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**Month/Year of Review:** November 2011
**End date of literature search:** Q3-2011
**Generic Name:** ticagrelor
**Manufacturer:** AstraZeneca
**Brand Name:** Brilinta™
**Dossier received:** No.
**PDL Class:** Antiplatelet
**Comparator Therapies:** clopidogrel

Preferred: aspirin, aspirin/dipyridamole, clopidogrel, dipyridamole
Non-Preferred: ticlopidine, prasugrel (pending review), ticagrelor (pending review)

**FDA Approved Indications:** To reduce the rate of thrombotic cardiovascular events in patient with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction).[1] Ticagrelor was studied in combination with aspirin for treatment of ACS. Maintenance doses of more than 100mg of aspirin decreased effectiveness.

**Summary:** The recent Drug Effectiveness Review Project (DERP) systematic, comparative effectiveness review[2] did not include ticagrelor so a stand alone new drug review was undertaken. Despite moderate evidence of superiority over clopidogrel for rate reductions of all-cause mortality, cardiovascular mortality and stent thrombosis with no increased risk of major bleeding in the published phase 3 PLATO study,[3, 4] a sub-analysis of the US arm of the study showed no benefit. Serious issues regarding PLATO have been raised by Food and Drug Administration reviewers.[5]

There was no evidence for ticagrelor use in other indications (secondary stroke prophylaxis, peripheral vascular disease or primary prevention of cardiovascular events in high risk individuals).

**PDL Placement Recommendation:**

| | | | |
|---|---|---|---|
| *Required* | | *Recommended with restriction* | |
| *Recommended depending on price* | | *Not recommended* | X |

**Utilization Control Recommendations:**

| | | | |
|---|---|---|---|
| *OHP Coverage* | | | |
| *Step Therapy* | X | | |
| *Dose Limit* | | *Therapy Length Limit* | |
| *Age Restriction* | | *Gender Restriction* | |

**Evidence Grade[1]:**

| | |
|---|---|
| *Effectiveness for ACS* | *Moderate* |
| *Safety* | *Low-Moderate* |

**BACKGROUND/CURRENT LANDSCAPE**

Antiplatelet drugs are used to prevent cardiovascular events and premature death in patients with multiple risk factors and in patients who have experienced Acute Coronary Syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction), transient ischemic attacks or thromboembolic stroke, or symptomatic peripheral arterial disease. Aspirin has been considered the gold standard. Aspirin is effective in reducing the occurrence of major cardiovascular events including death, recurrent myocardial infarction, recurrent angina, or progression to severe angina and nonfatal stroke. Several practice guidelines have been published that provide recommendations regarding the role of aspirin.[6,7,8,9,10,11] Newer antiplatelet agents, and in particular clopidogrel, are used as an adjunct to or substitution for aspirin in specific clinical situations, particularly in those who have contraindications to aspirin. However, the role of individual antiplatelet agents relative to each other is still evolving. There is reported variability in patient platelet aggregation response to clopidogrel, though the risk of adverse outcomes due to this has yet to be fully elucidated. [12,13,14]

**CLINICAL PHARMACOLOGY**

Ticagrelor is an inhibitor of platelet activation and aggregation through the reversible binding to the P2Y12 class of ADP receptors on platelets.[1] It belongs to a new class of antiplatelet agents called cyclopentyl-triazolo-pyrimidines. In contrast to clopidogrel and prasugrel, ticagrelor is not a prodrug and thus binds and inhibits the P2Y12 receptor directly with no need for metabolic activation, thus limiting any potential impact of genetic variations in CYP enzymes on its pharmacological profile.[15] The metabolite of ticagrelor is equally potent.[1]

**COMPARATIVE CLINICAL EFFICACY**

**Relevant Endpoints**:
1) All cause mortality
2) Cardiovascular (CV) mortality
3) Total Stent Thrombosis
4) Major Bleeding (more inclusive than CURE or TIMI definitions)
5) Withdrawals due to adverse events

