the method results in syncope in 0.9% of patients;

38. the method results in a reversible increase in serum uric acid levels;

39. the method results in a serum uric acid level increase of approximately 0.2 mg/dL relative to serum uric acid levels prior to administration;

40. the method results in a numerical increase in the relative risk of TIMI major bleeding of approximately 142% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only based on the final dose-exposure-response model;

41. the method results in a numerical increase in the relative risk of TIMI major bleeding of 142% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only based on the final dose-exposure-response model;

42. the method results in an absolute risk increase for TIMI major bleeding at three years of approximately 2.38% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg, wherein the patient is more than 75 years of age;

43. the method results in an absolute risk increase for TIMI major bleeding at three years of approximately 1.05% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg, wherein the patient is less than 65 years of age;

44. the method results in an absolute risk increase of approximately 1.24% for TIMI major bleeding relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

45. the method results in an absolute risk increase of 1.24% for TIMI major bleeding relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

46. the method results in an absolute risk increase of approximately 0.14% for intracranial hemorrhage relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

47. the method results in an absolute risk increase of 0.14% for intracranial hemorrhage relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

48. the method results in an absolute risk reduction of approximately 0.01% for fatal bleeding relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

49. the method results in an absolute risk reduction of 0.01% for fatal bleeding relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

50. the method results in a TIMI major bleeding number needed to harm of approximately 81 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

51. the method results in a TIMI major bleeding number needed to harm of 81 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

52. the method results in an intracranial hemorrhage number needed to harm of approximately 714 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only; or

53. the method results in an intracranial hemorrhage number needed to harm of 714 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only.

[00248]   In some embodiments, the disclosed method results in one of the efficacy endpoints recited above. In some further embodiments, the disclosed method results in at least one of the efficacy endpoints recited above. In some further embodiments, the disclosed method results in at least two of the efficacy

endpoints recited above. In still some further embodiments, the disclosed method results in two, three, or four of the efficacy endpoints recited above. In some further embodiments, the disclosed methods results in five to 251 of the efficacy endpoints recited above.

[00249]   In some embodiments, the disclosed method results in one of the safety endpoints recited above. In some further embodiments, the disclosed method results in at least one of the safety endpoints recited above. In some further embodiments, the disclosed method results in at least two of the safety endpoints recited above. In still some further embodiments, the disclosed method results in two, three, or four of the safety endpoints recited above. In some further embodiments, the disclosed methods results in five to 53 of the safety endpoints recited above.

[00250]   In some embodiments, the disclosed method results in one of the efficacy endpoints recited above and one of the safety endpoints recited above. In some further embodiments, the disclosed method results in at least one of the efficacy endpoints recited above and at least one of the safety endpoints recited above. In still some further embodiments, the disclosed method results in two, three, four, five, or six of the efficacy endpoints recited above and two, three, four, five, or six of the safety endpoints recited above. In some further embodiments, the disclosed method results in one to 251 of the efficacy endpoints recited above and one to 53 of the safety endpoints recited above.

[00251]   For example, in some embodiments, the method satisfies at least one of the following combined safety and efficacy conditions:

(a) the method numerically reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years

relative to a dosing regimen where the patient receives the daily maintenance dose

of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio

for fatal bleeding at 3 years of greater than one relative to a dosing regimen where

the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(b) the method results in a relative risk of the composite endpoint of

cardiovascular death, myocardial infarction, or stroke of less than one relative to a

dosing regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only and the method does not result in a hazard ratio for fatal

bleeding at 3 years of greater than one relative to a dosing regimen where the

patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(c) the method numerically reduces the Kaplan-Meier rate for the composite

endpoint of cardiovascular death, myocardial infarction, or stroke compared to a

dosing regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only and the method does not result in a hazard ratio for fatal

bleeding at 3 years of greater than one relative to a dosing regimen where the

patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(d) the method results in a statistically significant reduction in the rate of the

composite endpoint of cardiovascular death, myocardial infarction, or stroke relative

to a dosing regimen where the patient receives the daily maintenance dose of aspirin

of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal

bleeding at 3 years of greater than one relative to a dosing regimen where the

patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(e) the method results in a relative risk of the composite endpoint of

cardiovascular death, myocardial infarction, or stroke that is statistically significantly

less than one relative to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(f) the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of approximately 7.8% and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(g) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(h) the method results in a numerical reduction in the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(i) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke that is statistically significantly less than 1 relative to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(j) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of approximately 0.84 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(k) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(l) the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(m) the method reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.27% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(n) the method results in a relative risk reduction of approximately 17% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(o) the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only; or

(p) the method reduces the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.3% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result

in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only.

[00252]   In some other exemplary embodiments, the method satisfies at least one of the following combined safety and efficacy conditions:

(a) the method numerically reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(b) the method results in a relative risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(c) the method numerically reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to

a dosing regimen where the patient receives a daily maintenance dose of aspirin of

75 mg to 150 mg only;

(d) the method results in a statistically significant reduction in the rate of the

composite endpoint of cardiovascular death, myocardial infarction, or stroke relative

to a dosing regimen where the patient receives the daily maintenance dose of aspirin

of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal

bleeding at 3 years that is nominally significantly greater than one relative to

a dosing regimen where the patient receives a daily maintenance dose of aspirin of

75 mg to 150 mg only;

(e) the method results in a relative risk of the composite endpoint of

cardiovascular death, myocardial infarction, or stroke that is statistically significantly

less than one relative to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result

in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater

than one relative to a dosing regimen where the patient receives a daily maintenance

dose of aspirin of 75 mg to 150 mg only;

(f) the method results in a Kaplan-Meier rate for the composite endpoint of

cardiovascular death, myocardial infarction, or stroke at three years of approximately

7.8% and the method does not result in a hazard ratio for fatal bleeding at 3 years

that is nominally significantly greater than one relative to a dosing regimen where the

patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(g) the method results in a hazard ratio for time to first composite endpoint of

cardiovascular death, myocardial infarction, or stroke of less than 1 relative to a

dosing regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only and the method does not result in a hazard ratio for fatal

bleeding at 3 years that is nominally significantly greater than one relative to

a dosing regimen where the patient receives a daily maintenance dose of aspirin of

75 mg to 150 mg only;

(h) the method results in a numerical reduction in the percentage of patients

with composite endpoint events of cardiovascular death, myocardial infarction, or

stroke relative to a dosing regimen where the patient receives the daily maintenance

dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard

ratio for fatal bleeding at 3 years that is nominally significantly greater than one

relative to a dosing regimen where the patient receives a daily maintenance dose of

aspirin of 75 mg to 150 mg only;

(i) the method results in a hazard ratio for time to first composite endpoint of

cardiovascular death, myocardial infarction, or stroke that is statistically significantly

less than 1 relative to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result

in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater

than one relative to a dosing regimen where the patient receives a daily maintenance

dose of aspirin of 75 mg to 150 mg only;

(j) the method results in a hazard ratio for time to first composite endpoint of

cardiovascular death, myocardial infarction, or stroke at three years of approximately

0.84 relative to a dosing regimen where the patient receives the daily maintenance

dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard

ratio for fatal bleeding at 3 years that is nominally significantly greater than one

relative to a dosing regimen where the patient receives a daily maintenance dose of

aspirin of 75 mg to 150 mg only;

(k) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at 3 years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(l) the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at 3 years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(m) the method reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.27% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(n) the method results in a relative risk reduction of approximately 17% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard

ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(o) the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only; or

(p) the method reduces the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke at 3 years by approximately 1.3% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only.

[00253]   In some further exemplary embodiments, the method satisfies at least one of the following combined safety and efficacy conditions:

(a) the method numerically reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(b) the method results in a relative risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(c) the method numerically reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(d) the method results in a statistically significant reduction in the rate of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(e) the method results in a relative risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke that is statistically significantly less than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result

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in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(f) the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of approximately 7.8% and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(g) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(h) the method results in a numerical reduction in the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(i) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke that is statistically significantly less than 1 relative to a dosing regimen where the patient receives the daily

maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(j) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at 3 years of approximately 0.84 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(k) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at 3 years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(l) the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at 3 years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(m) the method reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.27% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(n) the method results in a relative risk reduction of approximately 17% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(o) the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only; or

(p) the method reduces the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke at 3 years by approximately 1.3% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result

in a hazard ratio for intracranial hemorrhage at 3 years of greater than one relative to

a dosing regimen where the patient receives a daily maintenance dose of aspirin of

75 mg to 150 mg only.

[00254]   In some still further exemplary embodiments, the method satisfies at

least one of the following combined safety and efficacy conditions:

(a) the method numerically reduces the absolute risk of the composite

endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing

regimen where the patient receives the daily maintenance dose of aspirin of 75 mg

to 150 mg only and the method does not result in a hazard ratio for intracranial

hemorrhage at 3 years that is nominally significantly greater than one relative to

a dosing regimen where the patient receives a daily maintenance dose of aspirin of

75 mg to 150 mg only;

(b) the method results in a relative risk of the composite endpoint of

cardiovascular death, myocardial infarction, or stroke of less than one relative to a

dosing regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only and the method does not result in a hazard ratio for

intracranial hemorrhage at 3 years that is nominally significantly greater than one

relative to a dosing regimen where the patient receives a daily maintenance dose of

aspirin of 75 mg to 150 mg only;

(c) the method numerically reduces the Kaplan-Meier rate for the composite

endpoint of cardiovascular death, myocardial infarction, or stroke compared to a

dosing regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only and the method does not result in a hazard ratio for

intracranial hemorrhage at 3 years that is nominally significantly greater than one

relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(d) the method results in a statistically significant reduction in the rate of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(e) the method results in a relative risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke that is statistically significantly less than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(f) the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of approximately 7.8% and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(g) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke of less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of

75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(h) the method results in a numerical reduction in the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(i) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke that is statistically significantly less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(j) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at 3 years of approximately 0.84 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(k) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at 3 years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(l) the method results in a 95% confidence interval for the hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke at 3 years of 0.74 to 0.95 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(m) the method reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.27% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(n) the method results in a relative risk reduction of approximately 17% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard

ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(o) the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only; or

(p) the method reduces the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke at 3 years by approximately 1.3% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only.

[00255]   In some embodiments, the method results in a numerical reduction in the rate of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only.

[00256]   In some embodiments, the method results in a statistically significant reduction in the rate of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only.

[00257]   In some embodiments, the method results in a numerical reduction in the rate of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only.

[00258]   In some embodiments, the method results in a statistically significant reduction in the rate of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only.

[00259]   In some embodiments, the method results in a statistically significant reduction in the rate of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result

in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only.

[00260] In some embodiments, the method results in a statistically significant reduction in the rate of the composite endpoint of cardiovascular death, myocardial infarction, or stroke relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only and the method does not result in a hazard ratio for intracranial hemorrhage at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only.

[00261] The discussion of documents, acts, materials, devices, articles and the like is included in this specification solely for the purpose of providing a context for the present invention. It is not suggested or represented that any or all of these matters formed part of the prior art base or were common general knowledge in the field relevant to the present invention as it existed before the priority date of each claim of this application.

[00262] Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises", is not intended to exclude other additives, components, integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1.   A method for reducing the rate of a composite endpoint of cardiovascular death, myocardial infarction, or stroke in a patient in recognized need thereof, comprising administering to the patient twice daily a pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier;

wherein the patient has a history of myocardial infarction at least 12 months prior to the twice daily administration of the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier;

wherein the patient is also administered a daily maintenance dose of aspirin of 75 mg to 150 mg;

wherein the method results in a statistically significant reduction in the rate of the composite endpoint relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only; and

wherein the method does not result in a hazard ratio for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only.

