HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use TICAGRELOR TABLETS safely and effec

Acute Ischemic Stroke

of the product. (4.3)

wice daily for up to 30 days. (2.4)

---- CONTRAINDICATIONS -

persensitivity to ticagrelor or any component

spnea was reported more frequently with

icagrelor than with control agents in clinical rials. Dyspnea from ticagrelor is self-limiting.

----- ADVERSE REACTIONS -----

To report SUSPECTED ADVERSE REACTIONS,

contact Teva at 1-888-838-2872 or FDA at

----- DRUG INTERACTIONS -----

Patients receiving more than 40 mg per day of

simvastatin or lovastatin may be at increased risk of statin-related adverse effects. (7.4)

Rosuvastatin plasma concentrations may increase. Monitor for statin-related adverse

See 17 for PATIENT COUNSELING INFORMATION

USE IN SPECIFIC POPULATIONS

Pediatric Use

12 CLINICAL PHARMACOLOGY

14 CLINICAL STUDIES

2.1 Mechanism of Actior2.2 Pharmacodynamics

14.2 Coronary Artery Disease but No Prior

Stroke or Myocardial Infarctio

14.3 Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

16 HOW SUPPLIED/STORAGE AND HANDI INC

prescribing information are not listed

*Sections or subsections omitted from the full

Geriatric Use

Simvastatin, Lovastatin, Rosuvastatin

Revised: 12/2024

1-800-FDA-1088 or www.fda.gov/medwatch.

TICAGRELOR tablets, for oral use Initial U.S. Approval: 201

WARNING: BLEEDING RISK See full prescribing information for comple boxed warning.

cause significant, sometimes fatal bleeding. (5.1, 6.1) Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial hemorrhage. (4.1, 4.2)

Do not start ticagrelor in patients undergoing

urgent coronary artery bypass graft surgery (CABG). (5.1, 6.1) If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events. (5.2)

---RECENT MAJOR CHANGES--Dosage and Administration (2.2, 2.4) 03/2024

----INDICATIONS AND USAGE-Ticagrelor is a P2Y₁₂ platelet inhibitor indicated • to reduce the risk of cardiovascular (CV) death myocardial infarction (MI), and stroke in patie with acute coronary syndrome (ACS) or a history of MI. For at least the first 12 months

following ACS, it is superior to clopidogrel. Ticagrelor tablets also reduce the risk of stent hrombosis in patients who have been stented or treatment of ACS. (1.1) • to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. While use is not

limited to this setting, the efficacy of ticagrelor was established in a population with type 2 with acute ischemic stroke (NIH Stroke Scale score ≤5) or high-risk transient ischemic attack (TIA). (1.3)

---DOSAGE AND ADMINISTRATION-----• ACS or History of MI
• Initiate treatment with 180 mg oral loading

Patients with CAD and No Prior Stroke or MI
 Administer 60 mg ticagrelor tablets twic

FULL PRESCRIBING INFORMATION: CONTENTS* 7 DRUG INTERACTIONS WARNING: BLEEDING RISK NDICATIONS AND USAGE

Ticagrelor Tablets

Ticagrelor Tablets

Coronary Artery Disease but No Prior troke or Myocardial Infarction

2.1 General Instructions2.2 Acute Coronary Syndrome or a History

of Myocardial Infarction ary Artery Disease but No Prior

DOSAGE FORMS AND STRENGTHS

WARNINGS AND PRECAUTIONS Risk of Bleeding Discontinuation of Ticagrelor in

Severe Hepatic Impairment Central Sleep Apnea

6 ADVERSE REACTIONS 6.1 Clinical Trials Experience6.2 Postmarketing Experience

FULL PRESCRIBING INFORMATION

atients Treated for Coronary Artery

WARNING: BLEEDING RISK

Ticagrelor, like other antiplatelet agents, can cause significant, sometimes fatal bleeding (5.1, 6.1). • Do not use ticagrelor in patients with active pathological bleeding or a history of intracranial • Do not start ticagrelor in patients undergoing urgent coronary artery bypass graft surgery (CABG)

If possible, manage bleeding without discontinuing ticagrelor. Stopping ticagrelor increases the risk of subsequent cardiovascular events (5.2).

Acute Coronary Syndrome or a History of Myocardial Infarction

MI), and stroke in patients with acute coronary syndrome (ACS) or a history of MI. For at least the first 2 - Marie total ville - Min. 2 - Marie total ville - Min.

Ticagrelor tablets also reduce the risk of stent thrombosis in patients who have been stented for

Coronary Artery Disease but No Prior Stroke or Myocardial Infarction disease (CAD) at high risk for such events *[see Clinical Studies (14.2)]*. While use is not limited to this setting, the efficacy of ticagrelor was established in a population with type 2 diabetes mellitus (T2DM).

Acute Ischemic Stroke or Transient Ischemic Attack (TIA) (NIH Stroke Scale score ≤5) or high-risk transient ischemic attack (TIA) [see Clinical Studies (14.3) DOSAGE AND ADMINISTRATION

Advise patients who miss a dose of ticagrelor tablets to take their next dose at its scheduled time. For patients who are unable to swallow tablets whole, ticagrelor tablets can be crushed, mixed with water, and drunk. The mixture can also be administered via a nasogastric tube (CH8 or greater) [see

Do not administer ticagrelor tablets with another oral P2Y₁₂ platelet inhibitor

Avoid aspirin at doses higher than recommended *[see Clinical Studies (14.1)]*. Acute Coronary Syndrome or a History of Myocardial Infarction nitiate treatment with a 180 mg loading dose of ticagrelor tablets. Administer the first 90 mg maintenance dose of ticagrelor tablets, 6 to 12 hours after the loading dose. Administer 90 mg of

ticagrelor tablets twice daily during the first year after an ACS event. After one year, administer 60 mg of ticagrelor tablets twice daily Initiate ticagrelor tablets with a daily maintenance dose of aspirin of 75 mg to 100 mg. However, in patients who have undergone percutaneous coronary intervention (PCI), consider single antiplatelet therapy with ticagrelor tablets based on the evolving risk for thrombotic versus bleeding events [see Warnings and Precautions (5.1) and Clinical Studies (14)].

2.3 Coronary Artery Disease but No Prior Stroke or Myocardial Infarction

of aspirin of 75 mg to 100 mg [see Clinical Studies (14) DOSAGE FORMS AND STRENGTHS elor tablets 60 mg is supplied as a light vellow to vellow, oval shaped, film-coated tablet debossed

with "137" on one side and "A" on the other side. Ticagrelor tablets 90 mg is supplied as a light vellow to vellow, round shaped, film-coated tablet debossed with "A91" on one side and plain on the other side

CONTRAINDICATIONS History of Intracranial Hemorrhage

icagrelor is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [see Clinical Studies (14.1, 14.2)]. **4.2 Active Bleeding**Ticagrelor is contraindicated in patients with active pathological bleeding such as peptic ulcer or

intracranial hemorrhage [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]. **4.3 Hypersensitivity** Ticagrelor is contraindicated in patients with hypersensitivity (e.g., angioedema) to ticagrelor or any

WARNINGS AND PRECAUTIONS

5.1 Risk of Bleeding
Drugs that inhibit platelet function including ticagrelor increase the risk of bleeding [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)].

When antiplatelet therapy was stopped 5 days be ticagrelor treated patients and 79% on clopidogrel.

Patients treated for acute ischemic stroke or TIA

Patients at NIHSS >5 and patients receiving thrombolysis were excluded from THALES and use of Initiate treatment with a 180 mg loading dose tinue with 90 ma ticagrelor in such patients is not recommended

5.2 Discontinuation of Ticagrelor in Patients Treated for Coronary Artery Disease ation of ticagrelor will increase the risk of myocardial infarction, stroke, and death in patien being treated for coronary artery disease. If ticagrelor must be temporarily discontinued (e.g., to trea However, in patients who have undergone PCI. bleeding or for significant surgery) restart it as soon as possible. When possible interrupt therap with ticagrelor for five days prior to surgery that has a major risk of bleeding. Resume ticagrelor as tablets based on the evolving risk for thrombotic Dyspnea ---DOSAGE FORMS AND STRENGTHS----

n clinical trials, about 14% (PLATO and PEGASUS) to 21% (THEMIS) of patients treated with ticagrelor developed dyspnea. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment but led to study drug discontinuation in 0.9% (PLATO), 1.0% (THALES), 4.3% (PEGASUS), and 6.9% (THEMIS) of patients.

In a substudy of PLATO, 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.

--WARNINGS AND PRECAUTIONS---spnea was reported more frequently with agrelor than with control agents in clinical

Severe Hepatic Impairment: Likely increase in exposure to ticagrelor. (5.5) Elasymptomical studies and may be at increased risk of developing bradyarrhythmias including AV block or bradycardia-related syncope not protected by a pacemaker were excluded from clinical studies and may be at increased risk of developing bradyarrhythmias with ticagrelor.

5.5 Severe Hepatic Impairment
Avoid use of ticagrelor in patients with severe hepatic impairment. Severe hepatic impairment is likely to increase serum concentration of ticagrelor. There are no studies of ticagrelor patients with severe hepatic impairment [see Clinical Pharmacology (12.3)

Most common adverse reactions (>5%) are bleeding and dyspnea. (5.1, 5.3, 6.1)

S.6 Central Sleep Apnea Central sleep apnea (CSA) inclu Central sleep apnea (CSA) including Cheyne-Stokes respiration (CSR) has been reported in the postmarketing setting in patients taking ticagrelor, including recurrence or worsening of CSA/CSR following rechallenge. If central sleep apnea is suspected, consider further clinical assessment.

