TICAGRELOR (Brilinta®) CLINICIAN SUMMARY

Mechanism of Action: Selective and reversibly bound antagonist of the $P2Y_{12}$ receptor. Inhibits ADP-mediated platelet activation and aggregation.

BACKGROUND

Ticagrelor is a cyclopentyltriazolopyrimidine antiplatelet agent.

Place in Therapy

Use of ticagrelor at UHN is limited to any patient presenting with an acute coronary syndrome, with or without ST segment elevation, regardless of management strategy. (This includes patients managed invasively and those managed conservatively). Patients treated with fibrinolysis are excluded. Compared to clopidogrel, ticagrelor is considered to provide more rapid, more consistent, and more potent platelet inhibition at a cost of higher bleeding rates.

Summary of Efficacy Endpoints from PLATO:[1]

In patients presenting with ACS, with or without ST segment elevation, use of ticagrelor compared with clopidogrel was associated with a significant reduction in the rate of the primary endpoint of cardiovascular death/MI/stroke and a significant reduction in overall mortality.

End Point	Ticagrelor (n=9333)	Clopidogrel (n=9291)	HR (95% CI)	P Value
Primary end point, n (%) ***CV death/MI/stroke***	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	<0.001
Secondary end points, n (%) *Total death/MI/ stroke*	901 (10.2)	1,065 (12.3)	0.84 (0.77–0.92)	<0.001
CV death/MI/stroke/ ischaemia/TIA/arterial thrombotic events	1,290 (14.6)	1,456 (16.7)	0.88 (0.81–0.95)	<0.001
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.005
CV death	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.001
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.22
Total death	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	<0.001

Dosing: Loading Dose: 180 mg (2 x 90 mg tablets) PO once, then 90 mg PO BID

Dose Adjustments: No dosage adjustment is required in patients with renal or mild hepatic impairment. Ticagrelor is contraindicated in those with moderate to severe hepatic impairment.

Administration

- Ticagrelor can be taken without regard to food.
- If a patient has difficulty swallowing a whole tablet, the film-coated tablets may be administered by dispersing them in 200 mL water and giving the dispersion orally or via nasogastric tube.

Switching from ticagrelor to clopidogrel: Refer to *Antiplatelet Therapy Switching - Clinician Guide.*

PHARMACOLOGIC PROFILE AND LABORATORY MONITORING

TICAGRELOR (Brilinta®) CLINICIAN SUMMARY

There is no specific lab parameter which indicates the extent of antiplatelet activity.

Onset of Platelet Aggregation Inhibition: <30 minutes with 180 mg loading dose

Peak Effect: 2.5 hours

Half-Life: of active metabolite is approximately 8.6 hours (6.5-12.8 hours)

Duration of Effect: 2-3 days; platelet aggregation will return to baseline 5-7 days after discontinuation

Bioavailability: 36% (25.4%-64.0%)

Elimination: 26% urine, 58% feces

CONTRAINDICATIONS

- hypersensitivity to ticagrelor or any ingredient in the formulation
- patients with active bleeds or high bleeding risk (advanced age, gastric ulcer, previous bleeding)
- patients with history of intracranial hemorrhage
- patients with moderate to severe hepatic impairment
- concomitant use of strong CYP3A4 inhibitors (increased plasma concentration of ticagrelor):
  - ketoconazole, clarithromycin, ritonavir, atazanavir

PRECAUTIONS

- Caution in patients with bradycardia, hyperuricemia and in patients likely to have dyspnea

- **Pharmacodynamic drug interactions**
  - Concomitant use of other antiplatelet agents (e.g., ASA, clopidogrel) or other anticoagulants (warfarin, low molecular weight heparins, unfractionated heparin, fondaparinux, dabigatran) will increase the risk of bleeding.
  - During clinical studies, ticagrelor was commonly administered with ASA, heparin, low molecular weight heparin, intravenous GpIIb/IIIa inhibitors, proton pump inhibitors, statins, beta-blockers, angiotensin converting enzyme inhibitors and angiotensin receptor blockers as needed for concomitant conditions, and did not produce any evidence of clinically significant drug interactions.
- **Pharmacokinetic drug interactions**
  - CYP3A4 inhibitors (increase serum concentration of ticagrelor, decrease serum concentration of active metabolite):
    - Ketoconazole, clarithromycin, ritonavir, atazanavir
  - CYP3A4 inducers (decrease serum concentration of ticagrelor):
    - Rifampin, dexamethasone, phenytoin, carbamazepine, phenobarbital
  - PGP substrates
    - Increase serum concentration of digoxin

ADVERSE EFFECTS

- bleeding
- dyspnea (mild-moderate, transient)
- headache
- nausea, vomiting, diarrhea

- hyperuricemia

Summary of safety endpoints from PLATO[4]

Compared to clopidogrel, use of ticagrelor was associated with significantly higher rates of:
- Non-CABG-related major bleeding
- intracranial bleeding
- fatal intracranial bleeding

There was no significant difference in the rates of major bleeding or in the rates of CABG-related major bleeding with ticagrelor.

PREPARATION FOR SURGICAL PROCEDURES INCLUDING CABG

Excess bleeding risk due to recent administration of ticagrelor in patients selected to have CABG should be weighed against the potential lost benefit of adequate platelet inhibition in early ACS. In patients who may require urgent CABG or urgent non-cardiac surgery, consider discontinuation with the knowledge that platelet function will recover in 5-7 days.

MANAGEMENT OF BLEEDING

- Due to the reversible antagonism of the $P2Y_{12}$ receptor, recovery of platelet function is faster with ticagrelor than with irreversible $P2Y_{12}$ receptor antagonists, such as clopidogrel or prasugrel.
- Because the drug is reversibly bound, platelet transfusion is unlikely to be effective.
- No antidote exists for reversal of antiplatelet effect.
- Ticagrelor is not expected to be dialyzable.
- May Consider:
    - transfusion of blood products
    - Haematology consult should be obtained for assistance

REFERENCES

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Notice to Healthcare Providers:

The Pharmacotherapy Handbook is intended to be used as a tool to aid in the appropriate prescribing and administration of cardiovascular formulary agents.

This information in this Handbook is intended for use by and with experienced physicians and pharmacists. The information is not intended to replace sound professional judgment in individual situations, and should be used in conjunction with other reliable sources of information. Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about Cardiovascular illness and the treatments in question.

Due to the rapidly changing nature of cardiovascular treatments and therapies, users are advised to recheck the information contained herein with the original source before applying it to patient care.

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