2.   The method of claim 1, wherein the daily maintenance dose of aspirin is 75 mg to 100 mg.

3.   The method of claim 1 or claim 2, wherein the patient has a history of myocardial infarction 12 to 36 months prior to the twice daily administration of the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier.

4.   The method of any one of claims 1 to 3, wherein the patient has a history of myocardial infarction as a result of an acute coronary syndrome.

5.   The method of claim 4, wherein prior to the administration, the patient was administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier for a portion of 12 months after the acute coronary syndrome.

6.   The method of claim 4, wherein prior to the administration, the patient was administered twice daily a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier for 12 months after the acute coronary syndrome.

7.   The method of claim 5 or claim 6, wherein the patient was administered a pharmaceutical composition comprising a 180 mg ticagrelor loading dose prior to administration twice daily of a pharmaceutical composition comprising 90 mg ticagrelor and a pharmaceutically acceptable carrier for a portion of the 12 months after the acute coronary syndrome.

8.   The method of any one of claims 1 to 7, wherein the method satisfies at least one of the following conditions:

(a) the method numerically reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(b) the method results in a Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years of approximately 7.8%;

(c) the method results in a hazard ratio for time to first composite endpoint of cardiovascular death, myocardial infarction, or stroke that is statistically significantly less than 1 relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(d) the method reduces the absolute risk of the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.27% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(e) the method results in a relative risk reduction of approximately 17% for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only;

(f) the method reduces the Kaplan-Meier rate for the composite endpoint of cardiovascular death, myocardial infarction, or stroke at three years by approximately

1.2% compared to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only; or

(g) the method reduces the percentage of patients with composite endpoint events of cardiovascular death, myocardial infarction, or stroke at three years by approximately 1.3% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only.

9.   The method of any one of claims 1 to 8, wherein the method satisfies at least one of the following conditions:

(a) the method does not result in a hazard ratio for fatal bleeding at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(b) the method does not result in a relative risk for fatal bleeding at 3 years that is nominally significantly greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only;

(c) the method does not result in a relative risk for intracranial hemorrhage at 3 years of greater than one relative to a dosing regimen where the patient receives a daily maintenance dose of aspirin of 75 mg to 150 mg only; or

(d) the method results in a difference in the Kaplan-Meier rate of fatal bleeding at three years of less than 0.05% relative to a dosing regimen where the patient receives the daily maintenance dose of aspirin of 75 mg to 150 mg only.

10. The method of any one of claims 1 to 9, wherein the method satisfies condition (a) of claim 9.

11. The method of any one of claims 1 to 9, wherein the method satisfies condition (b) of claim 9.

12. The method of any one of claims 1 to 9, wherein the method satisfies condition (c) of claim 9.

13. The method of any one of claims 1 to 9, wherein the method satisfies condition (d) of claim 9.

14. The method of any one of claims 1 to 13, wherein the pharmaceutical composition comprising 60 mg ticagrelor and a pharmaceutically acceptable carrier is a tablet administered orally.

15. The method of claim 14, wherein the tablet comprises a filler present in an amount of 20 to 70% by weight, a binder present in an amount of 3 to 6% by weight, a disintegrant present in an amount of 2 to 6% by weight, and a lubricant present in an amount of 0.5 to 1% by weight.

16. A method for reducing the rate of a composite endpoint of cardiovascular death, myocardial infarction, or stroke in a patient in recognized need thereof, comprising

administering to the patient twice daily a pharmaceutical composition comprising 60 mg

ticagrelor and a pharmaceutically acceptable carrier;

wherein the patient has or had acute coronary syndrome;

wherein the patient is also administered a daily maintenance dose of aspirin of

75 mg to 150 mg; and

wherein the rate of the composite endpoint in the patient is reduced relative to a

dosing regimen where the patient receives the daily maintenance dose of aspirin of 75

mg to 150 mg only.

17.   The method of claim 16, wherein the patient has acute coronary syndrome.

18.   The method of claim 16, wherein the daily maintenance dose of aspirin is 75 mg

to 100 mg.

Figure 1

Preliminary data – pending verification

Randomized
21,162

Randomized to Ticagrelor 90 BID
(n=7050)

Received at least 1 dose (n=6988, 99%)
Never received a dose (n=62)

Premature permanent drug discontinuation
(n=2,233, 32%)

Due to adverse event (n=1434)
Due to patient decision (n=689)
Due to protocol non-compliance (n=35)
Other (n=43)

Withdrew Consent (n=52)
Vital status known (alive/dead) (n=48)
Not listed as dead in registry (n=3)
Vital status not searched (n=1)

Died during follow up (n=334)

Lost to Follow-up* (n=3)

Included in Primary Efficacy Analysis
(n=7050)

Included in Primary Safety Analysis
(n=6988)

Excluded because never received
study drug (n=62)

Randomized to Ticagrelor 60 BID
(n=7045)

Received at least 1 dose (n=6958, 99%)
Never received a dose (n=87)

Premature permanent drug discontinuation
(n=1,999, 29%)

Due to adverse event (n=1257)
Due to patient decision (n=635)
Due to protocol non-compliance (n=23)
Other (n=46)

Withdrew Consent (n=50)
Vital status known (alive/dead) (n=46)
Not listed as dead in registry (n=2)
Vital status not searched (n=2)

Died during follow up (n=297)

Lost to Follow-up* (n=6)

Included in Primary Efficacy Analysis
(n=7045)

Included in Primary Safety Analysis
(n=6958)

Excluded because never received
study drug (n=87)

Randomized to Placebo
(n=7067)

Received at least 1 dose (n=6996, 99%)
Never received a dose (n=71)

Premature permanent drug discontinuation
(n=1,496, 21%)

Due to adverse event (n=784)
Due to patient decision (n=590)
Due to protocol non-compliance (n=16)
Other (n=61)

Withdrew Consent (n=52)
Vital status known (alive/dead) (n=47)
Not listed as dead in registry (n=4)
Vital status not searched (n=1)

Died during follow up (n=331)

Lost to Follow-up* (n=1)

Included in Primary Efficacy Analysis
(n=7067)

Included in Primary Safety Analysis
(n=6996)

Excluded because never received
study drug (n=71)

*Did not have a contact after the Common Study End Date (CSED) or not listed in death registry

Figure 2-Panel A

Cardiovascular Death, MI, or Stroke

Figure 2-Panel B

End point	3-year KM Event Rates		HR (95% CI)	P value
	Ticagrelor	Placebo		
CV Death, MI, or Stroke	7.85%	9.04%	0.85 (0.75-0.96)	0.0080
	7.77%	9.04%	0.84 (0.74-0.95)	0.0043
	7.81%	9.04%	0.84 (0.76-0.94)	0.0012
CV Death	2.94%	3.39%	0.87 (0.71-1.06)	0.15
	2.86%	3.39%	0.83 (0.68-1.01)	0.068
	2.90%	3.39%	0.85 (0.71-1.00)	0.057
Myocardial Infarction	4.40%	5.25%	0.81 (0.69-0.95)	0.010
	4.53%	5.25%	0.84 (0.72-0.98)	0.031
	4.47%	5.25%	0.83 (0.72-0.95)	0.0055
Stroke	1.61%	1.94%	0.82 (0.63-1.07)	0.14
	1.47%	1.94%	0.75 (0.57-0.98)	0.034
	1.54%	1.94%	0.78 (0.62-0.98)	0.034

Legend: Ticagrelor 90 mg twice daily; Ticagrelor 60 mg twice daily; Ticagrelor pooled

Ticagrelor better   Placebo better

0.4   0.6   0.8   1   1.25   1.67

Figure 3.

Ti = Ticagrelor BID, CI = Confidence interval; HR = Hazard ratio; KM = Kaplan-Meier; N = Number of patients.

Figure 4.

Characteristics	HR (95% CI)	Ticagrelor n/N (%/yr)	Placebo n/N (%/yr)	HR (95% CI)
Overall Treatment Effect				
Primary endpoint (100%)		487/7045 (2.62)	578/7067 (3.10)	0.84 (0.74, 0.95)
Age group				
<65 years (46%)		195/3283 (2.24)	243/3154 (2.93)	0.76 (0.63, 0.91)
65-75 years (42%)		209/2913 (2.71)	225/3074 (2.76)	0.98 (0.81, 1.18)
>75 years (12%)		83/849 (3.81)	110/839 (5.01)	0.76 (0.57, 1.01)
Sex				
Male (76%)		351/5384 (2.47)	435/5350 (3.09)	0.79 (0.69, 0.91)
Female (24%)		136/1661 (3.09)	143/1717 (3.14)	0.98 (0.78, 1.24)
Race				
Caucasian (86%)		411/6077 (2.55)	509/6124 (3.13)	0.81 (0.71, 0.92)
Non-Caucasian (14%)		76/968 (3.09)	69/943 (2.90)	1.07 (0.77, 1.48)
Weight group				
<70 kg (23%)		112/1636 (2.63)	145/1575 (3.54)	0.74 (0.58, 0.95)
70-90 kg (50%)		232/3457 (2.53)	277/3658 (2.86)	0.88 (0.74, 1.05)
>90 kg (27%)		142/1941 (2.74)	155/1822 (3.23)	0.85 (0.67, 1.06)
BMI				
<30 kg/m^2 (67%)		290/4692 (2.35)	391/4827 (3.07)	0.76 (0.65, 0.88)
>=30 kg/m^2 (32%)		194/2335 (3.13)	186/2223 (3.18)	0.99 (0.81, 1.21)
Geographic region				
US (12%)		65/863 (2.93)	82/872 (3.67)	0.78 (0.56, 1.08)
Outside US (88%)		422/6182 (2.58)	496/6195 (3.03)	0.85 (0.74, 0.96)
History of >1 MI (>=1 year prior to randomization)				
Yes (17%)		143/1168 (4.66)	168/1188 (5.43)	0.85 (0.68, 1.06)
No (83%)		344/5876 (2.21)	410/5879 (2.64)	0.83 (0.72, 0.96)
Time from qualifying MI to randomization				
<2 years (61%)		293/4331 (2.60)	375/4333 (3.34)	0.77 (0.66, 0.90)
>=2 years (38%)		194/2704 (2.65)	202/2724 (2.74)	0.96 (0.79, 1.17)
Type of qualifying MI				
STEMI (54%)		218/3757 (2.19)	268/3809 (2.68)	0.81 (0.68, 0.97)
NSTEMI (40%)		231/2842 (3.09)	262/2843 (3.47)	0.89 (0.74, 1.06)
Diabetes Mellitus				
Yes (32%)		205/2308 (3.38)	239/2257 (4.03)	0.83 (0.69, 1.00)
No (68%)		282/4736 (2.25)	339/4810 (2.67)	0.84 (0.72, 0.98)
Multivessel Coronary Artery Disease				
Yes (60%)		290/4190 (2.64)	355/4213 (3.23)	0.81 (0.70, 0.95)
No (40%)		196/2852 (2.57)	223/2854 (2.92)	0.88 (0.72, 1.06)
Creatinine clearance (Cockroft Gault) at enrolment				
<60 mL/min (19%)		128/1320 (3.75)	184/1382 (5.09)	0.72 (0.58, 0.91)
>=60 mL/min (79%)		352/5610 (2.36)	383/5565 (2.60)	0.90 (0.78, 1.05)
History of PCI				
Yes (83%)		362/5874 (2.34)	430/5835 (2.79)	0.83 (0.72, 0.96)
No (17%)		125/1170 (4.03)	148/1231 (4.61)	0.87 (0.68, 1.10)
Type of stent				
Any DES (39%)		188/2769 (2.63)	222/2784 (3.08)	0.85 (0.70, 1.03)
BMS only (36%)		140/2598 (2.00)	156/2532 (2.29)	0.87 (0.69, 1.09)
Current smoker				
Yes (17%)		94/1206 (2.99)	108/1143 (3.64)	0.82 (0.62, 1.08)
No (83%)		393/5838 (2.54)	469/5919 (3.00)	0.84 (0.74, 0.96)
Time since prev. ADP receptor blocker treatment				
<30 days (34%)		165/2391 (2.70)	216/2403 (3.52)	0.76 (0.62, 0.93)
30 days to 12 months (32%)		143/2231 (2.41)	175/2230 (2.98)	0.81 (0.65, 1.01)
>12 months (23%)		108/1661 (2.39)	100/1645 (2.21)	1.08 (0.82, 1.42)

0.5   0.75   1.0   1.5   2.0

Ticagrelor Better | Placebo Better

Figure 5.