**Primary Study Endpoint:** 1) Composite of cardiovascular mortality, nonfatal myocardial infarction, or nonfatal stroke

[1] High – results unlikely to change with further research; Moderate – results may change with further research; Low- results likely to change; Insufficient – effect can't be estimated with available evidence:

## Evidence Table

| Ref./ Study Design[a] | Drug Regimens | Patient Population | N | Duration | Efficacy Results[b] | ARR / NNT[c] | Safety Results (CI, p-values) | ARI / NNH[c] | Quality Rating[d]; Comments |
|---|---|---|---|---|---|---|---|---|---|
| PLATO[3,4] | | | | | | | | | Fair; |
| Wallentin et. al. Phase III, RCT, DB, PG | T: Ticagrelor 180 mg load, followed by 90 mg BID + placebo matched to clopidogrel<br><br>C:Clopidogrel 300-600 mg load, followed by 75 mg QD + placebo matched to ticagrelor<br><br>ASA 75 to 100 mg daily unless not tolerated; 325 mg was also permitted as the daily dose for 6 months after stent placement.<br>X6-12 months; mean: 277 days | Mean Age: 62 yrs<br>Male: 72%<br>White: 92%<br><br>ACS patients with moderate to high risk (62% NSTEMI or unstable angina, 38% STEMI) | T: 9333<br><br>C: 9291 | Outcomes assessed @ 12 months<br><br>(average F/U 11 months) | <u>All Cause Mortality:</u><br>T: 399 (4.5%)<br>C: 506 6 (5.9%)<br>HR: 0.78<br>95% CI: 0.69 – 0.89<br>P=<0.001<br><br><u>CV Mortality:</u><br>T: 353 (4.0%)<br>C: 442 ((5.1%)<br>HR: 0.79<br>95% CI: 0.69-0.91<br>P=0.001<br><br><u>Total Stent Thrombosis*:</u><br>T: 155/5640 (2.9%)<br>C: 202/5649(3.8%)<br>RR: 0.77<br>95% CI: 0.62-0.95<br>P=0.01<br>*of those who received a stent not ITT | ARR: 1.4%%<br>NNT: 71<br><br>ARR: 1.1%%<br>NNT: 91<br><br>ARR: 0.9%<br>NNT: 111 | <u>Major Bleeding*:</u><br>T: 961/9235 (11.6%)<br>C: 929/9186 (11.2%)<br>RR: 1.04<br>95% CI: 0.95-1.13<br>P=0.43<br><br><u>Withdrawals due to Adverse events:</u><br>T: 690 (7.4%)<br>C: 556 (6.0%)<br>RR:1.09<br>95% CI^:<br>0.98 – 1.21<br>P=<0.001<br><br>*reported for patients taking the drug and not ITT<br><br>^vl.academicdirect.org/applied_statistics/binomial.../CIcalculator.xls | ARI: 1.4%%<br>NNH: 71 | Study was powered for composite efficac outcome only. Statistical analysis confirms statistical significance of secondary outcomes of interest. Stent thrombosis was also statistically significant.<br><br>Total attrition rates:<br>T : 2186 (23.4%)<br>C: 1999 (21.5%)<br>P = 0.002<br><br>Authors report total adherence to >80% of study drug as 82.8%. Differential loss to follow-up not reported (5 patients total).<br><br>The FDA summary review highlights and discusses several potential study quality issues including: data errors, adjudication, and blinding but in the end approved ticagrelor. [5] |

[a]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[b]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI=absolute risk increase
NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat
[c]**NNT/NNH** are reported only for statistically significant results
[d]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
**TIMI** = Thrombolysis In Myocardial Infarction bleeding criteria **NSTEMI =** non-ST-elevation myocardial infarction **STEMI= ST-elevation myocardial infarction**

**Summary of Findings –**

Ticagrelor was compared to clopidogrel in the phase 3 trial, PLATO.[3,4] It included 18,624 patients admitted to 862 centers in 43 countries from October 2006 through July 2008. Patients were admitted to hospital with acute coronary syndromes (62% non-ST segment elevation myocardial infarction or unstable angina, 38% ST segment elevation myocardial infarction), 64% received percutaneous coronary interventions. It was a fair-quality, multi-site, head-to-head trial. The primary efficacy outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. All outcomes were assessed at a median of 11 months.

