In patients with acute ischemic

STROKE

(NIHSS ≤5) or high-risk TIA (ABCD^2 ≥6)

START BRILINTA WITHIN 24 HOURS

The only $P2Y_{12}$ inhibitor FDA approved for initiation in the acute setting to reduce the risk of subsequent stroke[1,2]

ABCD^2=Age, Blood pressure, Clinical features, Duration of TIA, and Diabetes mellitus; NIHSS=National Institutes of Health Stroke Scale; TIA=transient ischemic attack.

INDICATIONS

BRILINTA is indicated to reduce the risk of cardiovascular death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or a history of myocardial infarction. For at least the first 12 months following ACS, it is superior to clopidogrel. BRILINTA also reduces the risk of stent thrombosis in patients who have been stented for treatment of ACS.
BRILINTA is indicated 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 diabetes.
BRILINTA is indicated to reduce the risk of stroke in patients with acute ischemic stroke (NIH Stroke Scale Score ≤5) or high-risk transient ischemic attack (TIA).

DOSING

In the management of ACS, initiate BRILINTA treatment with a 180-mg loading dose. Administer 90 mg twice daily during the first year after an ACS event. After one year administer 60 mg twice daily.
In patients with CAD but no prior stroke or MI, administer 60 mg twice daily.
In patients with acute ischemic stroke or high-risk TIA, initiate treatment with a 180-mg loading dose of BRILINTA and then continue with 90 mg twice daily for up to 30 days. The treatment effect accrued early in the course of therapy.
Use BRILINTA with a loading dose of aspirin (300 to 325 mg).
Use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg.

IMPORTANT SAFETY INFORMATION FOR BRILINTA® (ticagrelor) 60-MG AND 90-MG TABLETS

WARNINGS:

A. BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal bleeding**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage**
- **Do not start BRILINTA in patients undergoing urgent coronary artery bypass graft surgery**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events**

B. ASPIRIN DOSE AND BRILINTA EFFECTIVENESS IN PATIENTS WITH ACS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided**

CONTRAINDICATIONS

- BRILINTA is contraindicated in patients with a history of intracranial hemorrhage or active pathological bleeding such as peptic ulcer or intracranial hemorrhage. BRILINTA is also contraindicated in patients with hypersensitivity (eg, angioedema) to ticagrelor or any component of the product

WARNINGS AND PRECAUTIONS

- Dyspnea was reported more frequently with BRILINTA than in patients treated with control agents. Dyspnea from BRILINTA is often self-limiting
- In patients being treated for coronary artery disease, discontinuation of BRILINTA will increase the risk of MI, stroke, and death. When possible, interrupt therapy with BRILINTA for 5 days prior to surgery that has a major risk of bleeding. If BRILINTA must be temporarily discontinued, restart as soon as possible
- Ticagrelor can cause ventricular pauses. Bradyarrhythmias including AV block have been reported in the post-marketing setting. Clinical trials excluded patients at increased risk of bradyarrhythmias not protected by a pacemaker, and they may be at increased risk of developing bradyarrhythmias
- Avoid use of BRILINTA in patients with severe hepatic impairment. Severe hepatic impairment is likely to increase serum concentration of ticagrelor and there are no studies of BRILINTA in these patients
- Central sleep apnea (CSA) including Cheyne-Stokes respiration (CSR) has been reported in the post-marketing setting in patients taking ticagrelor, including recurrence or worsening of CSA/CSR following rechallenge.
- In patients with Heparin Induced Thrombocytopenia (HIT): False negative results for HIT-related platelet functional tests, including the heparin-induced platelet aggregation (HIPA) assay, have been reported with BRILINTA. BRILINTA is not expected to impact PF4 antibody testing for HIT