Cardiovascular Death, Myocardial Infarction, or Stroke

▤ Ticagrelor 90 mg bid
☐ Ticagrelor 60 mg bid

	Total	Treatment KM	Placebo KM	HR (95%CI)	P-Value for Interaction
Age at randomization					
Age >=75	2,065	13.94%	13.50%	1.02 (0.80,1.30)	0.0885
	2,045	11.02%	13.50%	0.77 (0.59,1.01)	0.4965
Age <75	12,052	6.77%	8.27%	0.80 (0.70,0.92)	
	12,067	7.23%	8.27%	0.86 (0.75,0.98)	
Sex					
Male	10,718	8.23%	8.99%	0.89 (0.77,1.02)	0.2115
	10,734	7.37%	8.99%	0.79 (0.69,0.91)	0.122
Female	3,399	6.67%	9.15%	0.74 (0.57,0.95)	
	3,378	9.03%	9.15%	0.98 (0.78,1.24)	
Type of MI					
QE NSTEMI	5,741	9.53%	10.14%	0.92 (0.77,1.09)	0.3967
	5,685	9.32%	10.14%	0.89 (0.74,1.06)	0.6315
QE STEMI	7,572	6.52%	7.83%	0.81 (0.68,0.97)	
	7,566	6.43%	7.83%	0.81 (0.68,0.97)	
QE MI unknown	804	8.17%	12.43%	0.68 (0.44,1.07)	
	861	9.24%	12.43%	0.72 (0.47,1.11)	
Time from MI					
Qualifying MI < 2 years prior	8,649	8.15%	9.74%	0.83 (0.71,0.96)	0.5793
	8,664	7.79%	9.74%	0.77 (0.66,0.90)	0.0868
Qualifying MI >= 2 years prior	5,451	7.33%	7.94%	0.89 (0.72,1.08)	
	5,428	7.76%	7.94%	0.96 (0.79,1.17)	
Any Diabetes					
Hx Diabetes	4,498	10.14%	11.60%	0.85 (0.71,1.03)	0.9735
	4,565	10.00%	11.60%	0.83 (0.69,1.00)	0.9552
NO Hx Diabetes	9,619	6.77%	7.83%	0.85 (0.73,0.99)	
	9,546	6.68%	7.83%	0.84 (0.72,0.98)	
ASA does at 75mg					
ASA dose > 75mg at rand	10,983	7.74%	8.76%	0.87 (0.76,1.00)	0.6225
	10,943	7.71%	8.76%	0.86 (0.75,0.98)	0.8336
ASA dose <= 75mg at rand	2,728	7.46%	9.03%	0.81 (0.61,1.06)	
	2,769	7.72%	9.03%	0.83 (0.63,1.09)	
History of PCI					
Hx Prior PCI	11,689	7.20%	8.09%	0.85 (0.74,0.98)	0.8849
	11,716	6.87%	8.09%	0.83 (0.72,0.96)	0.7151
No Hx Prior PCI	2,426	10.97%	13.44%	0.84 (0.66,1.06)	
	2,394	12.06%	13.44%	0.87 (0.69,1.11)	
Regions					
North America	2,610	9.12%	9.77%	0.86 (0.66,1.13)	0.9951
	2,600	7.79%	9.77%	0.75 (0.57,0.99)	0.827
South America	1,644	8.60%	9.75%	0.83 (0.60,1.16)	
	1,636	9.94%	9.75%	0.90 (0.65,1.24)	
Europe	8,282	7.64%	8.96%	0.85 (0.73,1.00)	
	8,300	7.54%	8.96%	0.85 (0.72,0.99)	
Asia	1,581	6.08%	6.86%	0.82 (0.54,1.23)	
	1,576	7.11%	6.86%	0.90 (0.60,1.34)	

0.4   0.6   0.8   1.0   1.2   1.4
Hazard Ratio

Figure 6.

Characteristics	HR (95% CI)	Total Patients	KM % at Month 36 Ti / PI	HR (95% CI)	p-value (int)
Primary endpoint					
	■	14117	7 8 9 0	0 85 (0 75 0 96)	
	□	14112	7 8 9 0	0 84 (0 74 0 95)	
Age group					
<65 Years	■	6344	6 1 8 6	0 70 (0 58 0 85)	0 0492
	□	6437	6 7 8 6	0 76 (0 63 0 91)	0 1243
65-75 Years	■	6051	7 8 8 0	0 95 (0 78 1 14)	
	□	5987	8 0 8 0	0 98 (0 81 1 18)	
>75 Years	■	1722	14 1 14 4	0 97 (0 74 1 25)	
	□	1685	11 5 14 4	0 76 (0 57 1 01)	
Sex					
Male	■	10718	8 2 9 0	0 89 (0 77 1 02)	0 2115
	□	10734	7 4 9 0	0 79 (0 69 0 91)	0 1220
Female	■	3399	6 7 9 2	0 74 (0 57 0 95)	
	□	3378	9 0 9 2	0 98 (0 78 1 24)	
Race					
Caucasian	■	12250	8 1 9 1	0 86 (0 76 0 98)	0 4947
	□	12201	7 6 9 1	0 81 (0 71 0 92)	0 1185
Not Caucasian	■	1867	5 9 8 3	0 75 (0 53 1 08)	
	□	1911	8 8 8 3	1 07 (0 77 1 48)	
Weight group					
<70 kg	■	3148	7 6 10 2	0 75 (0 59 0 96)	0 2050
	□	3211	8 1 10 2	0 74 (0 58 0 94)	0 4955
70-90 kg	■	7173	8 2 8 4	0 94 (0 80 1 12)	
	□	7115	7 5 8 4	0 88 (0 74 1 05)	
>90 kg	■	3776	7 3 9 4	0 76 (0 60 0 96)	
	□	3763	8 0 9 4	0 84 (0 67 1 06)	
BMI					
<30 kg/m^2	■	9558	7 8 8 8	0 86 (0 74 0 99)	0 7277
	□	9519	7 0 8 8	0 76 (0 65 0 88)	0 0386
>=30 kg/m^2	■	4530	7 8 9 6	0 82 (0 66 1 01)	
	□	4558	9 3 9 6	0 99 (0 81 1 21)	
Geographic region					
Asia and Australia	■	1581	6.1 6 9	0.82 (0.54, 1.23)	0.9951
	□	1576	7.1 6 9	0.89 (0.60, 1.33)	0.8270
Europe and South Africa	■	8282	7 6 9 0	0.85 (0.73, 1.00)	
	□	8300	7 5 9 0	0.85 (0.72, 0.99)	
North America	■	2610	9 1 9 8	0 86 (0.66, 1.13)	
	□	2600	7 8 9 8	0.75 (0.57, 0.99)	
South America	■	1644	8 6 9 8	0.83 (0 60, 1.16)	
	□	1636	9.9 9 8	0.90 (0.65, 1.24)	
> 1 MI prior to rand.					
Yes	■	2331	14.7 15.2	0.91 (0.73, 1.13)	0.5412
	□	2356	13.7 15 2	0.85 (0.68, 1 06)	0.8804
No	■	11786	6 5 7.8	0.83 (0.72, 0.96)	
	□	11755	6.6 7.8	0.83 (0.72, 0.96)	
Time fr. qualifying MI to rand.					
<2 years	■	8649	8.1 9 7	0.83 (0.71, 0.96)	0.5721
	□	8664	7 8 9.7	0.77 (0.66, 0.90)	0.0855
>= 2 years	■	5447	7 3 7.9	0.89 (0.73, 1.09)	
	□	5426	7 8 7 9	0.96 (0.79, 1.17)	
Type of qualifying MI					
STEMI	■	7572	6.5 7.8	0.81 (0.68, 0.97)	0.3354
	□	7566	6 4 7 8	0.81 (0.68, 0.97)	0 5033
NSTEMI	■	5741	9 5 10 1	0.92 (0.77, 1.09)	
	□	5685	9 3 10 1	0.88 (0 74, 1.06)	

0.6 0.8 1 1.2 1.6 2

■ Ticagrelor 90mg bd vs. Placebo
□ Ticagrelor 60mg bd vs. Placebo

Figure 7.

Characteristics	HR (95% CI)	Total Patients	KM % at Month 36 Ti. Pl	HR (95% CI)	p-value (int.)
Primary endpoint		14117	7.8 9.0	0.85 (0.75, 0.96)	
		14112	7.8 9.0	0.84 (0.74, 0.95)	
Creatinine cl. (Cockcroft Gault) enrollm					
<60 mL/min		2739	12.4 14.8	0.84 (0.68, 1.04)	0.8957
		2682	11.1 14.8	0.73 (0.58, 0.91)	0.1250
>=60 mL/min		11084	6.8 7.6	0.86 (0.74, 0.99)	
		11125	7.0 7.6	0.90 (0.78, 1.04)	
History of PCI					
Yes		11681	7.2 8.1	0.85 (0.74, 0.98)	0.8718
		11709	6.9 8.1	0.83 (0.72, 0.96)	0.7848
No		2434	11.0 13.5	0.84 (0.66, 1.06)	
		2401	12.0 13.5	0.87 (0.68, 1.10)	
History of coronary stent implantation					
Yes		11233	7.1 8.0	0.86 (0.75, 0.99)	0.5646
		11279	6.8 8.0	0.84 (0.73, 0.97)	0.9464
No		2837	10.5 13.2	0.80 (0.64, 1.00)	
		2785	11.7 13.2	0.85 (0.68, 1.06)	
Type of Stent					
Any DES		5525	8.3 8.7	0.89 (0.73, 1.07)	0.9060
		5553	7.5 8.7	0.85 (0.70, 1.03)	0.8611
BMS only		5119	5.9 6.9	0.87 (0.69, 1.09)	
		5130	6.0 6.9	0.87 (0.69, 1.09)	
Current smoker at enrollment					
Yes		2330	9.3 10.6	0.86 (0.65, 1.13)	0.9203
		2349	9.0 10.6	0.81 (0.62, 1.07)	0.8232
No		11779	7.6 8.7	0.85 (0.74, 0.97)	
		11757	7.5 8.7	0.84 (0.74, 0.96)	
Time fr. previous ADP rec. block.					
<30 days		4797	7.3 10.0	0.68 (0.56, 0.84)	0.0839
		4790	8.2 10.0	0.76 (0.62, 0.93)	0.1078
30 days to 12 months		4416	8.1 8.7	0.91 (0.73, 1.13)	
		4461	7.1 8.7	0.81 (0.65, 1.00)	
>12 months		3321	6.2 6.8	0.96 (0.72, 1.26)	
		3306	7.0 6.8	1.08 (0.82, 1.42)	
ASA dose at randomization					
<=75 mg		2753	7.4 9.1	0.79 (0.60, 1.04)	0.6220
		2789	7.7 9.1	0.82 (0.63, 1.07)	0.8449
>75 mg		11328	7.8 9.0	0.86 (0.75, 0.98)	
		11291	7.7 9.0	0.84 (0.74, 0.97)	
History of angina					
Yes		4331	9.6 11.4	0.83 (0.68, 1.00)	0.7336
		4397	10.1 11.4	0.88 (0.73, 1.07)	0.4581
No		9785	7.1 7.9	0.86 (0.74, 1.01)	
		9714	6.7 7.9	0.81 (0.69, 0.94)	

0.6   0.8   1   1.2   1.6   2

■ Ticagrelor 90mg bd vs. Placebo
□ Ticagrelor 60mg bd vs. Placebo

Figure 8.