Laboratory Test Interferences False negative functional tests for Heparin Induced Thrombocytopenia (HIT)

 Avoid use with strong CYP3A inhibitors or CyP3A inhib heparin-induced platelet aggregation (HIPA) assay) for patients with Heparin Induced Thrombocytopenia (HIT). This is related to inhibition of the P2Y₁₂-receptor on the healthy donor platelets in the test bicagrelor in the affected patient's serum/plasma. Information on concomitant treatment with ticagrelor is required for interpretation of HIT functional tests. Based on the mechanism of ticagrelor interference, ticagrelor is not expected to impact PF4 antibody testing for HI

ADVERSE REACTIONS

6.1 Clinical Trials Experience

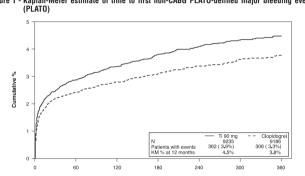
• Monitor digoxin levels with initiation of or any change in ticagrelor. (7.5)

----USE IN SPECIFIC POPULATIONS---and may not reflect the rates observed in practice.

• Lactation: Breastfeeding not recommended. Ticagrelor has been evaluated for safety in more than 58,000 patients. Bleeding in PLATO (Reduction in risk of thrombotic events in ACS)

Figure 1 is a plot of time to the first non-CABG major bleeding event

Figure 1 - Kaplan-Meier estimate of time to first non-CABG PLATO-defined major bleeding event (PLATO)



7563 7648 7170 6900 5428 7302 7065 5540

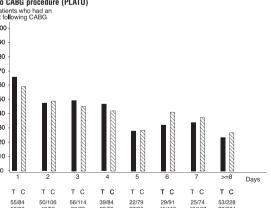
Frequency of bleeding in PLATO is bleeding events were in the first 30		About half of the non-CABG major
Table 1 - Non-CABG related blee	ds (PLATO)	
	Ticagrelor* N=9,235	Clopidogrel N=9,186
	n (%) patients with event	n (%) patients with event
PLATO Major + Minor	713 (7.7)	567 (6.2)
Major	362 (3.9)	306 (3.3)
Fatal/Life-threatening	171 (1.9)	151 (1.6)
Fatal	15 (0.2)	16 (0.2)
Intracranial hemorrhage (Fatal/Life-threatening)	26 (0.3)	15 (0.2)

tamponade; hypovolemic shock or severe hypotension requiring intervention; signi g., intraocular with permanent vision loss); associated with a decrease in Hb of at least 3 g/dL (or fall in hematocrit (Hct) of at least 9%); transfusion of 2 or more units

PLATO Major bleed, fatal/life-threatening; any major bleed as described above and associated with Fatal: A bleeding event that directly led to death within 7 days * 90 mg BIE

No baseline demographic factor altered the relative risk of bleeding with ticagrelor compared to

cagrelor tablets are indicated to reduce the risk of cardiovascular (CV) death, myocardial infarction In PLATO, 1,584 patients underwent CABG surgery. The percentages of those patients who bled are Figure 2 – 'Major fatal/life-threa ning' CABG-related bleeding by days from last dose of study drug to CABG procedure (PLATO



Generally, use ticagrelor tablets with a daily maintenance dose of aspirin of 75 mg to 100 mg [see Clinical Studies (14)]. 24 hours prior to surgery and use of aprotinin or other hemostatic agents was allowed. If local practice Initiate treatment with a 180 mg loading dose of ticagrelor tablets and then continue with 90 mg twice daily for up to 30 days. Administer the first maintenance dose 6 to 12 hours after the loading dose. Use ticagrelor tablets with a loading dose of aspirin (300 mg to 325 mg) and a daily maintenance dose

T Ticagrelor; C Clopidogrel. Table 2 - CARG-related bleeding (PLATO)

Ticagrelo N=770 n (%) patients with event with event PLATO Total Maio 626 (81 : 666 (81.8 Fatal/Life-threatening 350 (43.0

PLATO Major bleed: any one of the following: fatal; intrac intrapericardial with cardiac imponade; hypovolemic shock or severe hypotension requiring intervention; significantly disabling s.g., intraocular with permanent vision loss); associated with a decrease in Hb of at least 3 g/dL (or

fall in hematocrit (Hct) of at least 9%); transfusion of 2 or more units. PLATO Major bleed, fatal/life-threatening: any major bleed as described above and associated with a decrease in Hb of more than 5 g/dL (or a fall in hematocrit (Hct) of at least 15%); transfusion of

When antiplatelet therapy was stopped 5 days before CABG, major bleeding occurred in 75% of 7.1

Other Adverse Reactions in PLATO Adverse reactions that occurred at a rate of 4% or more in PLATO are shown in Table 3. Strong CYP3A Inducers

entage of patients reporting non-hemorrhagic adverse reactions at least 4% or more

Ticagrelor increases serum concentration of rosuvastatin because rosuvastatin is a BCRP substrate [see Clinical Pharmacology (12.3)]. Digoxin

USE IN SPECIFIC POPULATIONS

TIMI Major: Fatal bleeding, OR any intracranial bleeding, OR clinically overt signs of hemorrh ed with a drop in hemoglobin (Hgb) of ≥5 g/dL, or a fall in hematocrit (Hct) of ≥15%. bleeding event that directly led to death within 7 days.

N=6.996

The bleeding profile of ticagrelor 60 mg compared to aspirin alone was consistent across multiple

pre-defined subgroups (e.g., by age, gender, weight, race, geographic region, concurrent conditions, concomitant therapy, stent, and medical history) for TIMI Major and TIMI Major or Minor bleeding Other Adverse Reactions in PEGASUS

Adverse reactions that occurred in PEGASUS at rates of 3% or more are shown in Table 5. Table 5 - Non-hemorrhagic adverse reactions reported in >3.0% of patients in the ticagrelor 60 mg

Bleeding in PEGASUS (Secondary Prevention in Patients with a History of Myocardial Infarction)

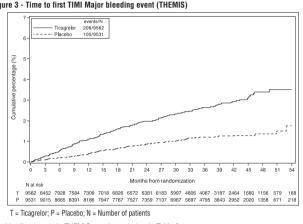
N=6.958

erall outcome of bleeding events in the PEGASUS study are shown in Table 4.

nor: Clinically apparent with 3 to 5 g/dL decrease in hemoglo

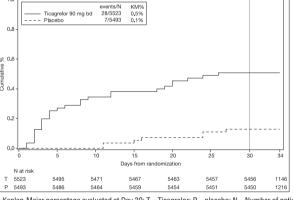
	Ticagrelor* N=6,958	Placebo N=6,996	
Dyspnea	14.2%	5.5%	
Dizziness	4.5%	4.1%	
Diarrhea	3.3%	2.5%	

Bleeding in THEMIS (Prevention of major CV events in patients with CAD and Type 2 Diabetes Mellitus The Kaplan-Meier curve of time to first TIMI Major bleeding event is presented in Figure 3. Figure 3 - Time to first TIMI Major bleeding event (THEMIS)



	Ticagrelor N=9,562	Placebo N=9,531
	Events / 1,000 patient years	Events / 1,000 patient years
TIMI Major	9	4
TIMI Major or Minor	12	5
TIMI Major or Minor or Requiring medical attention	46	18
Fatal bleeding	1	0
Intracranial hemorrhage	3	2

he Kaplan-Meier curve of time course of GUSTO severe bleeding events is presented in Figure 4. DESCRIPTION Figure 4 - Time course of GUSTO severe bleeding events



KM%: Kaplan-Meier percentage evaluated at Day 30; T = Ticagrelor; P = placebo; N = Number of patients GUSTO Severe: Any one of the following: fatal bleeding, intracranial bleeding (excluding asymptomatic tions of ischemic brain infarctions and excluding microhemorrhages <10 mm revident only on gradient-echo magnetic resonance imaging), bleeding that caused hemodynamic compromise requiring intervention (e.g., systolic blood pressure <90 mmg Hg that required blood or fluid replacement, or vasopressor/inotropic support, or surgical intervention).

Mechanism of Action

Ticagrelor and its major metabolite reversibly interact with the platelet P2Y₁₂ ADP-receptor to signal transduction and platelet activation. Ticagrelor and its active metabolite are approximately equipotent.

Intracranial bleeding and fatal bleeding in THALES: In total, there were 21 intracranial hemorrhages 12.2 Pharmacodynamics

In a Holter substudy of about 3000 patients in PLATO, more patients had ventricular pauses with ticagrelor (6.0%) than with clopidogrel (3.5%) in the acute phase; rates were 2.2% and 1.6%, respectively, after 1 month, PLATO, PEGASUS, THEMIS and THALES excluded patients at increased maximum IPA effect of ticagrelor was reached at around 2 hours, and was maintained for at least 8 hours. sk of bradycardic events (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block, or The offset of IPA was examined after 6 weeks on ticagrelor 90 mg twice daily or clopidogrel 75 mg daily, bradycardic-related syncope and not protected with a pacemaker). Lab abnormalities

X-axis is days from last dose of study drug prior to CABG.

The PLATO protocol recommended a procedure for withholding study drug prior to CABG or other major surgery without unblinding. If surgery was elective or non-urgent, study drug was interrupted temporarily, as follows: If local practice was to allow antiplatelet effects to dissipate before surgery, cansules (blinded clopidogrel) were withheld 5 days before surgery and tablets (blinded ticagrelor) were decreased after treatment was stopped.

Treatment. Reports of gout did not differ between treatment groups in PLATO (0.0% in each group).

The PLATO protocol recommended a procedure for withholding study drug prior to CABG.

The PLATO protocol recommended a procedure for withholding study drug prior to CABG or other major surgery without unblinding. If surgery was elective or non-urgent, study drug was interrupted to asspirate and no elevation was observed on aspirin alone. Gout occurred more commonly in patients on ticagrelor than in patients on aspirin alone (1.5%, 1.1%). Mean serum uric acid concentrations decreased after treatment was stopped.