There was moderate-strength evidence of a benefit of ticagrelor over clopidogrel in the most important effectiveness outcomes of all-cause mortality (hazard ratio, 0.78; 95% CI, 0.69 to 0.89) and cardiovascular mortality (hazard ratio, 0.79; 95% CI, 0.69-0.91) outcomes. The study was not powered or designed to detect differences in these secondary outcomes but the statistical analysis did plan for and confirm the statistical significance of them. Despite the lack of power, PLATO provided moderate-strength evidence of superiority of ticagrelor over clopidogrel for prevention of stent thrombosis post-percutaneous coronary intervention (hazard ratio, 0.77; 95% CI, 0.62 to 0.95). Moderate-strength evidence also indicated that there was no more major bleeding with ticagrelor. There was low strength evidence of increased withdrawals due to adverse events with ticagrelor (relative risk 1.09; 95% CI, 0.98 – 1.21).

Despite the published positive findings the Food and Drug Administration (FDA) delayed approval of ticagrelor for more than 6 months. A FDA report[5] identifies several issues. One critical point is the regional difference noted. The discussion on that point is pasted below[5]:

As shown below, effects were heterogeneous with respect to region with the US results being the main driver of the North American anomaly. Substantial efforts have been made by the sponsor and the review team to investigate the cause of the discrepancy in results in the US vs. the rest of the world.

As shown in the table below (Table 1 in the statistical review of 31 August), in the US, ticagrelor fared worse with respect to each of the components of the primary end point.

| | Characteristic | Ticagrelor 90 mg bd | Clopidogrel 75 mg od | Hazard ratio (95% CI) |
|---|---|---|---|---|
| Non-US | Composite of CV Death/MI (excl. silent MI)/Stroke | 780 | 947 | 0.82 (0.74,0.90) |
| | CV death | 329 | 423 | 0.77 (0.67, 0.89) |
| | MI (excl. silent MI) | 440 | 546 | 0.80 (0.70, 0.90) |
| | Stroke | 118 | 102 | 1.15 (0.88, 1.50) |
| US | Composite of CV Death/MI (excl. silent MI)/Stroke | 84 | 67 | 1.27 (0.92,1.75) |
| | CV death | 24 | 19 | 1.26 (0.69, 2.30) |
| | MI (excl. silent MI) | 64 | 47 | 1.38 (0.94, 2.01) |
| | Stroke | 7 | 4 | 1.73 (0.51, 5.92) |

In the US the point estimate of the hazard ratio was about 1.27. The point estimates for the hazard ratios in placebo-controlled studies of clopidogrel are in the ballpark of 1/1.27, so, by the most generous of non-inferiority calculations, based solely on point estimates, the US results are entirely consistent with there being no effect whatsoever of ticagrelor in the US.

No single or combination of baseline covariates was found to explain the US-foreign differences in outcome. However, post-randomization dose of aspirin does appear to account for regional differences, at least in the statistical sense.

There was no evidence for ticagrelor used for other indications (secondary stroke prophylaxis, peripheral vascular disease or primary prevention of cardiovascular events in high risk individuals).