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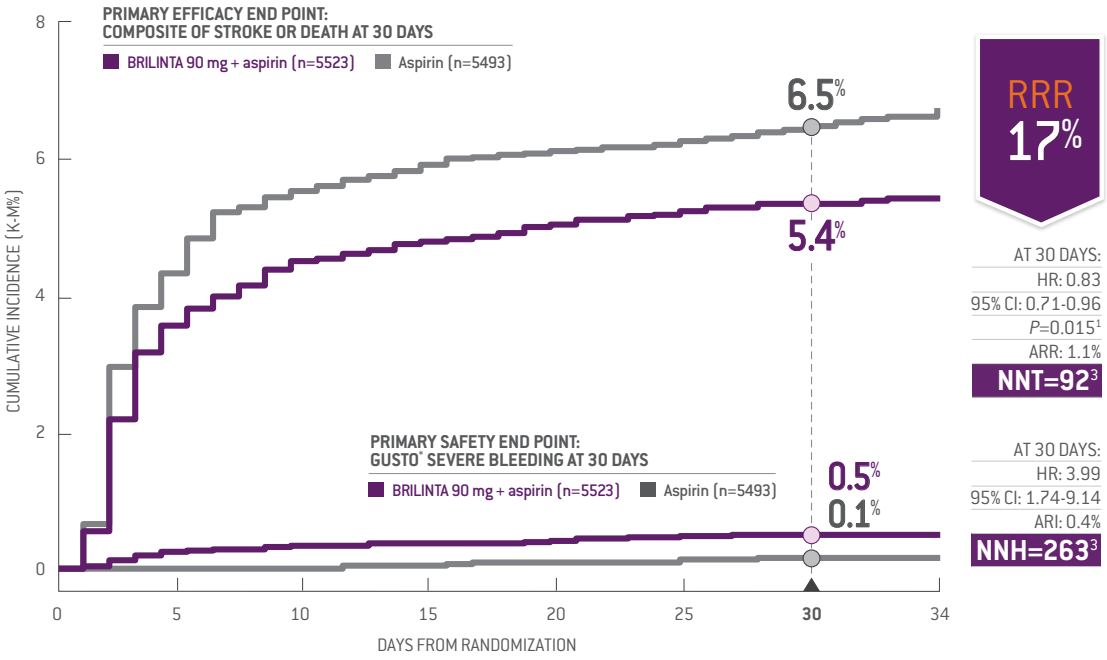
BRILINTA®
ticagrelor tablets
LIVING BRILLIANTLY

THALES PRIMARY END POINTS

BRILINTA initiated within 24 hours showed significantly lower risk in the composite of subsequent stroke or death vs aspirin alone[1,3]

THALES primary efficacy end point (composite of stroke [ischemic or hemorrhagic] or death at 30 days) and primary safety end point (GUSTO* severe bleeding)



RRR 17%

AT 30 DAYS:
HR: 0.83
95% CI: 0.71-0.96
P=0.015[1]
ARR: 1.1%
NNT=92[3]

AT 30 DAYS:
HR: 3.99
95% CI: 1.74-9.14
ARI: 0.4%
NNH=263[3]

INITIATE BRILINTA WITHIN 24 HOURS

- The composite end point was driven by the stroke component of the primary composite efficacy end point (19% RRR, 1.1% ARR)[1]
- BRILINTA is not indicated to reduce death in patients with acute ischemic stroke or high-risk TIA[1]
- Intracranial bleeding and fatal bleeding seen in THALES for BRILINTA 90 mg + aspirin vs aspirin alone, respectively[1]:
  — ICH: 21 vs 6 — Fatal bleeding: 11 vs 2
- BRILINTA'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 benefit and reduced bleeding risk[1]

***GUSTO severe bleeding:** Any one of the following: fatal bleeding, intracranial bleeding (excluding asymptomatic hemorrhagic transformations of ischemic brain infarctions and excluding microhemorrhages <10 mm evident only on gradient-echo magnetic resonance imaging), bleeding that caused hemodynamic compromise requiring intervention (eg, systolic blood pressure <90 mm Hg that required blood or fluid replacement, or vasopressor/inotropic support, or surgical intervention).[1]

THALES was a randomized, international, double-blind, placebo-controlled, multicenter study to investigate dual antiplatelet therapy with BRILINTA (90 mg twice daily with loading dose of 180 mg) and aspirin vs aspirin alone in the prevention of stroke and death in patients with acute ischemic stroke or transient ischemic attack (N=11,016). The primary end point was the first occurrence of the composite of stroke and death up to 30 days. Ischemic stroke was assessed as one of the secondary end points. Patients were ≥40 years of age, had mild-to-moderate acute noncardioembolic ischemic stroke (NIHSS score ≤5 and persistent signs or symptoms at the time of randomization or acute ischemic brain lesion determined by CT scan or MRI), or high-risk TIA (ABCD^2 score ≥6 or with large-vessel disease [ie, ipsilateral ≥50% stenosis of extra- or intracranial artery]). Patients were randomized within 24 hours and treated for 30 days.[1,3] BRILINTA is not indicated to reduce the risk of death in patients with acute ischemic stroke or high-risk TIA.[1]

ARI=absolute risk increase; ARR=absolute risk reduction; CT=computed tomography; CI=confidence interval; GUSTO=Global Use of Strategies to Open Occluded Coronary Arteries; HR=hazard ratio; ICH=intracranial hemorrhage; K-M=Kaplan-Meier; MRI=magnetic resonance imaging; NNH=number needed to harm; NNT=number needed to treat; RRR=relative risk reduction; THALES=Acute STroke or Transient IscHemic Attack Treated with TicAgreLor and ASA for PrEvention of Stroke and Death.