Figure 9.

Characteristics	HR (95% CI)	Total Patients	KM % at Month 36 Ti Pi	HR (95% CI)	p-value (int.)
TIMI Major bleeding					
		13954	2.6 1.1	2.69 (1.96, 3.70)	
		13954	2.3 1.1	2.32 (1.68, 3.21)	
Age group					
<65 Years		6283	2.2 0.9	2.80 (1.67, 4.68)	0.7138
		6376	1.5 0.9	1.86 (1.08, 3.21)	0.5484
65-75 Years		5999	2.3 1.1	2.37 (1.45, 3.87)	
		5918	2.8 1.1	2.78 (1.72, 4.47)	
>75 Years		1702	5.5 1.8	3.39 (1.65, 6.98)	
		1661	4.1 1.8	2.51 (1.18, 5.32)	
Sex					
Male		10619	2.7 1.1	2.78 (1.94, 3.97)	0.6721
		10614	2.3 1.1	2.27 (1.57, 3.27)	0.7866
Female		3365	2.1 1.1	2.34 (1.17, 4.71)	
		3340	2.3 1.1	2.52 (1.27, 5.00)	
Race					
Caucasian		12145	2.5 1.1	2.61 (1.85, 3.68)	0.6497
		12071	2.1 1.1	2.05 (1.44, 2.93)	0.1417
Not Caucasian		1839	3.0 1.0	3.23 (1.37, 7.65)	
		1883	3.6 1.0	4.04 (1.76, 9.29)	
Race					
Caucasian		12145	2.5 1.1	2.61 (1.85, 3.68)	
		12071	2.1 1.1	2.05 (1.44, 2.93)	
Black		229	1.1 1.1	1.04 (0.07, 16.7)	
		240	6.1 1.1	5.31 (0.64, 44.1)	
Asian		1491	2.9 1.1	3.03 (1.19, 7.74)	
		1511	3.2 1.1	3.59 (1.44, 8.93)	
Other		128	7.4	3E5 (0.00, ****)	
		132	2.7	1E5 (0.00, ****)	
Weight group					
<60 kg		1011	3.2 2.0	2.52 (0.96, 6.63)	0.8872
		1018	3.6 2.0	2.43 (0.94, 6.33)	0.9138
>=60 kg		12959	2.6 1.0	2.71 (1.94, 3.80)	
		12927	2.2 1.0	2.30 (1.63, 3.24)	

1   2   3   4 5   7 10

■ Ticagrelor 90mg bd vs Placebo
☐ Ticagrelor 60mg bd vs Placebo

Figure 10.

Characteristics	HR (95% CI)	Total Patients	KM % at Month 36 Ti	PI	HR (95% CI)	p-value (int.)
TIMI Major bleeding						
		13984	2.6	1.1	2.69 (1.96, 3.70)	
		13954	2.3	1.1	2.32 (1.68, 3.21)	
Weight group						
<70 kg		3116	3.0	1.9	1.84 (1.08, 3.13)	0.2291
		3170	2.7	1.9	1.38 (0.79, 2.40)	0.0548
70-90 kg		7105	2.5	0.8	3.46 (2.08, 5.74)	
		7043	2.4	0.8	3.47 (2.09, 5.75)	
>90 kg		3749	2.5	0.8	2.95 (1.52, 5.70)	
		3732	1.8	0.8	2.18 (1.10, 4.33)	
BMI						
<30 kg/m^2		9469	2.6	1.2	2.45 (1.69, 3.56)	0.3639
		9419	2.3	1.2	2.10 (1.44, 3.07)	0.3305
>=30 kg/m^2		4492	2.5	0.8	3.44 (1.84, 6.43)	
		4514	2.2	0.8	3.02 (1.61, 5.67)	
Geographic region						
Asia and Australia		1558	3.0	1.4	2.39 (1.03, 5.53)	0.9151
		1553	3.7	1.4	3.23 (1.45, 7.19)	0.6507
Europe and South Africa		8209	2.2	0.9	2.74 (1.75, 4.30)	
		8209	1.7	0.9	2.09 (1.31, 3.33)	
North America		2585	3.1	1.4	2.36 (1.18, 4.73)	
		2573	3.6	1.4	2.67 (1.36, 5.24)	
South America		1632	3.5	1.1	3.41 (1.45, 8.03)	
		1619	2.0	1.1	1.57 (0.60, 4.13)	
> 1 MI prior to rand.						
Yes		2311	2.3	0.7	3.39 (1.43, 8.01)	0.5693
		2329	3.2	0.7	3.81 (1.64, 8.85)	0.2009
No		11673	2.7	1.1	2.59 (1.84, 3.65)	
		11625	2.1	1.1	2.10 (1.48, 2.99)	
Time fr. qualifying MI to rand.						
<2 years		8562	2.4	1.2	2.19 (1.48, 3.23)	0.0699
		8566	2.4	1.2	2.05 (1.38, 3.03)	0.2262
>= 2 years		5403	2.9	0.7	4.15 (2.34, 7.35)	
		5369	2.2	0.7	3.17 (1.76, 5.70)	
Type of qualifying MI						
STEMI		7500	2.8	0.9	3.10 (1.98, 4.86)	0.6014
		7484	2.1	0.9	2.42 (1.52, 3.84)	0.8640
NSTEMI		5688	2.4	1.1	2.59 (1.57, 4.28)	
		5625	2.7	1.1	2.57 (1.56, 4.23)	

1   2   3   4   5   7   10

■ Ticagrelor 90mg bd vs. Placebo
□ Ticagrelor 60mg bd vs. Placebo

Figure 11.

Characteristics	HR (95% CI)	Total Patients	KM % at Month 36 Ti PI	HR (95% CI)	p-value (int.)
TIMI Major bleeding		13984	2.6 1.1	2.69 (1.96, 3.70)	
		13954	2.3 1.1	2.32 (1.68, 3.21)	
Diabetes Mellitus					
Yes		4454	2.6 1.0	2.68 (1.52, 4.73)	0.9906
		4519	2.5 1.0	2.47 (1.40, 4.36)	0.7860
No		9530	2.6 1.1	2.69 (1.83, 3.96)	
		9435	2.2 1.1	2.25 (1.52, 3.33)	
Multivessel CAD					
Yes		8277	2.5 1.1	2.67 (1.75, 4.07)	0.9612
		8310	2.6 1.1	2.69 (1.77, 4.09)	0.2563
No		5707	2.8 1.0	2.71 (1.67, 4.42)	
		5642	1.9 1.0	1.83 (1.09, 3.07)	
Creatinine cl (Cockcroft Gault) enrollm					
<60 mL/min		2739	2.5 1.7	1.66 (0.87, 3.16)	0.1047
		2682	3.7 1.7	2.40 (1.32, 4.37)	0.8605
>=60 mL/min		11084	2.6 0.9	3.07 (2.12, 4.46)	
		11125	2.0 0.9	2.25 (1.53, 3.31)	
History of PCI					
Yes		11566	2.6 1.1	2.77 (1.96, 3.93)	0.6784
		11574	2.4 1.1	2.42 (1.70, 3.44)	0.5485
No		2417	2.5 1.0	2.31 (1.04, 5.10)	
		2379	1.6 1.0	1.84 (0.80, 4.20)	
History of coronary stent implantation					
Yes		11120	2.7 1.1	2.86 (2.01, 4.08)	0.4299
		11152	2.5 1.1	2.45 (1.71, 3.51)	0.4712
No		2818	2.3 1.1	2.06 (1.00, 4.28)	
		2756	1.7 1.1	1.81 (0.85, 3.82)	
Type of Stent					
Any DES		5465	2.8 1.4	2.29 (1.44, 3.65)	0.1945
		5489	2.5 1.4	1.90 (1.18, 3.04)	0.2718
BMS only		5074	2.9 0.8	3.71 (2.12, 6.50)	
		5076	2.4 0.8	2.88 (1.62, 5.11)	
Current smoker at enrolment					
Yes		2313	3.6 1.2	3.62 (1.73, 7.61)	0.3669
		2321	3.2 1.2	3.09 (1.46, 6.55)	0.3908
No		11666	2.4 1.0	2.48 (1.74, 3.54)	
		11630	2.1 1.0	2.15 (1.50, 3.08)	
Time fr previous ADP rec block					
<30 days		4742	2.4 0.7	3.43 (1.87, 6.26)	0.9065
		4727	2.7 0.7	3.37 (1.85, 6.15)	0.6103
30 days to 12 months		4380	2.7 1.2	2.86 (1.60, 5.12)	
		4421	2.7 1.2	2.93 (1.65, 5.20)	
>12 months		3293	3.0 0.9	3.28 (1.70, 6.34)	
		3270	1.9 0.9	2.13 (1.06, 4.27)	
ASA dose at randomization					
<=75 mg		2739	2.4 0.7	3.35 (1.57, 7.15)	0.5259
		2770	1.4 0.7	1.81 (0.79, 4.14)	0.5390
>75 mg		11211	2.7 1.2	2.56 (1.80, 3.64)	
		11156	2.5 1.2	2.40 (1.69, 3.41)	
History of angina					
Yes		4303	2.0 1.3	1.70 (0.98, 2.96)	0.0537
		4368	2.5 1.3	2.02 (1.19, 3.43)	0.5229
No		9681	2.9 1.0	3.32 (2.24, 4.93)	
		9586	2.2 1.0	2.51 (1.67, 3.78)	
Spontaneous bleeding requiring hopitaliz					
Yes		169	4.7 4.3	1.66 (0.33, 8.22)	0.5381
		186	9.0 4.3	1.64 (0.37, 7.32)	0.6373
No		13815	2.6 1.0	2.77 (2.00, 3.84)	
		13768	2.2 1.0	2.37 (1.70, 3.30)	

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  1    2   3  4  5  7  10
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■ Ticagrelor 90mg bd vs. Placebo
□ Ticagrelor 60mg bd vs. Placebo

Figure 12

Figure 13.

The probability of event in each treatment arm is calculated given the median ticagrelor exposure for each arm. The vertical error bars illustrates the median probability of event (point) and the corresponding 95% CI based on parameter uncertainty and assuming a typical patient without risk factors.