**DRUG SAFETY**

*Serious (REMS, Black Box Warnings, Contraindications)*: BBW – serious, sometimes fatal bleeding. Do not use in patients with active pathological bleeding or a history of intracranial hemorrhage. Do not start in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue at least 5 days prior to any surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures. If possible, manage bleeding without discontinuing ticagrelor. Stopping it increased the risk of subsequent CV events. Maintenance doses of aspirin >100mg reduce the effectiveness of ticagrelor and should be avoided.[1]

*Tolerability:* Withdrawals due to adverse events were significantly higher with ticagrelor (7.4% vs. 6.0%, RR 1.09, 95% CI, 0.98 – 1.21).[3]

*Pregnancy/Lactation rating:* C. There are no adequate, well controlled studies in pregnant women. In animal studies, ticagrelor cause structural abnormalities at maternal doses about 5-7 times the maximum recommended human dose based on surface area.[1]

*Unanswered safety questions:* Ticagrelor has been shown to increase the occurrence of bradyarrythmias. PLATO excluded patients at increased risk of bradycardic events.[3] Gynecomastia was reported in 0.23% of men on ticagrelor and 0.05% of men on clopidogrel.[1]

*Dose Index (efficacy/toxic): Not reported.*

*Look-alike / Sound-alike (LA/SA) Error Risk Potential:*
LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

| NME Drug Name | Lexi-Comp | USP Online | ISMP | Drug Facts & Comparisons | Clinical Judgment |
|---|---|---|---|---|---|
| LA/SA for ticagrelor (generic) | None | None | None | None | Tegretol™, tigecycline, tiagabine |
| LA/SA for Brilinta™(brand) | None | None | None | None | Brevital™, Brevibloc™, Bicillin™ |

**ADVERSE REACTIONS[1]**

| ADE | ticagrelor | clopidogrel |
|---|---|---|
| | n=-9235 | n=9186 |
| dyspnea | 13.8% | 7.8% |
| headache | 6.5% | 5.8% |
| cough | 4.9% | 4.6% |
| Dizziness | 4.5% | 3.9% |
| Nausea | 4.3% | 3.8% |
| atrial fibrillation | 4.2% | 4.6% |
| hypertension | 3.8% | 4.0% |
| non-cardiac chest pain | 3.7% | 3.3% |
| diarrhea | 3.7% | 3.3% |
| back pain | 3.6% | 3.3% |
| hypotension | 3.2% | 3.3% |
| fatigue | 3.2% | 3.2% |
| chest pain | 3.1% | 3.5% |
| Non-CABG bleeding | | |
| Total Major+Minor | 8.7% | 7.0% |
| Major | 4.5% | 3.8% |
| Fatal/life-threatening | 2.1% | 1.9% |
| Fatal | 0.2% | 0.2% |
| Intracranial | 0.3% | 0.2% |
| CABG bleed | n=770 | n=814 |
| Total Major | 85.8% | 86.9% |
| Fatal/life-threatening | 48.1% | 47.9% |
| Fatal | 0.9% | 1.1% |

[a]includes: dyspnea, dyspnea exertional, dyspnea at rest, nocturnal dyspnea, dyspnea paroxysmal

nocturnal

**DOSE & AVAILABILITY**[1]

| STRENGTH | FORM | ROUTE | FREQUENCY | RENAL ADJ | HEPATIC ADJ | Pediatric Dose | Elderly Dose | OTHER DOSING CONSIDERATIONS |
|---|---|---|---|---|---|---|---|---|
| 90mg | Tablet | Oral | 180mg load, then BID | No adjustment.<br><br>Not studied in patients on dialysis | Not studied in patients with moderate hepatic impairment. Contraindicated in severe hepatic impairment | Not studied. | 43% of patients in PLATO ≥ 65 years old. No differences in safety or efficacy noted. | Without regard to food. |

**PHARMACOKINETICS**[1]

| Parameter | Result |
|---|---|
| Oral Bioavailability | ~36% (30-42%); metabolite is equally active |
| Protein Binding | >99% (ticagrelor + active metabolite) |
| Elimination | <1% of dose is recovered in the urine |
| Half-Life | 7 hours ticagrelor; 9 hours for metabolite |
| Metabolism | CYP3A4 metabolizes ticagrelor to active metabolite; both are weak p-glycoprotein substrates. |