IMPORTANT SAFETY INFORMATION FOR BRILINTA® (ticagrelor) 60-MG AND 90-MG TABLETS (CONT'D)

ADVERSE REACTIONS

- The most common adverse reactions (>5%) associated with the use of BRILINTA included bleeding and dyspnea

DRUG INTERACTIONS

- Avoid use with strong CYP3A inhibitors and strong CYP3A inducers. BRILINTA is metabolized by CYP3A4/5. Strong inhibitors substantially increase ticagrelor exposure and so increase the risk of adverse events. Strong inducers substantially reduce ticagrelor exposure and so decrease the efficacy of ticagrelor
- As with other oral $P2Y_{12}$ inhibitors, co-administration of opioid agonists delay and reduce the absorption of ticagrelor. Consider use of a parenteral anti-platelet in ACS patients requiring co-administration
- Patients receiving more than 40 mg per day of simvastatin or lovastatin may be at increased risk of statin-related adverse events
- Monitor digoxin levels with initiation of, or change in, BRILINTA therapy

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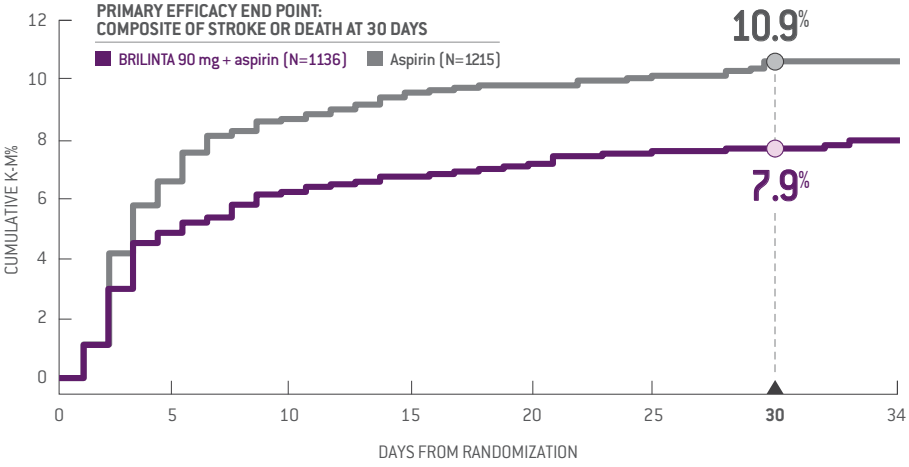
THALES PRESPECIFIED EXPLORATORY SUBGROUP

IPSILATERAL ATHEROSCLEROTIC STENOSIS SUBGROUP

BRILINTA + aspirin vs aspirin alone[4]

- 21.3% of patients in the overall THALES trial (2351/11,016) had ipsilateral atherosclerotic stenosis (≥30%) of the cervicocranial vasculature*

THALES PRESPECIFIED EXPLORATORY SUBGROUP: Primary composite end point of stroke or death at 30 days



RRR 27%

AT 30 DAYS:
HR: 0.73
95% CI: 0.56-0.96
ARR: 3.0%

CHOOSE BRILINTA FOR THESE PATIENTS

- **In patients without ipsilateral stenosis: Composite of stroke or death at 30 days:** 4.8% vs 5.3% with BRILINTA plus aspirin (N=4387) and aspirin alone (N=4278), respectively (HR 0.89; 95% CI 0.74-1.08; NNT for patients without ipsilateral atherosclerosis is 200)†
- BRILINTA is not indicated to reduce death in patients with acute ischemic stroke or high-risk TIA[1]

*Included patients with symptomatic intracranial or extracranial arterial stenosis, that is, ≥30% narrowing in the diameter of the lumen of an artery that could account for the clinical presentation (irrespective of >4 mm thick aortic arch plaque). Thirty percent narrowing was chosen as cutoff based on criteria of the atherosclerosis, small vessel disease, cardiac pathology, other disease, dissection (ASCOD) grading system.[4]

†NNT was calculated using 1/ARR of BRILINTA + ASA compared to ASA alone (0.5%).[4]

Bleeding outcomes in patients with and without ipsilateral atherosclerotic stenosis[4]