Figure 14.
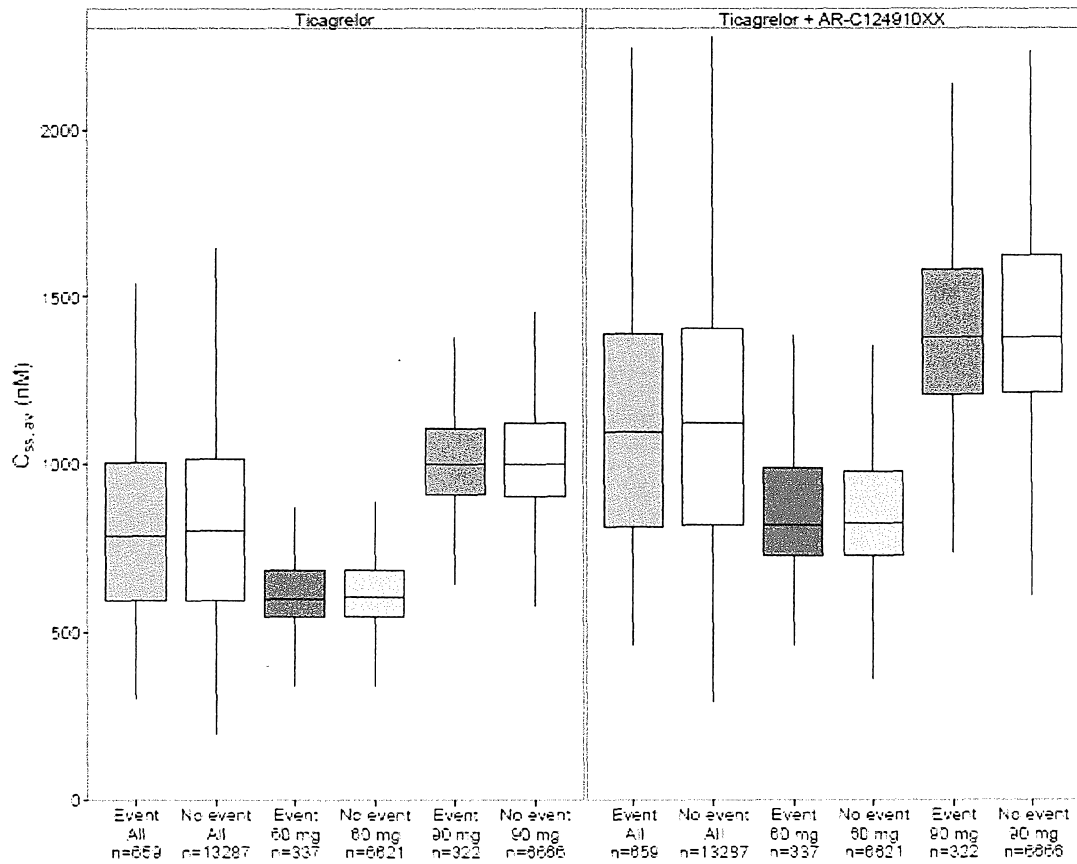
The horizontal line within each box represents the median. The box edges represent the lower (25th) and upper (75th) quartiles. The whiskers extend from the lower and upper quartiles to the furthest data points still within a distance of 1.5 interquartile ranges from the lower and upper quartiles

Figure 15.
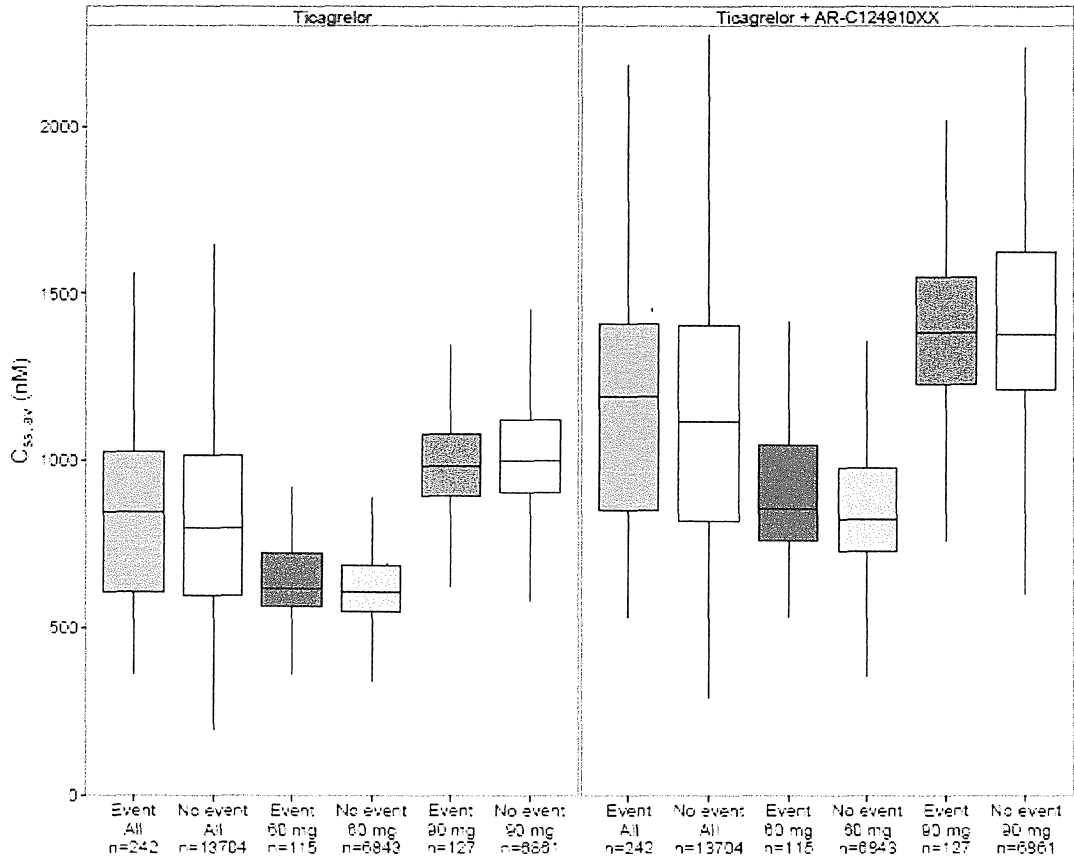
The horizontal line within each box represents the median. The box edges represent the lower (25th) and upper (75th) quartiles. The whiskers extend from the lower and upper quartiles to the furthest data points still within a distance of 1.5 interquartile ranges from the lower and upper quartile.

Figure 16.
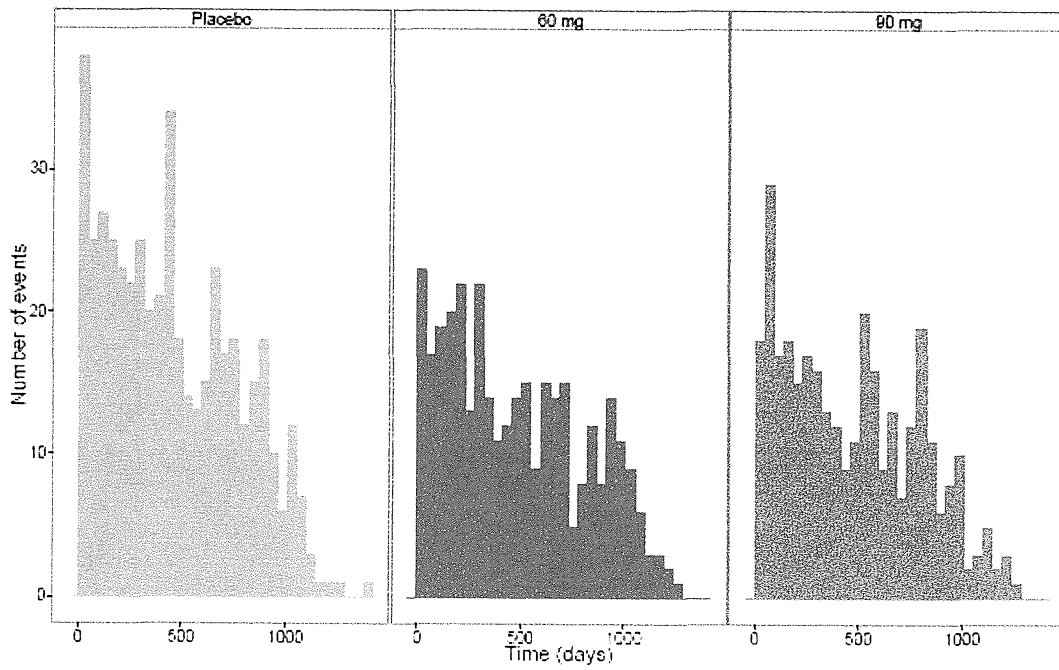
Figure 17.
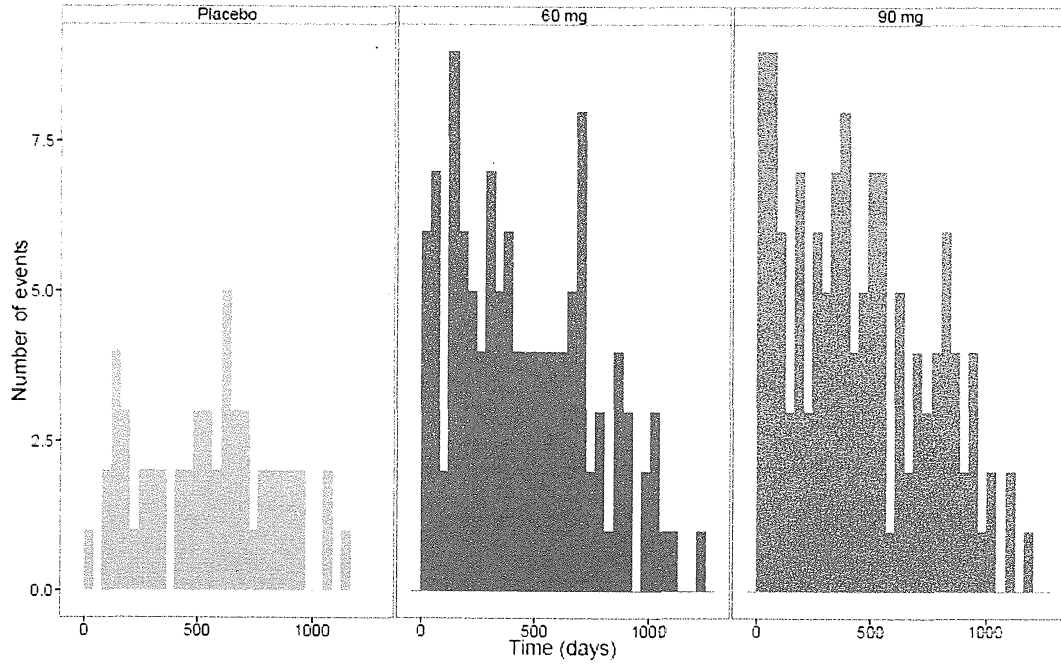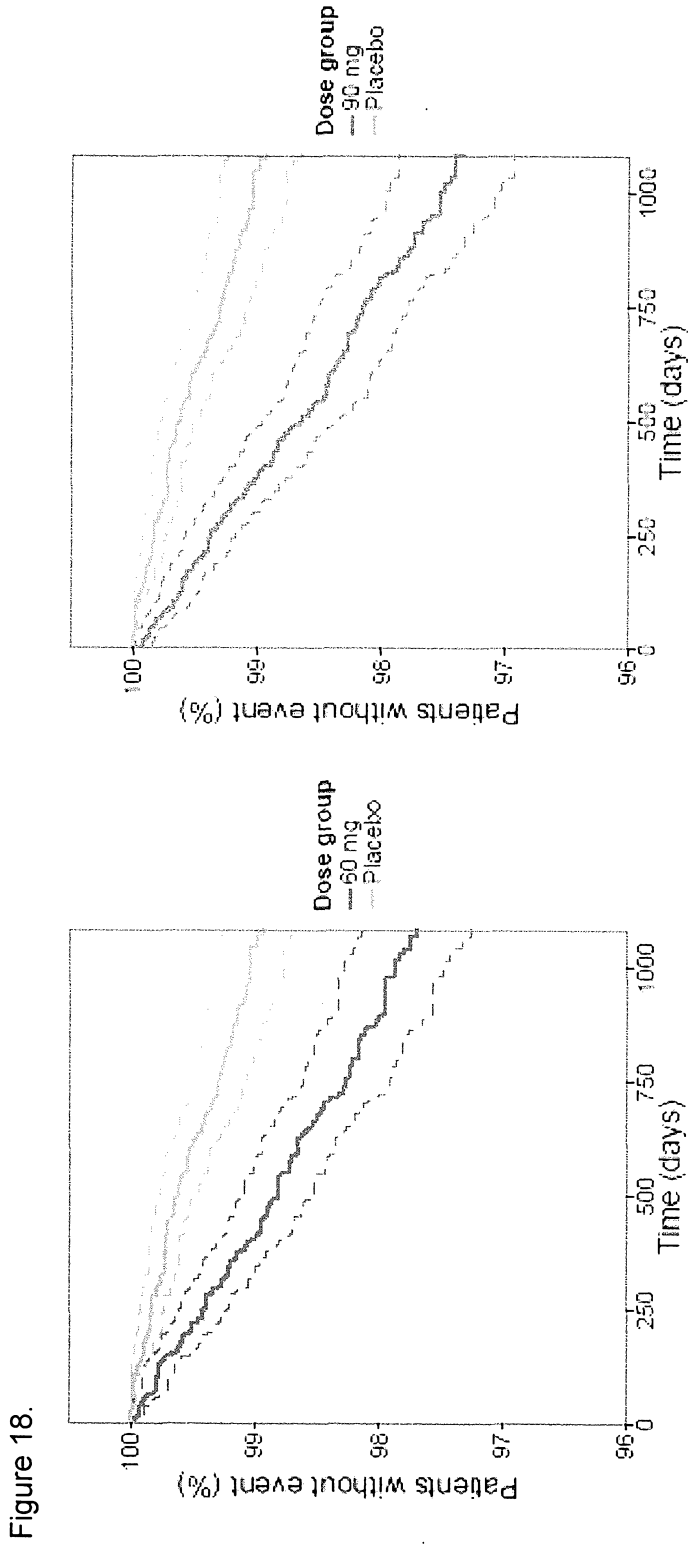
Figure 18.