Treatment. Reports of gout did not differ between treatment groups in PLATO (0.0% in each group).

The plato (0.0% in each group).

T and approximately 0.2 mg/dL on clopidogrel. The difference disappeared within 30 days of discontinuing

In PLATO, a >50% increase in serum creatinine levels was observed in 7.4% of patients receiving ticagrelor 90 mg compared to 5.9% of patients receiving clopidogrel. The increases typically did not progress with ongoing treatment and often decreased with continued therapy. Evidence of reversibility ation was observed even in those with the greatest on treatment increases. Treatment roups in PLATO did not differ for renal-related serious adverse events such as acute renal failure.

hronic renal failure, toxic nephropathy, or oliguria. In PEGASUS, serum creatinine concentration increased by >50% in approximately 4% of patients sceiving ticagrelor 60 mg, similar to aspirin alone. The frequency of renal related adverse events was imilar for ticagrelor and aspirin alone regardless of age and baseline renal function.

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-approval use of ticagrelor. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible o reliably estimate their frequency or establish a causal relationship to drug exposure. reported with the use of ticagrelor. TTP is a serious condition which can occur after a brief exposure (<2 weeks) and requires prompt treatment

mmune system disorders: Hypersensitivity reactions including angioedema [see Contraindications Respiratory Disorders: Central sleep apnea, Cheyne-Stokes respiration Skin and subcutaneous tissue disorders: Rash

pitors substantially increase ticagrelor exposure and so increase the risk of dyspnea. bleeding, and other adverse events. Avoid use of strong inhibitors of CYP3A (e.g., ketoconazole

itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinavir, indinavir, atazanavir and telithromycin) [see Clinical Pharmacology (12.3)].

Figure 6 – Mean inhibition of platelet aggregation (IPA) following 6 weeks on placebo, ticagrelor of Dispense with Medication Guide available at: www.tevausa.com/medguides

cers substantially reduce ticagrelor exposure and so decrease the efficacy of ticagrelo Avoid use with strong inducers of CYP3A (e.g., rifampin, phenytoin, carbamazepine and phenobarbita

f ticagrelor and its active metabolite presumably because of slowed gastric emptying *[see Clinica* Pharmacology (12.3)1. Consider the use of a parenteral anti-platelet agent in acute coronary syndrom istration of morphine or other opioid agonist

7.4 Simvastatin, Lovastatin, Rosuvastatin
Ticannelor increases serum concentrations of simvastatin and lovastatin because these drugs are lized by CYP3A4. Avoid simvastatin and lovastatin doses greater than 40 mg [see Člinica

r inhibits the P-glycoprotein transporter; monitor digoxin levels with initiation of or change in

Available data from case reports with ticagrelor use in pregnant women have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Ticagrelor given to pregnant rats and pregnant rabbits during organogenesis caused structural abnormities in the offspring at maternal doses about 5 to 7 times the maximum recommended human dose (MRHD) based

on body surface area. When ticagrelor was given to rats during late gestation and lactation, pup death and effects on pup growth were seen at approximately 10 times the MRHD (see Data). The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Animal Data In reproductive toxicology studies, pregnant rats received ticagrelor during organogenesis at doses from 20 to 300 mg/kg/day. 20 mg/kg/day is approximately the same as the MRHD of 90 mg twice daily for a 60 kg human on a mg/m² basis. Adverse outcomes in offspring occurred at doses of 300 mg/kg/day (16.5 times the MRHD on a mg/m² basis) and included supernumerary liver lobe and ribs, incomplete ossification of sternebrae, displaced articulation of pelvis, and misshapen/misaligned sternebrae. At the mid-dose of 100 mg/kg/day (5.5 times the MRHD on a mg/m² basis), delayed development of liver and skeleton was seen. When pregnant rabbits received ticagrelor during organogenesis at doses from 21 to 63 mg/kg/day, fetuses exposed to the highest maternal dose of 63 mg/kg/day (6.8 times the MRHD on a mg/m² basis) had delayed gall bladder development and incomplete ossification of the hyoid, pubis and sternebrae occurred. and sternebrae occurred.

late gestation and lactation. Pup death and effects on pup growth were observed at 180 mg/kg/day (approximately 10 times the MRHD on a mg/m² basis). Relatively minor effects such as delays in pinna folding and eye opening occurred at doses of 10 and 60 mg/kg (approximately one-half and 3.2 times Lactation Risk Summary

There are no data on the presence of ticagrelor or its metabolites in human milk, the effects on the

breastfed infant, or the effects on milk production. Ticagrelor and its metabolites were present in rat milk at higher concentrations than in maternal plasma. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Breastfeeding is not recommended during treatment with ticagrelor. Pediatric Use The safety and effectiveness of ticagrelor have not been established in pediatric patients. Effectiveness was not demonstrated in an adequate and well-controlled study conducted in 101 ticagrelor-treated pediatric patients, aged 2 to <18 for reducing the rate of vaso-occlusive crises in sickle cell disease.

8.5 Geriatric Use
About half of the patients in PLATO, PEGASUS, THEMIS, and THALES were ≥65 years of age and at least 15% were ≥75 years of age. No overall differences in safety or effectiveness were observed betweer elderly and younger patients

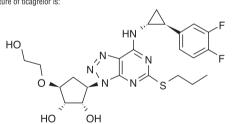
Hepatic Impairmen icagrelor is metabolized by the liver and impaired hepatic function can increase risks for bleeding and other adverse events. Avoid use of ticagrelor in patients with severe hepatic impairment. There is limited experience with ticagrelor in patients with moderate hepatic impairment; consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor. No dosage adjustment is needed in atients with mild hepatic impairment *(see Warnings and Precautions (5.5) and Clinical Pharmacolog*

Renal Impairment nent is needed in patients with renal impairment *[see Clinical Pharmacology (12.3)]*.

Patients with End-Stage Renal Disease on dialysis
Clinical efficacy and safety studies with ticagrelor did not enroll patients with end-stage renal disease
(ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, no clinically significant
difference in concentrations of ticagrelor and its metabolite and platelet inhibition are expected compared
to those observed in patients with normal renal function [see Clinical Pharmacology (12.3)]. It is not
known whether these concentrations will lead to similar efficacy and safety in patients with ESRD on
dialysis as were seen in PLATO, PEGASUS, THEMIS and THALES. OVERDOSAGE

There is currently no known treatment to reverse the effects of ticagrelor, and ticagrelor is not dialyzable. Treatment of overdose should follow local standard medical practice. Bleeding is the expected pharmacologic effect of overdosing. If bleeding occurs, appropriate supportive measures should be taken. latelet transfusion did not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding. Other effects of overdose may include gastrointestinal effects (nausea, vomiting, diarrhea) or ventricula pauses. Monitor the ECG.

for is a cyclopentyltriazolopyrimidine inhibitor of platelet activation and aggregation mediated by $\binom{1}{12}$ ADP-receptor. Chemically it is (1.5.25,3.8,5.5)-3-[7-[[(1.8.25)-2-(3,4-difluorophenyl)cyclopropyl -5- (propylthio)-3H-[1,2,3]-triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2 diol. The molecular formula of ticagrelor is $C_{23}H_{28}F_2N_6O_4S$ and its molecular weight is 522.57. The



Ticagrelor is a crystalline powder with an aqueous solubility of approximately 10 mcg/mL at room nistration contains 60 mg or 90 mg of ticagrelor and the following inactive Each tablet for oral adm rellow magnesium stearate, mannitol, polyethylene glycol 4000, povidone, sodium starch glycolate (type A), talc, and titanium dioxide,

CLINICAL PHARMACOLOGY Mechanism of Action Granelor and its major metabolite reversibly interact with the platelet P2Y₄₀ ADP-recentor to prevent

(ICHs) for ticagrelor and 6 ICHs for placebo. Fatal bleedings, almost all ICH, occurred in 11 for ticagrelor and in 2 for placebo.

Bradycardia

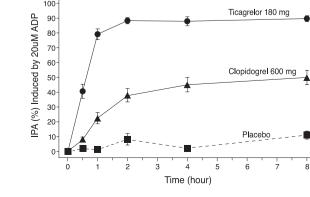
Inhibition of platelet aggregation (IPA) by ticagrelor and clopidogrel was compared in a 6-week study examining both acute and chronic platelet inhibition effects in response to 20 µM ADP as the platelet aggregation agonist. The onset of IPA was evaluated on Day 1 of the study following loading doses of 180 mg ticagrelor o

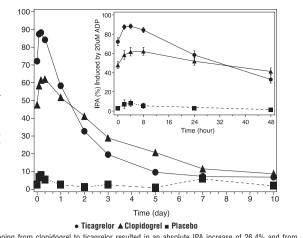
normalities
Uric Acid:

Uric Acid:

Uric Acid:

Or a shown in Figure 6, mean maximum IPA following the last dose of ticagrelor was 88% and 62% for clopidogrel. The insert in Figure 6 shows that after 24 hours, IPA in the ticagrelor group (58%) was similar to IPA in clopidogrel group (52%), indicating that patients who miss a dose of ticagrelor would still maintain IPA similar to IPA in the placebo group, It is not known how either bleeding risk or the protection of the province of the prov





Transitioning from clopidogrel to ticagrelor resulted in an absolute IPA increase of 26.4% and from ticagrelor to clopidogrel resulted in an absolute IPA decrease of 24.5%. Patients can be transitioned fro clopidogrel to ticagrelor without interruption of antiplatelet effect [see Dosage and Administration (2) **Pharmacokinetics**

Ficagrelor demonstrates dose proportional pharmacokinetics, which are similar in patients and healthy

r can be taken with or without food. Absorption of ticagrelor occurs with a median took of 1.5 h (range 1.0 to 4.0). The formation of the major circulation occurs with a median t_{max} of 2.5 h (range 1.5 to 5.0)

The mean absolute bioavailability of ticagrelor is about 36% (range 30% to 42%). Ingestion of a high-fat meal had no effect on ticagrelor C_{max} , but resulted in a 21% increase in AUC. The C_{max} of its major metabolite was decreased by 22% with no change in AUC. 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 AR-C124910XX) with a median t_{max} of 1.0 hour (range 1.0 to 4.0) for ticagrelor and 2.0 hours

(range 1.0 to 8.0) for AR-C124910XX The steady state volume of distribution of ticagrelor is 88 L. Ticagrelor and the active metabolite are

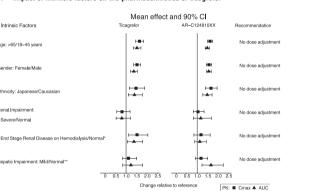
CYP3A4 is the major enzyme responsible for ticagrelor metabolism and the formation of its major active metabolite. Ticagrelor and its major active metabolite are weak P-glycoprotein substrates and inhibitors. The systemic exposure to the active metabolite is approximately 30% to 40% of the exposure of ticagrelor. Ticagrelor is a BCRP inhibitor.