	Patients with ipsilateral stenosis (≥30%)		Patients without ipsilateral stenosis (≥30%)	
	BRILINTA 90 mg + Aspirin (N=1136)	Aspirin (N=1215)	BRILINTA 90 mg + Aspirin (N=4387)	Aspirin (N=4278)
	Number of patients (%)		Number of patients (%)	
GUSTO severe bleeding	4 (0.4%)	3 (0.2%)	24 (0.5%)	4 (0.1%)
Fatal bleeding	1 (0.1%)	1 (0.1%)	10 (0.2%)	1 (0.0%)
ICH	4 (0.4%)	3 (0.2%)	16 (0.4%)	3 (0.1%)
Hemorrhagic stroke	0 (0.0%)	0 (0.0%)	10 (0.2%)	2 (0.0%)

- NNH for patients without ipsilateral atherosclerosis is 250[4]*

FROM THE PRESPECIFIED EXPLORATORY SUBGROUP ANALYSIS

NNT 34

For every 34 patients with ipsilateral atherosclerosis treated with BRILINTA 90 mg plus aspirin instead of aspirin, 1 additional event of stroke or death was prevented...

NNH 951

...and for every 951 patients with ipsilateral atherosclerosis, 1 additional GUSTO severe bleeding event occurred, respectively.[4,5†]

*NNH was calculated using 1/ARI of BRILINTA + ASA compared to ASA alone (0.4%).[4]

†Calculation of NNH is based off of 1/ARI (1/[0.352%-0.247%]).[4]

THALES was not designed or powered to demonstrate the efficacy or safety of BRILINTA compared with placebo in specific subgroups. Subgroup analyses were performed to evaluate consistency of results in different cohorts. Analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses.[3]

ASA=acetylsalicylic acid.

IMPORTANT SAFETY INFORMATION FOR BRILINTA® (ticagrelor) 60-MG AND 90-MG TABLETS (CONT'D)

SPECIAL POPULATIONS

- Lactation: Breastfeeding not recommended

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2021 AHA/ASA GUIDELINE for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack[6]

RECOMMENDATIONS FOR ANTITHROMBOTIC MEDICATIONS

- For patients with recent (<24 hours) minor to moderate stroke (NIHSS score ≤5), high-risk TIA (ABCD^2 score ≥6), or symptomatic intracranial or extracranial ≥30% stenosis of an artery that could account for the event, DAPT with ticagrelor plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke but may also increase the risk of serious bleeding events, including ICH

(Class 2b; LOE B-R^{SR})

SR indicates systematic review.

MANAGEMENT BY ETIOLOGY: RECOMMENDATIONS FOR INTRACRANIAL LARGE ARTERY ATHEROSCLEROSIS*

- In patients with recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral >30% stenosis of a major intracranial artery, the addition of ticagrelor 90 mg twice a day to aspirin for up to 30 days might be considered to further reduce recurrent stroke risk

(Class 2b; LOE B-NR)

CLASS OF RECOMMENDATION AND LEVEL OF EVIDENCE

- Class 2b recommendations state that the procedure/treatment may/might be reasonable/considered
- Level B-R is moderate-quality evidence from 1 or more RCTs or meta-analyses of moderate-quality RCTs
- Level B-NR is moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies or registry studies or meta-analyses of such studies

*This recommendation is derived from the prespecified exploratory ipsilateral atherosclerotic stenosis subgroup in THALES (see previous page).[4] THALES was not designed or powered to demonstrate the efficacy or safety of BRILINTA compared with placebo in specific subgroups. Subgroup analyses were performed to evaluate consistency of results in different cohorts. Analyses must be interpreted cautiously, as differences can reflect the play of chance among a large number of analyses.[3]

AHA=American Heart Association; ASA=American Stroke Association; LOE=level of evidence; RCT=randomized controlled trial; SR=systematic review.

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You may report side effects related to AstraZeneca products by clicking here.

References: 1. BRILINTA® (ticagrelor) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2021. **2.** Plavix® (clopidogrel bisulfate) [package insert]. Bridgewater, NJ: Sanofi-Aventis US LLC; 2020. **3.** Johnston SC, Amarenco P, Denison H, et al; for the THALES Investigators. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med.* 2020;383(3):207-217, Supplementary Appendix, and Protocol. **4.** Amarenco P, Denison H, Evans SR, et al; on behalf of the THALES Steering Committee and Investigators. Ticagrelor added to aspirin in acute nonsevere ischemic stroke or transient ischemic attack of atherosclerotic origin. *Stroke.* 2020;51(12):3504-3513. **5.** Data on file, REF-51076, AstraZeneca Pharmaceuticals LP. **6.** Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline from the American Heart Association/American Stroke Association. *Stroke.* 2021;52:00-00. Published online ahead of print. DOI: 10.1161/STR.0000000000000375

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