*The dashed thin lines represent the 95% confidence intervals of the KM estimator.

Figure 19.
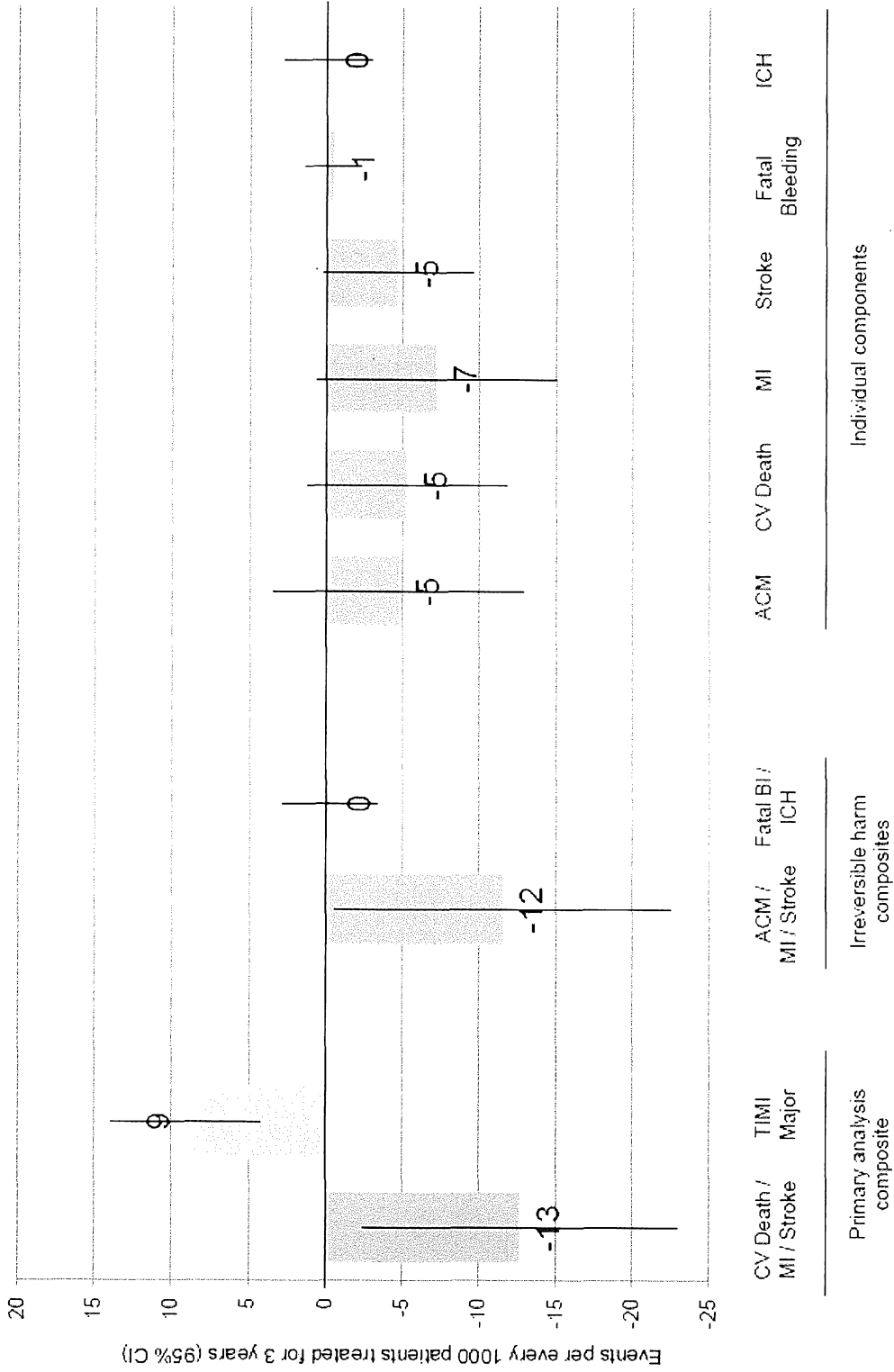
ACM = All Cause Mortality, ICH = Intracranial Haemorrhage