The primary route of ticagrelor elimination is hepatic metabolism. When radiolabeled ticagrelor is tered, the mean recovery of radioactivity is approximately 84% (58% in feces, 26% in urin administrate, the mean recovery of radioactivity is approximately 94% (95% in recess, 25% in unite). Recoveries of ticagrelor and the active metabolite in urine were both less than 1% of the dose. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean $t_{1/2}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite.

he effects of age, gender, ethnicity, renal impairment and mild hepatic impairment on the pharmacokinetics of ticagrelor are presented in Figure 7. Effects are modest and do not require dose

Patients with End-Stage Renal Disease on Hemodialysis Patients with Ends-Stage Henal Disease on Hemodialysis
In patients with end stage renal disease on hemodialysis AUC and C_{max} of ticagrelor 90 mg administered
on a day without dialysis were 38% and 51% higher respectively, compared to subjects with normal
renal function. A similar increase in exposure was observed when ticagrelor was administered
immediately prior to dialysis showing that ticagrelor is not dialyzable. Exposure of the active metabolite
increased to a lesser extent. The IPA effect of ticagrelor was independent of dialysis in patients with end stage renal disease and similar to healthy adults with normal renal function

Figure 7 – Impact of intrinsic factors on the pharmacokinetics of ticagrelor

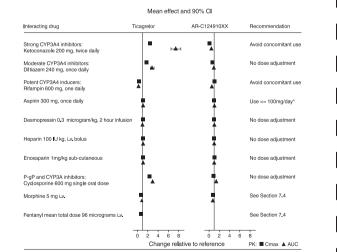


*Single dose of ticagrelor administered on a day without dialysis. lor has not been studied in patients with moderate or severe hepatic impairment

Effects of Other Drugs on Ticagrelor CYP3A4 is the major enzyme responsible for ticagrefor metabolism and the formation of its major active metabolis. The effects of other drugs on the pharmacokinetics of ticagrefor are presented in Figure 8 as change relative to ticagrefor given alone (test/reference). Strong CYP3A inhibitors (e.g., ketoconazole, itraconazole, and clarithromycin) substantially increase ticagrelor exposure. Moderate CYP3A inhibitors have lesser effects (e.g., diltiazem). CYP3A inducers (e.g., rifampin) substantially reduce ticagrelor blood levels. P-gp inhibitors (e.g., cyclosporine) increase ticagrelor exposure.

Coadministration of 5 mg intravenous morphine with 180 mg loading dose of ticagrelor decreased observed mean ticagrelor exposure by up to 25% in healthy adults and up to 36% in ACS patients undergoing PCI. T_{max} was delayed by 1 to 2 hours. Exposure of the active metabolite decreased to a similar extent. Morphine coadministration did not delay or decrease platelet inhibition in healthy adults. Mean platelet aggregation was higher up to 3 hours post loading dose in ACS patients coad

Coadministration of intravenous fentanyl with 180 mg loading dose of ticagrelor in ACS patients undergoing PCI resulted in similar effects on ticagrelor exposure and platelet inh Figure 8 – Effect of coadministered drugs on the pharmacokinetics of ticagrelor



*See Dosage and Administration (2) Effects of Ticagrelor on Other Drugs

In vitro metabolism studies demonstrate that ticagrelor and its major active metabolite are weak inhibitors of CYP3A4, potential activators of CYP3A5 and inhibitors of the P-gp transporter. In vitro metabolism studies demonstrate that ticagrelor is a BCRP inhibitor. Ticagrelor and AR-C124910XX were shown to have no inhibitory effect on human CYP1A2, CYP2C19, and CYP2E1 activity. For specific in vivo effects on the pharmacokinetics of simvastatin, atorvastatin, ethinyl estradiol, levonorgestero tolbutamide, digoxin and cyclosporine, see Figure 9.

MEDICATION GUIDE

Ticagrelor (tye ka' grel or) Tablets

What is the most important information I should know about ticagrelor tablets? Ticagrelor tablets are used to lower your chance of having, or dying from, a heart attack or stroke. Ticagrelor tablets (and similar drugs) can cause bleeding that can be serious and sometimes lead to death. In cases of serious bleeding, such

you may bruise and bleed more easily

 you are more likely to have nose bleeds • it will take longer than usual for any bleeding to stop

Call your healthcare provider right away, if you have any of these signs or symptoms of bleeding while taking ticagrelor

bleeding that is severe or that you cannot control

pink, red or brown urine

vomiting blood or your vomit looks like "coffee grounds"

red or black stools (looks like tar)

coughing up blood or blood clots

Do not stop taking ticagrelor tablets without talking to the healthcare provider who prescribes it for you. People who are treated with a stent, and stop taking ticagrelor tablets too soon, have a higher risk of getting a blood clot in the stent. having a heart attack, or dying. If you stop ticagrelor tablets because of bleeding, or for other reasons, your risk of a heart attack or stroke may increase

Your healthcare provider may instruct you to stop taking ticagrelor tablets 5 days before surgery. This will help to decrease your risk of bleeding with your surgery or procedure. Your healthcare provider should tell you when to start taking ticagrelor tablets again, as soon as possible after surgery.

healthcare provider about the dose of aspirin that you should take with ticagrelor tablets. In most cases, you should not

take a dose of aspirin higher than 100 mg daily. Do not take doses of aspirin higher than what your healthcare provider

Taking ticagrelor tablets with aspirin Ticagrelor tablets are taken with aspirin, unless your healthcare provider specifically tells you otherwise. Talk to your

tells you to take. Tell your healthcare provider if you take other medicines that contain aspirin, and do not take new overthe-counter medicines with aspirin in them. What are ticagrelor tablets? Ticagrelor tablets are a prescription medicine used to:

in people who have received stents for the treatment of ACS. · decrease your risk of a first heart attack or stroke in people who have a condition where the blood flow to the heart is decreased (coronary artery disease or CAD) who are at high risk for having a heart attack or stroke

 decrease your risk of stroke in people who are having a stroke (acute ischemic stroke) or mini-stroke (transient ischemic attack or TIA)

decrease your risk of death, heart attack, and stroke in people with a blockage of blood flow to the heart (acute coronary

syndrome or ACS) or a history of a heart attack. Ticagrelor tablets can also decrease your risk of blood clots in your stent

It is not known if ticagrelor tablets are safe and effective in children

Do not take ticagrelor tablets if you:

have a history of bleeding in the brain

• are bleeding now

 are allergic to ticagrelor or any of the ingredients in ticagrelor tablets. See the end of this Medication Guide for a complete list of ingredients in ticagrelor tablets. Before taking ticagrelor tablets, tell your healthcare provider about all of your medical conditions, if you:

have had bleeding problems in the past

ticagrelor tablets?

 have liver problems have a history of stroke

 are pregnant or plan to become pregnant. It is not known if ticagrelor tablets will harm your unborn baby. You and your healthcare provider should decide if you will take ticagrelor tablets. are breastfeeding or plan to breastfeed. It is not known if ticagrelor passes into your breast milk. You should not breastfeed during treatment with ticagrelor tablets. Talk to your healthcare provider about the best way to feed your baby

during treatment with ticagrelor tablets. Tell all of your healthcare providers and dentists that you are taking ticagrelor tablets. They should talk to the healthcare provider who prescribed ticagrelor tablets for you before you have any surgery or procedure.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Ticagrelor tablets may affect the way other medicines work, and other medicines may affect how ticagrelor tablets work. Certain medicines may increase your risk of bleeding.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine

How should I take ticagrelor tablets?

You may take ticagrelor tablets with or without food.

• Take ticagrelor tablets exactly as prescribed by your healthcare provider.

• Take ticagrelor tablets two times each day, around the same times each day.

• Your healthcare provider will tell you how many ticagrelor tablets to take and when to take them. • Take ticagrelor tablets with aspirin, unless your healthcare provider specifically tells you otherwise. See "What is the most important information I should know about ticagrelor tablets?'

• If you miss your scheduled dose of ticagrelor tablets, take your next dose at its scheduled time. Do not take 2 doses at the same time unless your healthcare provider tells you to.