**ALLERGIES/INTERACTIONS**

*Drug-Drug*: Avoid use of strong CYP3A inhibitors (ketoconazole, itraconazole, voriconazole, clarithromycin, nefazodone, ritonavir, saquinavir, nelfinafir, indinavir, atazanavir and telthromycin) and CYP3A inducers (rifampin, dexamethasone, phenytoin, carbamazepine and Phenobarbital). [1] Avoid use with aspirin doses >100mg/day. [1] Higher concentrations of simvastatin and lovastatin are expected with concomitant therapy; avoid simvastatin and lovastatin doses >40mg. [1] Digoxin competes for p-glycoprotein; monitor digoxin levels with ticagrelor initiation or change. [1]

Warfarin: Patients on chronic warfarin were excluded from PLATO[3]

*Food-Drug*: No food-drug interactions have been reported.[1]

**APPENDIX A: Suggested PA Criteria**

# Platelet Inhibitors

**Goal(s):**

- Promote safe and effective therapies for platelet inhibitors.

**Length of Authorization: 1 year**

**Covered Alternatives**: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

| Approval Criteria | | |
|---|---|---|
| **1.** What is the diagnosis? | Record ICD-9 code | |
| **2.** Is the diagnosis an OHP covered diagnosis? | **Yes:** Go to #3. | **No:** Pass to RPh, Deny for OHP Coverage. |
| **3.** Will the prescriber consider a change to a preferred product?<br><br>Message:<br><br>• Most preferred products do not require PA (e.g. aspirin, clopidogrel) | **Yes:** Inform provider of covered alternatives in class http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html | **No:** Go to #4 |
| **4.** Is the request for prasugrel AND one of the following:<br>≥75 years old<br>≤ 60 kg<br>s/p stroke or TIA | **Yes:** Pass to RPh, Deny for appropriateness. | **No:** Go to #5 |
| **5.** Is the patient unable to take clopidogrel due to one of the following:<br>- clopidogrel allergy<br>- contraindications to clopidogrel therapy (document)<br>- drug-drug interactions (document)<br>- intolerable side effects | **Yes:** Approve up to 1 year | **No:** Deny. Recommend clopidogrel trial |

APPENDIX B – Search Strategy

Search for: remove duplicates from 10 [4 and 9]

Results: 13 (6 excluded for ineligible design, 4 excluded because they were sub-group analyses, 1 for ineligible intervention). 2 papers, 1 study included[3,4]

Database: Ovid MEDLINE(R) without Revisions <1996 to September Week 4 2011>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 2011>, EBM Reviews - ACP Journal Club <1991 to September 2011>, EBM Reviews - Database of Abstracts of Reviews of Effects <3rd Quarter 2011>, EBM Reviews - Cochrane Central Register of Controlled Trials <3rd Quarter 2011>, EBM Reviews - Cochrane Methodology Register <4th Quarter 2011>, EBM Reviews - Health Technology Assessment <4th Quarter 2011>, EBM Reviews - NHS Economic Evaluation Database <4th Quarter 2011>
Search Strategy:
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1 Ticagrelor.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh] (201)
2 acute coronary syndrome.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh] (9275)
3 ACS.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh] (7237)
4 death.mp. [mp=ps, rs, ti, ot, ab, nm, hw, ui, tx, kw, ct, sh] (308542)
5 2 or 3 (13303)
6 1 and 5 (103)
7 limit 6 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained] (89)
8 limit 7 to humans [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained] (89)
9 limit 8 to (clinical trial or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or comparative study or controlled clinical trial or meta analysis or randomized controlled trial) [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR,CLHTA,CLEED; records were retained] (34)
10 4 and 9 (18)
11 remove duplicates from 10 (13)

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