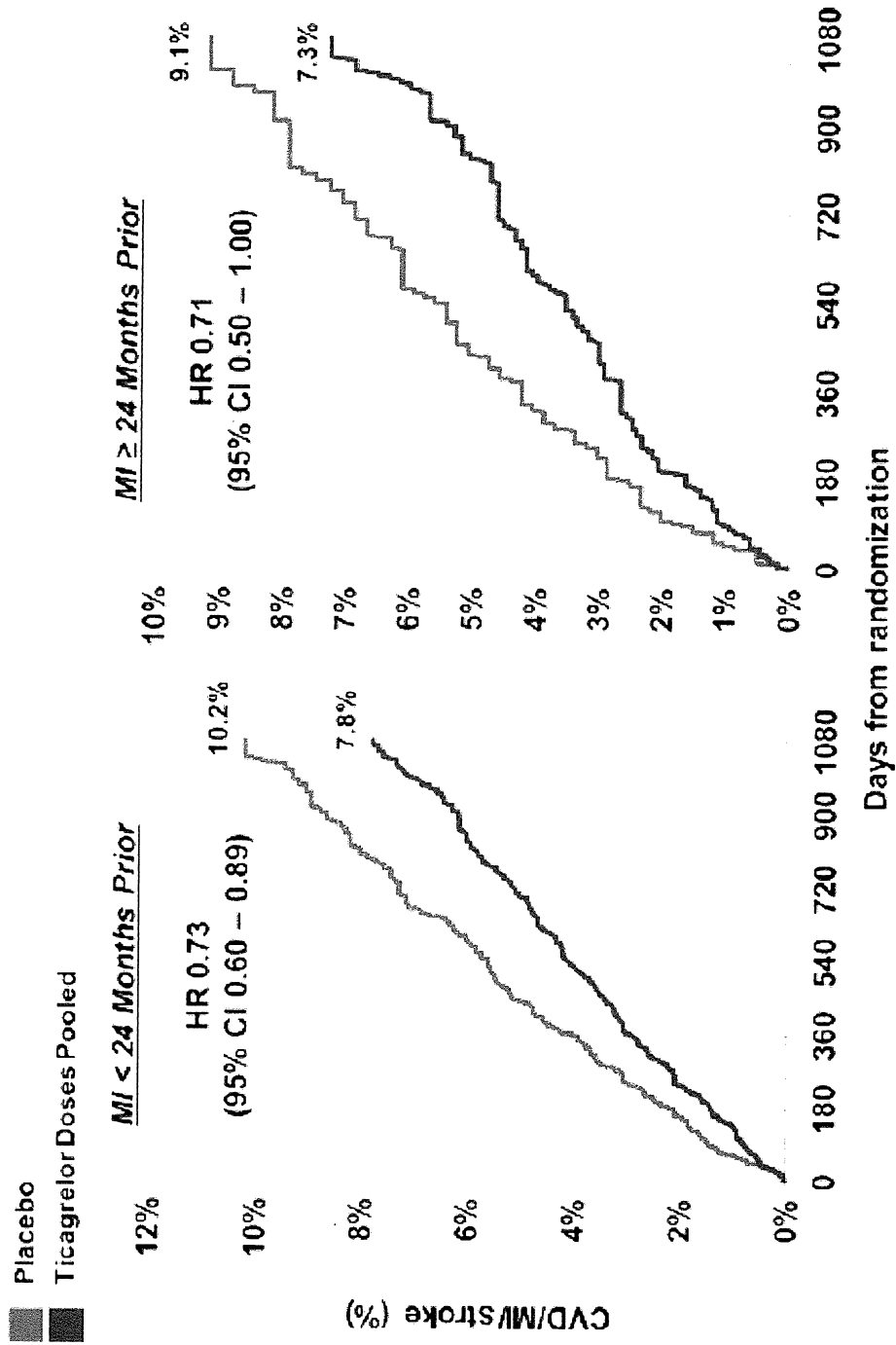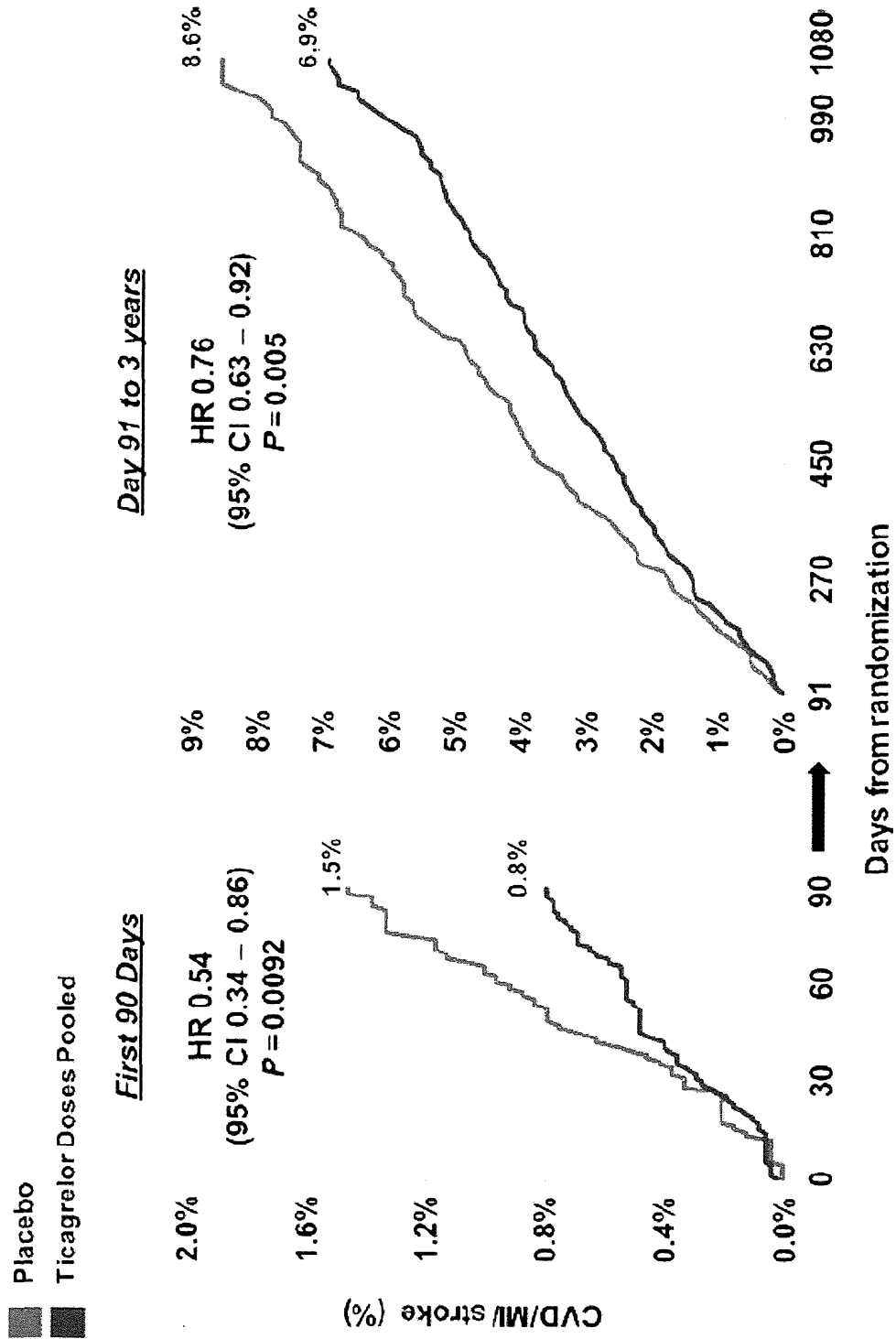
Figure 20.
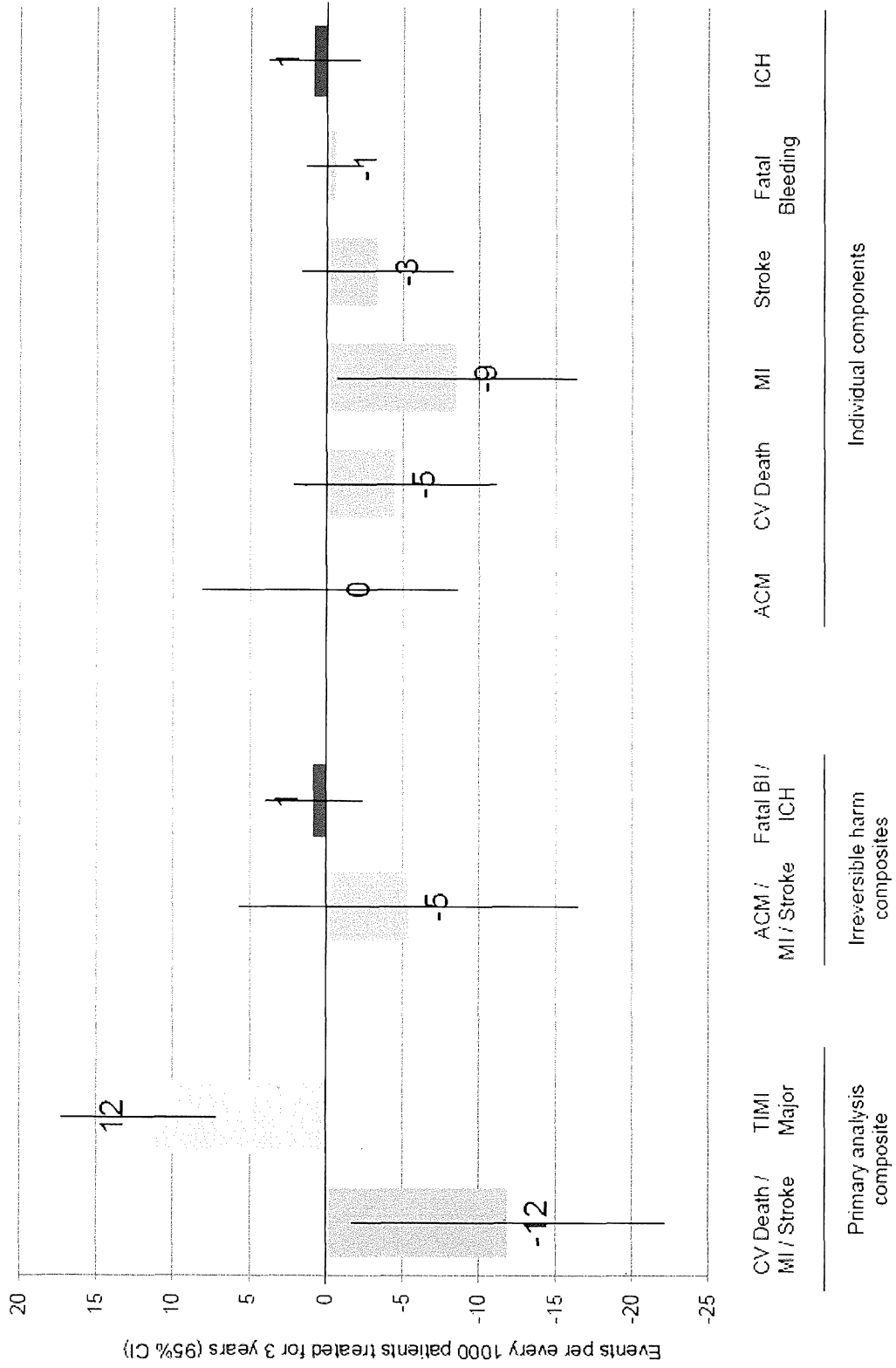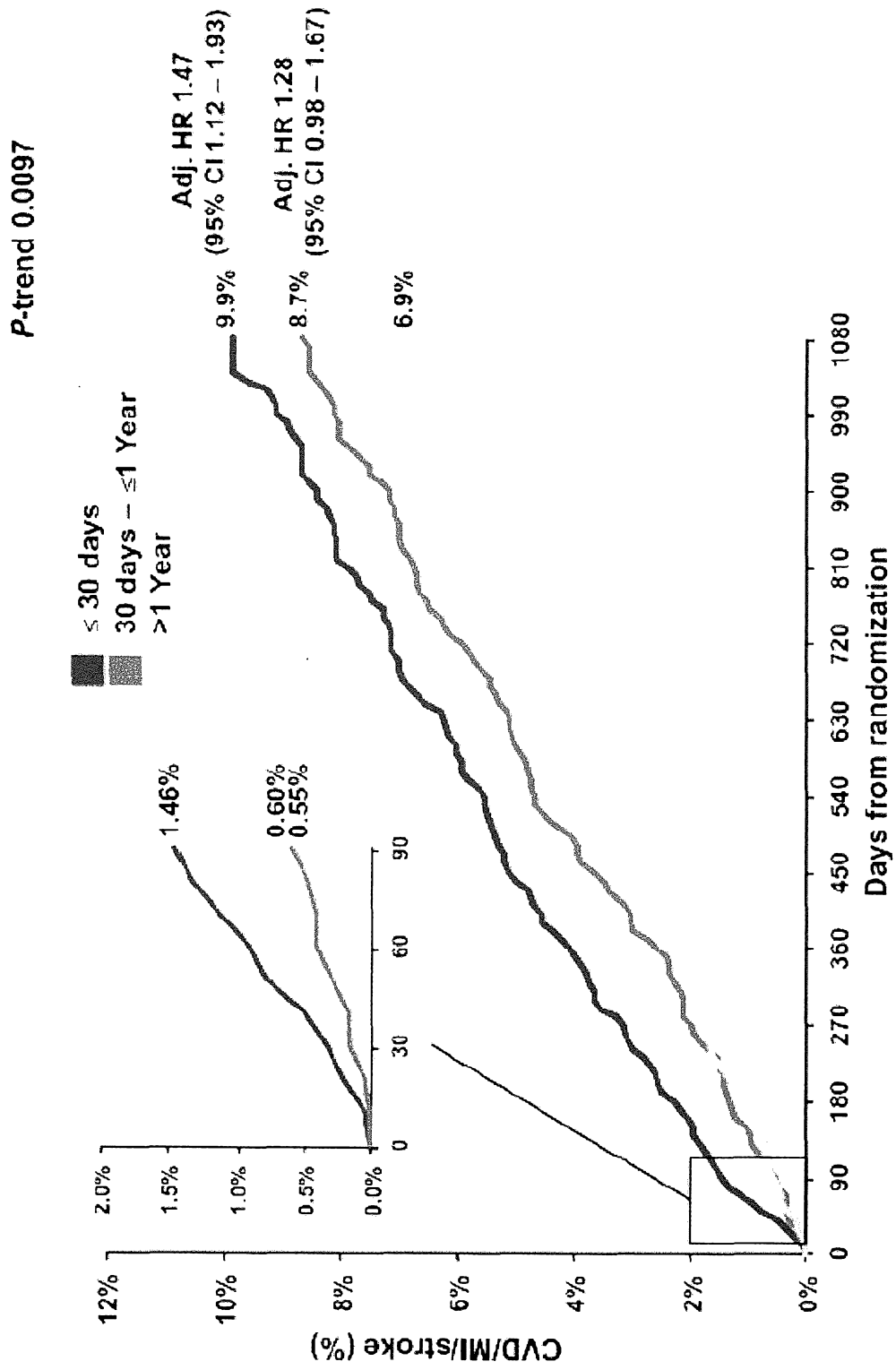
Figure 21.