 If you take too many ticagrelor tablets, call your healthcare provider or local poison control center or go to the nearest emergency room right away. If you are unable to swallow the tablet(s) whole, you may crush the ticagrelor tablet(s) and mix it with water. Drink all

the water right away. Refill the glass with water, stir, and drink all the water. Ticagrelor tablets may also be given through certain nasogastric (NG) tubes. Ask your healthcare provider for instructions

on how to take ticagrelor tablets through a NG tube.

as internal bleeding, the bleeding may result in the need for blood transfusions or surgery. While you take ticagrelor tablets:

· have had any recent serious injury or surgery plan to have surgery or a dental procedure. See "What is the most important information I should know about have a history of stomach ulcers or colon polyps have lung or breathing problems, such as COPD or asthma

What are the possible side effects of ticagrelor tablets?

Ticagrelor tablets can cause serious side effects, including:

See "What is the most important information I should know about ticagrelor tablets?"

- Shortness of breath. Tell your healthcare provider if you have new, worsening or unexpected shortness of breath when you are at rest, at night, or when you are doing any activity.
- Slow or irregular heartbeat.
- Irregular breathing. Tell your healthcare provider if you develop irregular breathing patterns when asleep or awake such as speeding up, slowing down or short pauses in breathing. Your healthcare provider will decide if you need further

These are not all of the possible side effects of ticagrelor tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ticagrelor tablets?

• Store ticagrelor tablets at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ticagrelor tablets and all medicines out of the reach of children.

General information about the safe and effective use of ticagrelor tablets.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ticagrelor tablets for a condition for which it was not prescribed. Do not give ticagrelor tablets to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ticagrefor tablets that is written for health professionals.

What are the ingredients in ticagrelor tablets?

Active ingredient: ticagrelor

Inactive ingredients: dibasic calcium phosphate (anhydrous), hypromellose 2910, iron oxide red, iron oxide yellow, magnesium stearate, mannitol, polyethylene glycol 4000, povidone, sodium starch glycolate (type A), talc, and titanium

Brands listed are trademarks of their respective owners.

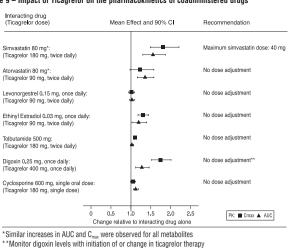
Manufactured In India By: Watson Pharma Private Limited, Verna, Salcette Goa 403 722 INDIA

Manufactured For: **Teva Pharmaceuticals**, Parsippany, NJ 07054

For more information call Teva at 1-888-838-2872.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Figure 9 – Impact of Ticagrelor on the pharmacokinetics of coadministered drugs



tic substudy cohort of PLATO, the rate of thrombotic CV events in the ticagrelor arm did not

NONCLINICAL TOXICOLOGY

Carcinogenesis Ticagrelor was not carcinogenic in the mouse at doses up to 250 mg/kg/day or in the male rat at doses up to 120 mg/kg/day (19 and 15 times the MRHD of 90 mg twice daily on the basis of AUC, respectively). Uterine carcinomas, uterine adenocarcinomas and hepatocellular adenomas were seen in female rats at doses of 180 mg/kg/day (29-fold the maximally recommended dose of 90 mg twice daily on the basis of AUC), whereas 60 mg/kg/day (8-fold the MRHD based on AUC) was not carcinogenic in female rats.

<u>Mutagenesis</u>
Ticagrelor did not demonstrate genotoxicity when tested in the Ames bacterial mutagenicity test, mouse lymphoma assay and the rat micronucleus test. The active O-demethylated metabolite did not demonstrate genotoxicity in the Ames assay and mouse lymphoma assay.

Impairment of Fertility
Ticagrelor had no effect on male fertility at doses up to 180 mg/kg/day or on female fertility at doses up to 200 mg/kg/day (>15-fold the MRHD on the basis of AUC). Doses of ≥10 mg/kg/day given to female rats caused an increased incidence of irregular duration estrus cycles (1.5-fold the MRHD based on AUC).

CLINICAL STUDIES Acute Coronary Syndromes and Secondary Prevention after Myocardial Infarction

PLATO PLATO (NCT00391872) was a randomized double-blind study comparing ticagrelor (N=9,333) to clopidogrel (N=9,291), both given in combination with aspirin and other standard therapy, in patients with acute coronary syndromes (ACS), who presented within 24 hours of onset of the most recent episode of chest pain or symptoms. The study's primary endpoint was the composite of first occurrence of cardiovascular death, non-fatal MI (excluding silent MI), or non-fatal stroke.

Patients who had already been treated with clopidogrel could be enrolled and randomized to either study treatment. Patients with previous intracranial hemorrhage, gastrointestinal bleeding within the past 6 months, or with known bleeding diathesis or coagulation disorder were excluded. Patients known bleeding diathesis or coagulation disorder were excluded. Patients taking anticoagulants were excluded from participating and patients who developed an indication for anticoagulation during the trial were discontinued from study drug. Patients could be included whether here was intent to manage the ACS medically or invasively, but patient randomization was not stratified

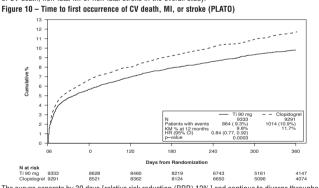
All patients randomized to ticagrelor received a loading dose of 180 mg followed by a maintenance dose of 90 mg twice daily. Patients in the clopidogrel arm were treated with an initial loading dose of clopidogrel 300 mg, if clopidogrel therapy had not already been given. Patients undergoing PCI could receive an additional 300 mg of clopidogrel at investigator discretion. A daily maintenance dose of spirin 75 mg to 100 mg was recommended, but higher maintenance doses of aspirin were allowed according to local judgment. Patients were treated for at least 6 months and for up to 12 months. according to local judgment. Patients were treated for all reast of months and to be of the PLATO patients were predominantly male (72%) and Caucasian (92%). About 43% of patients were >65 years and 15% were >75 years. Median exposure to study drug was 276 days. About half of the patients received pre-study clopidogrel and about 99% of the patients received aspirin at some time during PLATO. About 35% of patients were receiving a statin at baseline and 93% received a statin

Table 7 shows the study results for the primary composite endpoint and the contribution of each component to the primary endpoint. Separate secondary endpoint analyses are shown for the overall occurrence of CV death. MI and stroke and outsile productions.

	Ticagrelor* N=9,333	Clopidogrel N=9,291	Hazard Ratio (95% CI)	<i>p</i> -value
	Events / 1,000 patient years	Events / 1,000 patient years		
Composite of CV death, MI, or stroke	111	131	0.84 (0.77, 0.92)	0.0003
CV death	32	43	0.74	
Non-fatal MI	64	76	0.84	
Non-fatal stroke	15	12	1.24	
Secondary endpoints†				
CV death	45	57	0.79 (0.69, 0.91)	0.0013
MI‡	65	76	0.84 (0.75, 0.95)	0.0045
Stroke [‡]	16	14	1.17 (0.91, 1.52)	0.22
All-cause mortality	51	65	0.78 (0.69, 0.89)	0.0003

†Note: rates of first events for the components CV Death, MI and Stroke are the actual rates for first Finder. Takes of instructions to be component and do not add up to the overall rate of events in the composite endpoint Fincluding patients who could have had other non-fatal events or died.

The Kaplan-Meier curve (Figure 10) shows time to first occurrence of the primary composite endpoint



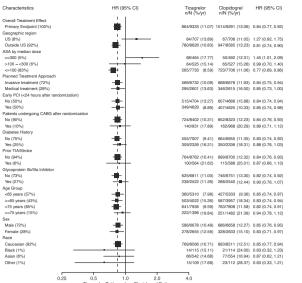
The curves separate by 30 days [relative risk reduction (RRR) 12%] and continue to diverge throughout the 12-month treatment period (RRR 16%). Among 11,289 patients with PCI receiving any stent during PLATO, there was a lower risk of stent thrombosis (1.3% for adjudicated "definite") than with clopidogrel (1.9%) (HR 0.67, 95% Cl 0.50 to

0.91; p=0.009). The results were similar for drug-eluting and bare metal stents. A wide range of demographic, concurrent baseline medications, and other treatment differences were examined for their influence on outcome. Some of these are shown in Figure 11. Such analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses. Most of the analyses show effects consistent with the overall results, but there are two exceptions: a finding of heterogeneity by region and a strong influence of the maintenance dose of aspirin. These

Most of the characteristics shown are baseline characteristics, but some reflect post-randomization

Both the 60 mg and 90 mg regimens of ticagrelor in combination with aspirin were superior to aspirin determinations (e.g., aspirin maintenance dose, use of PCI).

Figure 11 - Subgroup analyses of (PLATO)

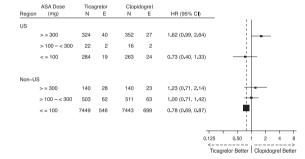


and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be

effect in North America, numerically inferior to the control and driven by the US subset. The statistical test for the US/non-US comparison is statistically significant (p=0.009), and the same trend is present for both CV death and non-fatal MI. The individual results and nominal p-values, like all subset analyses, need cautious interpretation, and they could represent chance findings. The consistency of the differences in both the CV mortality and non-fatal MI components, however, supports the possibility that the finding is reliable. A wide variety of baseline and procedural differences between the US and non-US (including intended

invasive vs. planned medical management, use of GPIlb/Illa inhibitors, use of drug eluting vs. bare-metal stents) were examined to see if they could account for regional differences, but with one exception, aspirin maintenance dose, these differences did not appear to lead to differences in outcome. Aspirin Dose
The PLATO protocol left the choice of aspirin maintenance dose up to the investigator and use patterns

were different in US sites from sites outside of the US. About 8% of non-US investigators administered aspirin doses above 100 mg, and about 2% administered doses above 300 mg. In the US, 57% of patients received doses above 100 mg and 54% received doses above 300 mg. Overall results favored iccaprelor when used with low maintenance doses (<100 mg) of aspirin, and results analyzed by aspirin dose were similar in the US and elsewhere. Figure 10 shows overall results by median aspirin dose. Figure 12 shows results by region and dose.



Like any unplanned subset analysis, especially one where the characteristic is not a true baseline characteristic (but may be determined by usual investigator practice), the above analyses must be treated with caution. It is notable, however, that aspirin dose predicts outcome in both regions with a similar pattern, and that the pattern is similar for the two major components of the primary endpoint Despite the need to treat such results cautiously, there appears to be good reason to restrict aspirir

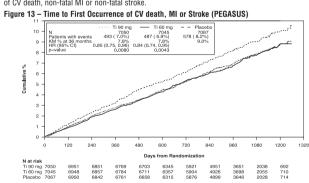
maintenance dosage accompanying ticagrelor to 100 mg. Higher doses do not have an established benefit in the ACS setting, and there is a strong suggestion that use of such doses reduces the

PEGASUS
The PEGASUS TIMI-54 study (NCT01225562) was a 21,162-patient, randomized, double-blind, placebocontrolled, parallel-group study. Two doses of ticagrelor, either 90 mg twice daily or 60 mg twice daily,
coadministered with 75 mg to 150 mg of aspirin, were compared to aspirin therapy alone in patients
with history of MI. The primary endpoint was the composite of first occurrence of CV death, non-fatal
MI and non-fatal stroke. CV death and all-cause mortality were assessed as secondary endpoints. Patients were eligible to participate if they were ≥50 years old, with a history of MI 1 to 3 years prior

The Kaplan-Meier curve (Figure 15) shows time to first occurrence of the primary composite endpoint Patients were eligible to participate if they were ≥50 years old, with a history of MI 1 to 3 years prior to randomization, and had at least one of the following risk factors for thrombotic cardiovascular events: age ≥65 years, diabetes mellitus requiring medication, at least one other prior MI, evidence of multivessel coronary artery disease, or creatinine clearance <60 mL/min. Patients could be randomized regardless of their prior ADP receptor blocker therapy or a lapse in therapy. Patients requiring or who were expected to require renal dialysis during the study were excluded. Patients with any previous intracranial hemorrhage, gastrointestinal bleeding within the past 6 months, or with known bleeding diathesis or coagulation disorder were excluded. Patients taking anticoagulants were excluded from participating and patients who developed an indication for anticoagulation during the trial were discontinued from study drug. A small number of patients with a history of stroke were included. Based on information external to PEGASUS, 102 patients with a history of stroke (90 of whom received study drug) were terminated early and no further such patients were enrolled. drug) were terminated early and no further such patients were enrolled

Patients were treated for at least 12 months and up to 48 months with a median follow up time of Patients were predominantly male (76%) Caucasian (87%) with a mean age of 65 years, and 99.8% of patients received prior aspirin therapy.

The Kaplan-Meier curve (Figure 13) shows time to first occurrence of the primary composite endpoint of CV death, non-fatal Mi or non-fatal stroke.



alone in reducing the incidence of CV death, MI or stroke. The absolute risk reductions for ticagrelor plus aspirin vs. aspirin alone were 1.27% and 1.19% for the 60 mg and 90 mg regimens, respectively. Although the efficacy profiles of the two regimens were similar, the lower dose had lower risks of bleeding and dyspnea.

Table 8 shows the results for the 60 mg plus aspirin regimen vs. aspirin alone.

Table 8 - Incidences of the primary composite endpoint, primary composite endpoint components

and seco	ndary endpoints (PE	GASUS)		
	Ticagrelor* N=7,045	Placebo N=7,067	HR (95% CI)	<i>p</i> -value
	Events / 1,000 patient years	Events / 1,000 patient years		
ime to first CV eath, MI, or roke†	26	31	0.84 (0.74, 0.95)	0.0043
V Death ^{‡,§}	9	11	0.83 (0.68, 1.01)	
lyocardial farction§	15	18	0.84 (0.72, 0.98)	
troke§	5	7	0.75 (0.57, 0.98)	
Il-cause	16	18	0.89 (0.76, 1.04)	

mortainty+

CI = Confidence interval; CV = Cardiovascular; HR = Hazard ratio; MI = Myocardial infarction
N = Number of patients.

60 mg BID

Primary composite endpoint

§ The event rate for the components CV death, MI and stroke are calculated from the actual number

Characteristics	HR (95% CI)	Ticagrelor n/N (%/yr)	Placebo n/N (%/yr)	HR (95% CI)
Overall Treatment Effect	<u> </u>			
Primary endpoint (100%) Age group		487/7045 (2.62)	578/7067 (3.10)	0.84 (0.74, 0.95
<65 years (46%)		195/3283 (2,24)	243/3154 (2,93)	0.76 (0.63, 0.9
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%) Weight group		76/968 (3.09)	69/943 (2.90)	1.07 (0.77, 1.48
<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/m²2 (32%)		194/2335 (3.13)	186/2223 (3,18)	0.99 (0.81, 1.21
Geographic region	: 1			
US (12%)	-	65/863 (2.93)	82/872 (3.67)	0.78 (0.56, 1.08
Outside US (88%) History of >1 MI (>=1 year	vior to randomization)	422/6182 (2.58)	496/6195 (3.03)	0.85 (0.74, 0.96
Yes (17%)	and to randomization)	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 <2 years (61%)	andomization		07511000 10 0 11	0.7710.00.00
<2 years (61%) >=2 years (38%)		293/4331 (2.60) 194/2704 (2.65)	375/4333 (3.34) 202/2724 (2.74)	0.77 (0.66, 0.90 0.96 (0.79, 1.17
Type of qualifying MI	_	10-12/04 (2:00)	EOLILIE (E.I.+)	0.00 (0.70, 1.71
STEMI (54%)		218/3757 (2.19)	268/3809 (2.68)	0.81 (0.68, 0.97
NSTEMI (40%) Diabetes Mellitus		231/2842 (3.09)	262/2843 (3.47)	0.89 (0.74, 1.06
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 Arter	/ Disease			
Yes (60%)	 -	290/4190 (2.64)	355/4213 (3.23)	0.81 (0.70, 0.95
No (40%) Creatinine clearance (Cocl	roft Gault) at enrolment	196/2852 (2.57)	223/2854 (2.92)	0.88 (0.72, 1.06
<60 mL/min (19%)	on dusty at oncoment	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	<u> </u>		100 HOOF 10 TO	
Yes (83%) No (17%)		362/5874 (2.34) 125/1170 (4.03)	430/5835 (2.79) 148/1231 (4.61)	0.83 (0.72, 0.96 0.87 (0.68, 1.10
Type of stent	1	123/170 (4.00)	14011201 (4.01)	0.07 (0.00, 1.10
Any DES (39%)		188/2769 (2.63)	222/2784 (3.08)	0.85 (0.70, 1.03
BMS only (36%) Current smoker		140/2598 (2.00)	156/2532 (2.29)	0.87 (0.69, 1.09
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 rece	otor 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 >12 months (23%)	70)	143/2231 (2.41) 108/1661 (2.39)	175/2230 (2.98) 100/1645 (2.21)	0.81 (0.65, 1.01 1.08 (0.82, 1.42

RRR) and from 361 days and onwards (16% RRR) were similar

Note: The figure above presents effects in various subgroups all of which are baseline characteristics and most of which were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interoreted.

Coronary Artery Disease but No Prior Stroke or Myocardial Infarction

HEMIS
The THEMIS study (NCT01991795) was a double-blind, parallel group, study in which 19,220 patients with CAD and Type 2 Diabetes Mellitus (12DM) but no history of MI or stroke were randomized to twice daily ticagrelor or placebo, on a background of 75 mg to 150 mg of aspirin. The primary endpoint was the composite of first occurrence of CV death, MI, and stroke. CV death, MI, ischemic stroke, and all-cause death were assessed as secondary endpoints.

Patients were eligible to participate if they were ≥50 years old with CAD, defined as a history of PCI or CABG, or angiographic evidence of ≥50% lumen stenosis of at least 1 coronary artery and T2DM treated for at least 6 months with glucose-lowering medication. Patients with previous intracerebral hemorrhage, gastrointestinal bleeding within the past 6 months, known bleeding diathesis, and coagulation disorder were excluded. Patients taking anticoagulants or ADP receptor antagonists were excluded from participating, and patients who developed an indication for those medications during the trial were discontinued from study drug.

Patients were treated for a median of 33 months and up to 58 months

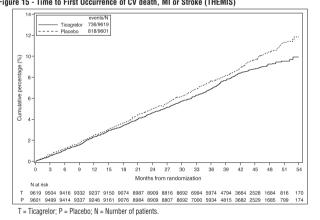
Patients were predominantly male (69%) with a mean age of 66 years. At baseline, 80% had a history of coronary artery revascularization; 58% had undergone PCI, 29% had undergone a CABG and 7% had undergone both. The proportion of patients studied in the US was 12%. Patients in THEMIS had established CAD and other risk factors that put them at higher cardiovascular risk. Ticagrelor was superior to placebo in reducing the incidence of CV death, MI, or stroke. The effect on the omposite endpoint was driven by the individual components MI and stroke; see Table 9.