Figure 22.
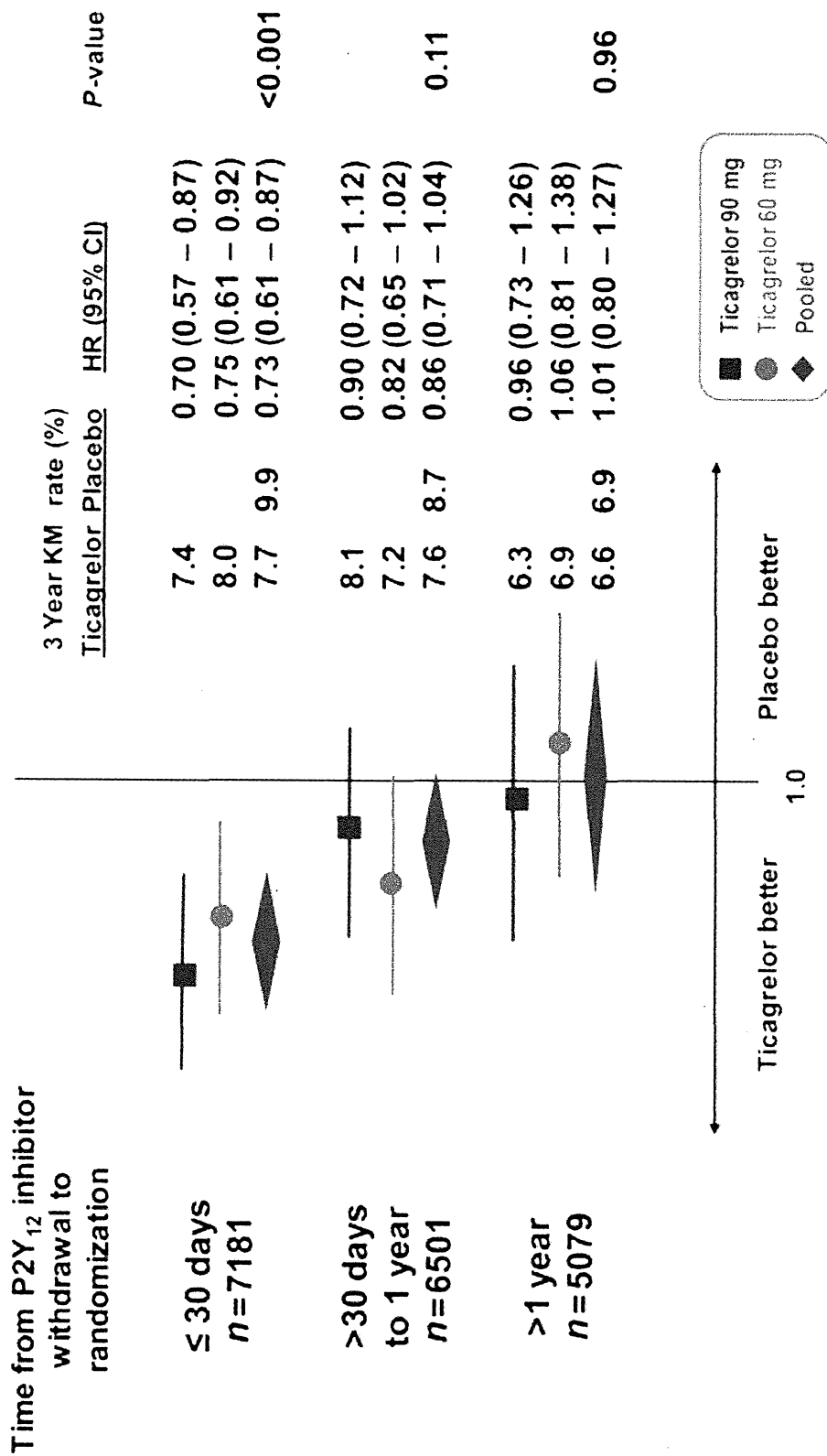
Figure 23.
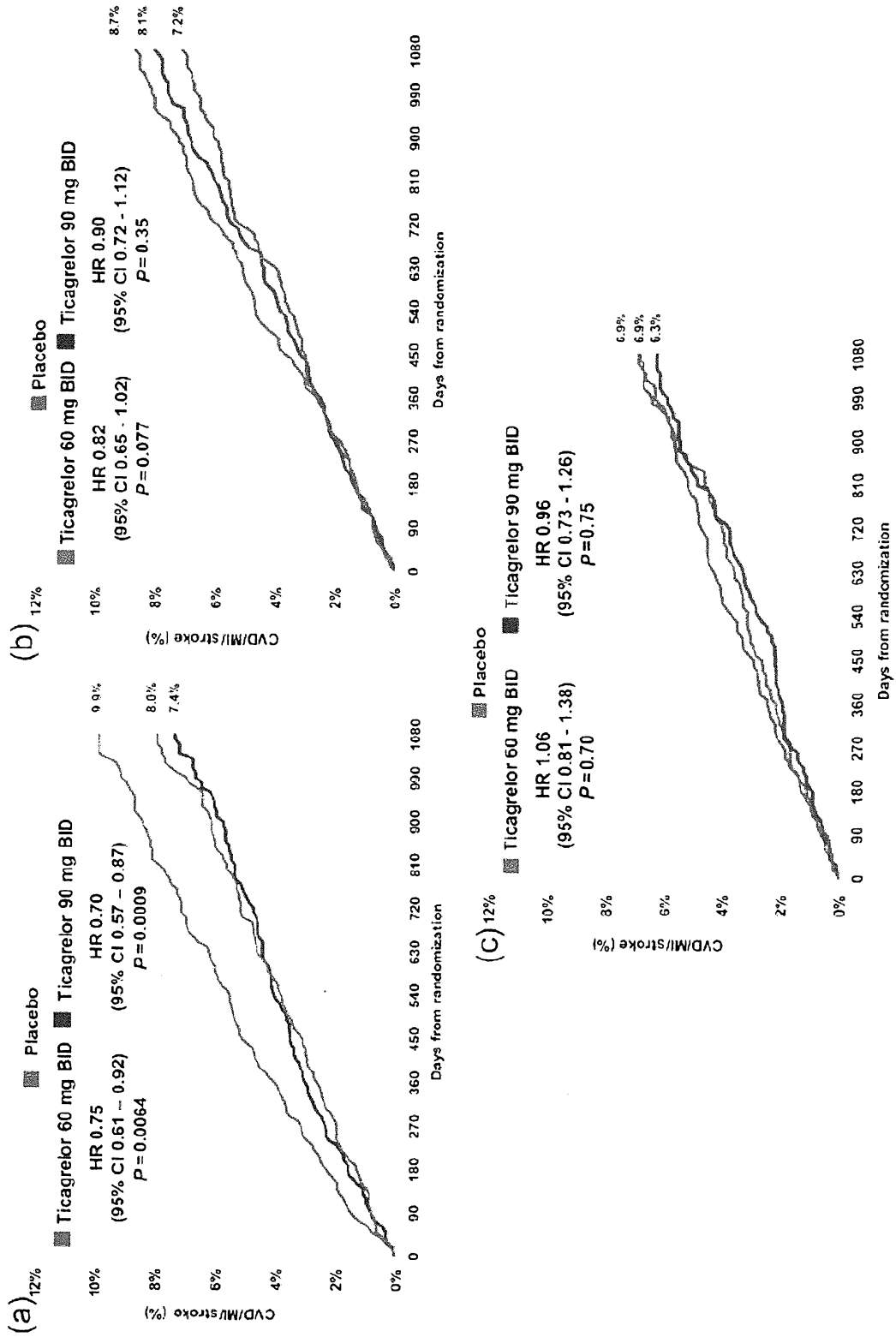
Figure 24.

Figure 25.

Figure 26.

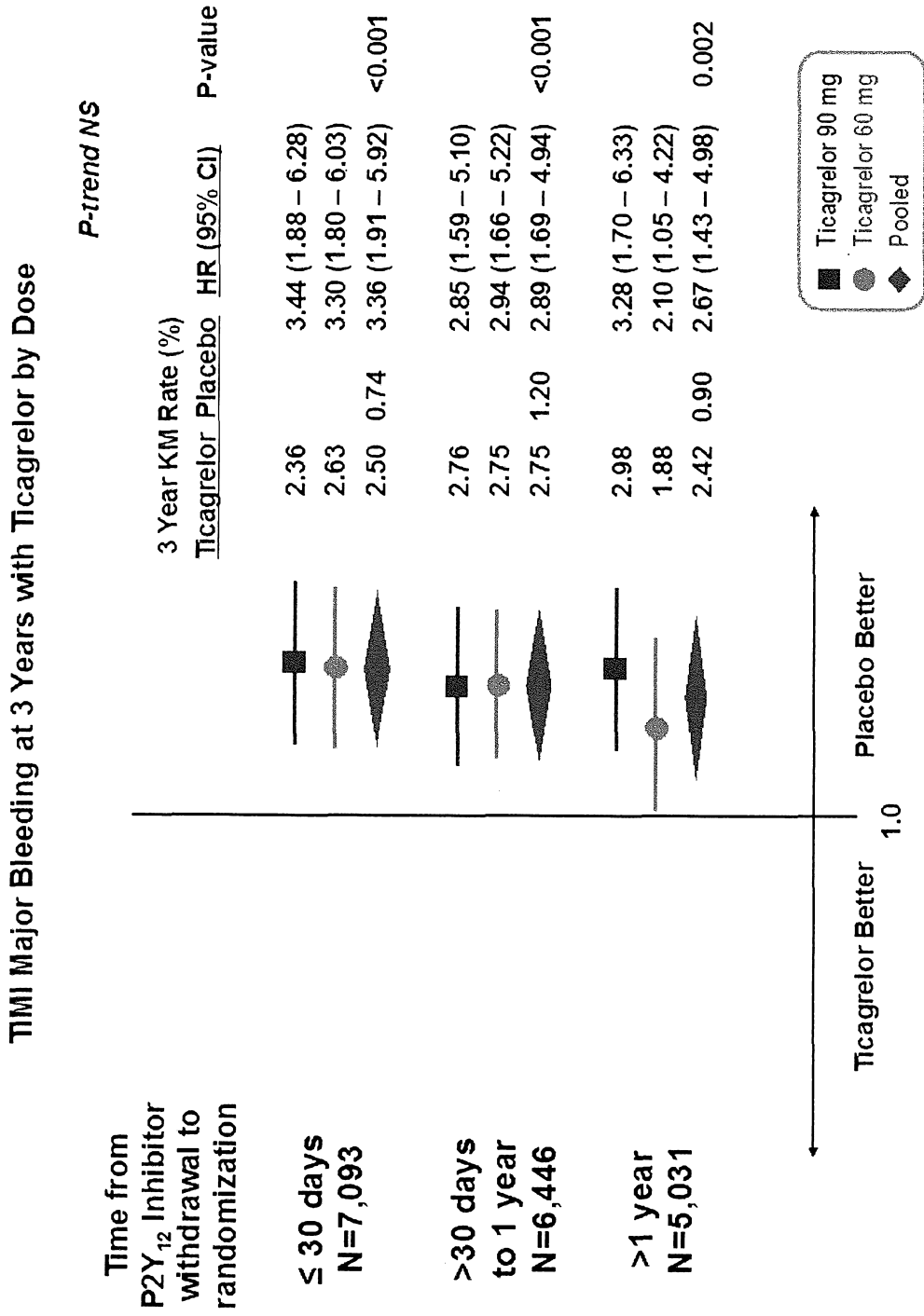TIMI Major Bleeding at 3 Years with Ticagrelor by Dose

Figure 27.

TIMI Major Bleeding at 3 Years with Ticagrelor in Patients with P2Y₁₂ Inhibitor Withdrawal ≤ 30 Days from Randomization