Table 9 - Primary composite endpoint, primary endpoint components, and secondary endpoints

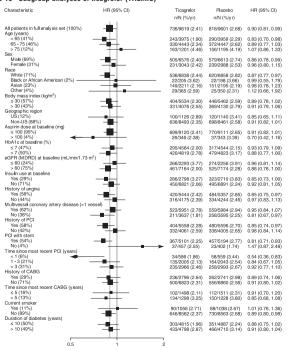
	Ticagrelor Placebo N=9,619 N=9,601		HR (95% CI)	<i>p</i> -value
	Events / 1,000 patient years	Events / 1,000 patient years		
Time to first CV death, MI, or stroke*	24	27	0.90 (0.81, 0.99)	0.04
CV death [†]	12	11	1.02 (0.88, 1.18)	
Myocardial infarction†	9	11	0.84 (0.71, 0.98)	
Stroke [†]	6	7	0.82 (0.67, 0.99)	
Secondary endpoints				
CV death	12	11	1.02 (0.88, 1.18)	
Myocardial infarction	9	11	0.84 (0.71, 0.98)	
Ischemic stroke	5	6	0.80 (0.64, 0.99)	
All-cause death	18	19	0.98 (0.87, 1.10)	

† The event rate for the components CV death, MI and stroke are calculated from the actual number

Figure 15 - Time to First Occurrence of CV death, MI or Stroke (THEMIS)



he treatment effect of ticagrelor appeared similar across patient subgroups, see Figure 16. Figure 16 -Subgroup analyses of ticagrelor (THEMIS)



n PEGASUS, the relative risk reduction (RRR) for the composite endpoint from 1 to 360 days (17% made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent

The treatment effect of ticagrelor 60 mg over aspirin appeared similar across most pre-defined 14.3 Acute Ischemic Stroke or Transient Ischemic Attack (TIA)

<u>FHALES</u>
The THALES study (NCT03354429) was a 11,016-patient, randomized, double-blind, parallel-group study of ticagrelor 90 mg twice daily versus placebo in patients with acute ischemic stroke or transient ischemic attack (TIA). The primary endpoint was the first occurrence of the composite of stroke and death up to 30 days. Ischemic stroke was assessed as one of the secondary endpoints.

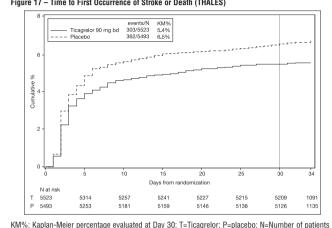
Patients were eligible to participate if they were \ge 40 years old, with non-cardioembolic acute ischemic stroke (NIHSS score \le 5) or high-risk TIA (defined as ABCD² score \ge 6 or ipsilateral atherosclerotic stenosis \ge 50% in the internal carotid or an intracranial artery). Patients who received thrombolysis or thrombectomy within 24 hours prior to randomization were not eligible.

Patients were randomized within 24 hours of onset of an acute ischemic stroke or TIA to receive 30 days of either ticagrelor (90 mg twice daily, with an initial loading dose of 180 mg) or placebo, on a background of aspirin initially 300 mg to 325 mg then 75 mg to 100 mg daily. The median treatment duration was 31 days.

Ticagrelor was superior to placebo in reducing the rate of the primary endpoint (composite of stroke and death), corresponding to a relative risk reduction (RRR) of 17% and an absolute risk reduction (ARR) of 1.1% (Table 10). The effect was driven primarily by a significant reduction in the stroke component of the primary endpoint (19% RRR, 1.1% ARR).

Table 10 - Incidences of the primary composite endpoint, primary composite endpoint components,

and seco	ndary endpo	int (THALE	S)			
	Ticagrelor N=5,523			Placebo N=5,493 HR (95% CI)		<i>p</i> -value
	n (patients with event)	KM%	n (patients with event)	KM%	1111 (55 /6 61)	p value
Time to first Stroke or Death	303	5.4%	362	6.5%	0.83 (0.71, 0.96)	0.015
Time to first Stroke*	284	5.1%	347	6.3%	0.81 (0.69, 0.95)	
Time to Death*	36	0.6%	27	0.5%	1.33 (0.81, 2.19)	
Secondary Endpoint						
Time to first Ischemic Stroke	276	5.0%	345	6.2%	0.79 (0.68, 0.93)	0.004
CI = Confidence interval *The number of patient						



Ticagrelor's treatment effect on stroke and on death accrued over the first 10 days and was sustained at 30 days. Although not studied, this suggests that shorter treatment could result in similar benefi The treatment effect of ticagrelor was generally consistent across pre-defined subgroups (Figure 18).

Figure 18 – Subgroup analyses of ticagrelor 90 mg (THALES)

gel gywans) (20 4 (98%) (20 4	haracteristic	HR (95% CI)	Ticagrelor n/N (%)	Placebo n/N (%)	HR (95% CI)
65-75 (20%) 101/1749 (6,849) 22/1869 (8,774) 0.08 (0.0		-	303/5523 (5.5%)	362/5493 (6.6%)	0.83 (0.71, 0.96)
275 C076	<65 (48%)	_	132/2676 (4.9%)	164/2632 (6.2%)	0.79 (0.63, 0.99)
ise. Make 1919 Make					0.85 (0.65, 1.11)
Make (1914) 1908/415 (6,194) 220,5322 (7.114) 0,08 (2.05 (6.			70/1098 (6.4%)	76/1052 (7.2%)	0.88 (0.64, 1.22)
Fermals (G99) 10927 108 (5.09) 12727 17 (6.79) 0.85 0.05 0.05 0.05 0.05 0.05 0.05 0.05		_	198/3415 (5.8%)	235/3322 (7.1%)	0.82 (0.68, 0.99)
When 64% 1002873 6,19% 1727848 6,47% 27280 6,00% 272 6,00% 27280 6,00% 2	Female (39%)				0.85 (0.65, 1.10)
Black or Arican American (-1%)		_			
Asian (45%) 1692/352 (7.1%) 212/359 (1.1%) 0.08 (0.7.6 (0.1%) 17/10 (6.7%) 0.08 (0.1%) 17/10 (6.7%) 0.08 (0.1%) 17/10 (6.7%) 0.08 (0.1%) 0					0.78 (0.60, 1.00)
Cher (15%) - (77,176 (20%) - (177,186 (27%) - (177,186 (2					0.86 (0.71, 1.05)
revent flag - 7.0 (23%) - 127,224 (6.5%) - 162,238 (6.8%) - 172,217 (6.6%) - 172,217 (6.9%) - 172,217 (6.9%) - 172,217 (6.9%) - 172,217 (6.9%) - 172,217 (6.9%) - 172,217 (6.9%) - 182,217 (6.9%)					0.69 (0.26, 1.82)
- 270 (43%)		_	11110 (41010)	10/11/4/01/70/	olos (oles, rise)
270 07%)		_	127/2324 (5.5%)	162/2388 (6.8%)	0.80 (0.63, 1.01)
Mil Sgurn' - (20 11%)		_			0.85 (0.69, 1.04)
300 (19%) 41/1047 (29%) 56/1026 (5.5%) C.71 (0.48 organization region region region region (4.0%) 18/2037 (7.4%) 21/2058 (0.7%) 0.7% (0.48 organization region regi	MI (kg/m²)	T I	(01.177)	(010 /0)	,-100) 110-1)
300 (19%) 41/1047 (29%) 56/1026 (5.5%) C.71 (6.4.8)			258/4446 (5.8%)	301/4429 (6.8%)	0.85 (0.72, 1.00)
segraphic region (475)	≥30 (19%) ———				0.71 (0.48, 1.06)
Europe (61%) Output and 20x1 A (17x)					
North America (c1%)		-			0.85 (0.70, 1.04)
Central and South America (81%) 13/234 (4.0%) 18/232 (5.0%) 0.71 (0.35 (80					0.79 (0.61, 1.03)
Image		_			
Sinche NNRS acces 38 81 N) 1580/3059 (4.7%) 190/312 (6.7%) 0.08 (2.06 N) 1580/312 (6.7%) 190/312 (6.7%) 0.08 (2.06 N) 1580/312 (6.7%) 190/312 (6.7%) 190/312 (6.7%) 10.08 (2.06 N) 1580/312 (6.7%) 190/312 (6.7%) 10.08 (2.06 N) 1580/312 (6.7%) 19			13/324 (4.0%)	18/323 (5.6%)	0.71 (0.35, 1.46)
Stroke NIK185 score 4 or 5 (00%) 129/1673 (77.7%) 50,046 (0.0.1%) 0.0.8 (0.0.6.1%) 129/1673 (77.7%) 50,046 (0.0.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.7%) 50,046 (0.0.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77.6.1%) 140/1673 (77.6.1%) 0.0.8 (0.0.6.1%) 140/1673 (77		<u> </u>	450 MOSO (4 70/)	10010010 (7 70)	0.00 (0.00 1.01)
TA (949) (3.39) 229-60 (4.19) 0.00 0.00 0.00 0.00 0.00 0.00 0.00 0.					0.82 (0.66, 1.01)
mer from irode event to randomisation (1) - 272 (239) - 389/1812 (6.4%) - 31/4/1776 (6.4%) - 30/4/17 (6.7%) - 30/4/					0.84 (0.66, 1.06)
12 (27%) 99(1912 (2.4%) 114/1776 (3.4%) 0.48 (0.48)			10/491 (3,3%)	zzronu (4.1%)	0.00 (0.42, 1.02)
2005771 (5.5%) 248977 (6.7%) 0.80 0.00 0.00 0.00 0.00 0.00 0.00 0.			98/1812 (5.4%)	114/1776 (6.4%)	0.84 (0.64, 1.10)
mer from indise event to loading dose (f) - (27 (20%) 88/1655 (6,4%) 109/1659 (8,4%) 0.44 (0.35 - (27 (20%) 88/1655 (6,4%) 24/1787 (2.7%) 0.82 (0.36 - (27 (20%) 11/1823 (6,5%) 24/1787 (2.7%) 0.82 (0.36 - (27 (20%) 11/1823 (6,5%) 24/1787 (2.7%) 0.82 (0.36 - (27 (20%) 11/1823 (6,5%) 24/1787 (2.7%) 0.82 (0.36 - (27 (20%) 11/1823 (6,5%) 24/1787 (2.7%) 0.82 (0.36 - (27 (20%) 11/1823 (6,5%) 24/1787 (2.7%) 0.82 (0.36 - (27 (20%) 11/1823 (6,5%) 0.47 (2.7%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (20%) 11/1823 (6,5%) 0.48 (0.36 - (27 (27 (27 (27 (27 (27 (27 (27 (27 (27		_			0.82 (0.69, 0.99)
12 (2009)		TI	200.0711 (0.070)	2 (0.170)	0.00 (0.00) 0.00)
12 (1994) 21 (1982) 2 (5.9) 29 (4787) (1797) 0.08 (0			89/1655 (5,4%)	106/1659 (6,4%)	0.84 (0.63, 1.11)
Selection melliflus		_	211/3823 (5.5%)	254/3787 (6.7%)	0.82 (0.68, 0.98)
No (71%)		T I			
Vest 1794 2844208 (6.31%) 28644222 (8.81%) 78 (0.7					0.93 (0.72, 1.20)
Ves (77%) Ves (77%) Page 444698 (5.3%) 28444298 (6.3%) 7871226 (5.1%) 28444298 (6.3%) 2844429 (6.7%) 28444298 (6.3%) 2844429 (6.7%) 2844429 (6.7%) 2844429 (6.7%) 2844429 (6.7%) 2844429 (6.7%) 2844429 (6.7%) 2844429 (6.7%) 2844429 (6.7%) 284449 (6.7%) 284449 (6.7%) 284449 (6.7%) 284449 (6.7%) 284476 (6.7%) 284449 (188/3934 (4.8%)	241/3936 (6.1%)	0.78 (0.64, 0.94)
No (23%) 75 1/22 (6.17) 6 76 1/27 (6.07) 5 1.02 (0.74 for the southwest stocks or TIA for the solutions and the solution of t		_			
Tree ischaemien stroke or TIA **Pag (D94)		——— L			0.78 (0.65, 0.93)
Ves (DN)		_	75/1225 (6.1%)	76/1271 (6.0%)	1.02 (0.74, 1.41)
No (80%) 2444401 (5.5%) 2744392 (2.7%) 0.80 (0.75 (7.76 (5.7	rior ischaemic stroke of TIA	_	EQ. (4.00 (E. 00/)	0001101 (0.000)	0.05 (0.46, 0.00)
Variety Vari					
Yes (10%) 31/53/2 (8.8%) 30/53/2 (8.8%) 30/53/3 (8.9%) 1.04 (0.05) No (00%) 272/499 (8.4%) 33/549 (8.4%) 33/5490 (8.7%) 0.41 (0.08) No (27%) 41/744 (8.4%) 96/79 (8.3%) 1.02 (0.05) No (27%) 262/479 (8.5%) 32/64/48 (8.8%) 30/79 (8.3%) 1.02 (0.05) No (27%) 41/754 (8.4%) 46/79 (8.2%) 0.30 (0.50) 0.00 (0.50) Yes (10%) 41/855 (4.7%) 46/79 (8.2%) 0.30 (0.50) 0.00 (0.50) No (27%) 41/855 (4.7%) 31/64/48 (8.8%) 0.00 (0.50) 0.00 (0.50) No (27%) 41/85 (4.7%) 31/64/48 (8.9%) 0.00 (0.50) 0.00 (0.50) No (27%) 41/85 (4.7%) 31/64/48 (8.9%) 0.00 (0.50) 0.00 (0.50) No (27%) 41/85 (4.7%) 31/64/48 (8.9%) 0.00 (0.50) 0.00 (0.50) Corrent (27%) 85/79 (0.5%) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) No (27%) 41/85 (4.7%) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) Corrent (27%) 50/80 (0.5%)			244/4401 (0,5%)	219/4392 (0.2%)	0.89 (0.75, 1.05)
No (90%) 272/4991 (6,14%) 332/4990 (87.7%) 0.81 (0.08 for 6.8A) 41774 (6.4%) 366/879 (6.3%) 1.02 (0.08 for 6.8A) 41774 (6.4%) 366/879 (6.3%) 1.02 (0.08 for 5.8A) 41774 (6.4%) 366/879 (6.3%) 1.02 (0.08 for 5.8A) 41774 (6.4%) 366/879 (6.3%) 1.02 (0.08 for 5.8A) 41774 (6.4%) 468/879 (6.2%) 0.80 (0.08 for 5.8A) 4188 (6.4%) 468/879 (6.2%) 0.80 (0.08 for 5.8A) 4188 (6.4%) 4188 (6.4%) 1.02 (0.08 for 5.8A) 4188 (6.4%) 4188 (6.4%) 1.02 (0.08 for 5.8A) 4188 (6.4%) 1.02 (0.08 for 5.8A) 4188 (6.5%) 1.0			31/532 /5 8941	30/533 /5 6941	1,04 (0,63, 1,71)
For ASA					0,81 (0,69, 0,95)
Ves (15%) 417/54 (54.44) 30679 (5.3%) 1.02 (0.50) No (87%) 202/4709 (5.5%) 204/4709 (5.5%) 204/404 (8.6%) 0.0 10.00 No (87%) 41865 (4.7%) 46979 (2.2%) 0.0 0.50 No (84%) 202/4685 (5.6%) 315444 (8.6%) 0.0 0.50 moking status 811004 (5.5%) 1001428 (7.1%) 0.7 70.37 Current (27%) 851004 (5.5%) 1001428 (7.1%) 0.08 (0.5%) Henry (64%) 1000008 (5.5%) 200008 (5.5%) 0.08 (0.5%)		7 1	2.12.4001 (0.470)	OUE -000 (0.1 70)	0.01 (0.00, 0.00)
No (87%) 2624789 (5.5%) 26244814 (6.8%) 0.81 (0.08)			41/754 (5,4%)	36/679 (5,3%)	1.02 (0.65, 1.60)
Formet (17%) 85/09/00 (5.7%) 40/09/20 (6.7%) 0.00 (0.50) Correlt (27%) 85/09/00 (5.5%) 50/09/00 (5.5%) 0.00 (0.50) Formet (17%) 50/09/00 (5.5%) 0.00 (0.50) 0.00 (0.50) Formet (17%) 50/09/00 (5.5%) 0.00 (0.50) 0.00 (0.50) Formet (17%) 60/09/00 (5.5%) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) Formet (17%) 60/09/00 (5.5%) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) Formet (17%) 60/09/00 (5.5%) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) 0.00 (0.50) 0.00		[0.81 (0.69, 0.95)
No (84%) 262/4688 (8,6%) 316/4614 (8,6%) 0.82 (0.08 (0				(0.070)	,
moking status 821504 (5.5%) 1021428 (7.1%) 0.77 (0.57 (6.5%) 1021428 (7.1%) 0.77 (0.57 (6.5%) 1021428 (7.1%) 0.83 (0.58 (6.5%) 0.83 (0.58			41/865 (4.7%)	46/879 (5.2%)	0.90 (0.59, 1.37)
Current (27%) 83/1564 (5.5%) 102/1428 (7.1%) 77/0.57 Former (17%) \$2,980 (5.3%) 5,092 (5.3%) 5,092 (5.3%) 5,092 (5.3%) 0,002 (5.3%) 0,002 (5.3%) 0,002 (6.6%)	No (84%)	-			0.82 (0.69, 0.96)
Former (17%) 52/980 (5.3%) 53/925 (5.7%) 0.93 (0.83 (0.5%) 168/3038 (5.5%) 207/3140 (6.6%) 0.83 (0.58		T			
Never (56%) 168/3038 (5.5%) 207/3140 (6.6%) 0.83 (0.68					0.77 (0.57, 1.03)
					0.93 (0.63, 1.36)
	Never (56%)	_	168/3038 (5.5%)	207/3140 (6.6%)	0.83 (0.68, 1.02)
0,5 0,8 1 1,25 2	0.5	0.8 1 1.25	2		

Note: The figure above presents effects in various subgroups all of which are baseline characteristics and were pre-specified. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted. At Day 30, there was an absolute reduction of 1.2% (95% CI: -2.1%, -0.3%) in the incidence of nonhemorrhagic stroke and death (excluding fatal bleed) favoring ticagrelor (294 events; 5,3%) over placebi (359 events: 6.5%) in the intention-to-treat population. In the same population, there was an absolute increase of 0.4% (95% CI: 0.2%, 0.6%) in the incidence of GUSTO severe bleeding unfavorable to ticagrelor arm (28 events: 0.5%) compared to the placebo arm (7 events: 0.1%).

16 HOW SUPPLIED/STORAGE AND HANDLING

60 mg - Light yellow to yellow, oval shaped, film-coated tablet debossed with "137" on one side and "A" on the other side. Tablets are supplied in bottles of 60 (NDC 0480-2688-06).

90 mg - Light yellow to yellow, round shaped, film-coated tablet debossed with "A91" on one side and plain on the other side. Tablets are supplied in bottles of 60 (NDC 0480-2695-06).

Storage and Handling Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP controlled room

Dispense in a tight container as defined in the USP.

Advise the patient to read the FDA-approved patient labeling (Medication Guide)

Advise patients daily doses of aspirin should not exceed 100 mg and to avoid taking any other medications that contain aspirin.

Will bleed and bruise more easily

Will take longer than usual to stop bleeding
 Should report any unanticipated, prolonged or excessive bleeding, or blood in their stool or urine.

Advise patients to contact their doctor if they experience unexpected shortness of breath, especially

Advise patients to inform physicians and dentists that they are taking ticagrelor tablets before any

Advise women that breastfeeding is not recommended during treatment with ticagrelor tablets [see Use

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Note: The figure above presents effects in various subgroups all of which are baseline characteristics The 95% confidence limits that are shown do not take into account how many comparisons were