

Use of Antiplatelet Therapy in the Outpatient Setting: Canadian Cardiovascular Society Guidelines

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- First year following ACS
- First year following PCI
- Beyond one year following ACS or PCI
- CABG
- Secondary prevention of cerebrovascular dx
- Vascular prevention in peripheral artery dx
- Primary prevention of vascular events
- Diabetes, heart failure, chronic kidney dx, pregnancy and lactation, periprocedural, minor bleeding, combination with warfarin, drug interactions

Table of Contents

- To outline the CCS guideline process
- To review the Acute Coronary Syndrome highlights of the new Canadian Cardiovascular Society Guidelines – The Use of Antiplatelet Therapy in the Outpatient Setting
- To explore some of the data behind specific recommendations
- To explore the issue of bleed risk

Objectives

- Underuse of antiplatelet therapy
- What contributes to underuse?
 - Complexity of regimens for various vascular risk situations
 - Existing guidelines are part of overall treatment recommendations for specific disease entities
- To create a concise, therapeutic-based statement on managing antiplatelet therapy in Canadian outpatients who have, or are at risk of developing vascular disease
 - AF, valves and pediatrics not included

Why Guidelines?



Preparation of Guidelines

- Instrument designed to assess 6 factors associated with guideline quality:
 - Scope and purpose ✓
 - Stakeholder involvement ?
 - Rigour of development
 - Clarity and presentation
 - Applicability ?
 - Editorial independence ✓

AGREE

| Class | Level |
|---------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| I: Evidence and/or general agreement that it is beneficial, useful and effective | A: Data derived from multiple RCTs or meta-analyses |
| IIa: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy with weight of evidence in favour | B: Data derived from a single RCT or large nonrandomized study |
| IIb: Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy with usefulness/efficacy less well established | C: Consensus of opinion by experts and/or small studies, retrospective studies and registries |
| III: Evidence that it is not useful and, in some cases, may be harmful | |

CCS Grading System

| | Clopidogrel | Prasugrel | Ticagrelor |
|------------------------|-------------|-----------|------------|
| Prodrug | X | X | |
| Individual variability | √ | | |
| Speed of onset | | √ | √ |
| Potency | | √ | √ |
| Reversibility | | | √ |

Platelet P2Y₁₂ Receptor Antagonists

- ASA 75-162 mg/d indefinitely (I A)
 - 75-162 mg/d is recommended to minimize bleeding complications (IIa B)
 - Clopidogrel 75 mg/d indefinitely in ASA allergy or intolerance (IIa B)
- ASA First Year Post ACS**

- Clopidogrel 75 mg/d x14 d minimum (I B)
 - May be continued for 12 months in absence of excess bleeding risk (IIa C)
 - Prasugrel – no recommendation
 - Ticagrelor 90 mg BID for 12 months (I B)
- First Year Post ACS Medically Managed STEMI**

• **Question:** In combination with ASA, is ticagrelor, superior to clopidogrel for the prevention of death from vascular causes, myocardial infarction or stroke in patients *with ACS?*

PLATO

NEJM 2009;361:1045-57.

- **Design:** Randomized, double-blind, double dummy trial
- **Follow-up:** total of 12 months and 5 patients (0.03%) lost to follow-up
- **Setting:** 862 sites and 43 countries
- **Patients:** ACS patients within 24 h of symptom onset
 - Without ST elevation or STEMI with intent for primary PCI
 - **Exclusions:** c/i to clopidogrel, fibrinolytic within 24h, need for oral anticoagulation, increased risk of bradycardia, concomitant therapy with CYP450 3A inducer or inhibitor

PLATO

NEJM 2009;361:1045-57.

- **Intervention:** Clopidogrel 300mg LD then 75mg daily (if not given open-label clopidogrel or taking it for at least 5 days prior to randomization) vs Ticagrelor 180mg LD then 90mg BID on background therapy of ASA 75-100mg daily (or 325mg x 6 months post-PCI)
- **Outcomes:** Primary efficacy variable time to first occurrence of composite of death from vascular causes, MI or stroke – also stent thrombosis
- Safety endpoints – major bleeding and dyspnea, bradyarrhythmias
- Independent central adjudication committee for efficacy and safety

PLATO

NEJM 2009;361:1045-57.

- **Patients:** 18,624 patients (7026 STEMI; 11,067 NSTEMI/UA)
- Median age 62 years, 72% male
- Smokers 36%; HTN 65%; ↑ lipids 47%; DM 25%; previous MI 20%
- Planned PCI 72% (64% underwent PCI)
- Study drug median of 11.3h post chest pain

PLATO

NEJM 2009;361:1045-57.

PLATO

| Endpoint | Ticagrelor | Clopid | HR |
|------------------|------------|--------|------------------|
| Primary | 9.8 | 11.7 | 0.84 (0.77-0.92) |
| Mortality | 4.5 | 5.9 | 0.78 (0.69-0.89) |
| Stent thrombosis | 1.3 | 1.9 | 0.67 (0.50-0.91) |
| TIMI major | 7.9 | 7.7 | 1.03 (0.93-1.15) |

NEJM 2009;361:1045-57.

PLATO - Stroke

| Endpoint | Ticagrelor | Clopid | Significance |
|-------------|------------|--------|--------------|
| Ischemic | 1.1 | 1.1 | P=0.74 |
| Hemorrhagic | 0.2 | 0.1 | P=0.10 |
| Unknown | 0.1 | 0.02 | P=0.04 |
| ICH | 0.3 | 0.2 | P=0.06 |
| Fatal ICH | 0.1 | 0.01 | P=0.02 |

NEJM 2009;361:1045-57.

PLATO

| Endpoint | Ticagrel | Clopid | HR |
|--------------|----------|--------|-------------------|
| Dyspnea | 13.8 | 7.8 | 1.84 (1.68-2.02) |
| D/C Dyspnea | 0.9 | 0.1 | 6.12 (3.41-11.01) |
| Pauses wk 1 | 5.8 | 3.6 | P=0.01 |
| Pauses 30 d | 2.1 | 1.7 | P=0.52 |
| Creatinine ↑ | 10% | 8% | P<0.001 |

NEJM 2009;361:1045-57.

- Ticagrelor reduced the primary endpoint in comparison to clopidogrel (NNT=53)
- Ticagrelor reduced all cause mortality (NNT=71)
- No increase in major bleeding, but fatal ICH may affect patient selection
- Need more information regarding other adverse effects in patients at risk
 - COPD, hyperuricemia, moderate or severe renal failure, bradyarrhythmias unprotected by pacemakers, a history of syncope
- Surveillance of consequences of non-compliance

PLATO SUMMARY

NEJM 2009;361:1045-57.

- Use of clopidogrel 300mg loading dose
- Not loading all patients, irrespective of whether they had been treated previously with clopidogrel
- 45% usage of proton-pump inhibitors after randomization (potential impact on clopidogrel)
- ICH risk – avoidance in previous CVA?

PLATO ISSUES

NEJM 2009;361:1045-57.

- **Contraindications**
 - History of intracranial hemorrhage
 - Moderate or severe hepatic impairment
 - Concomitant therapy with strong CYP3A4 inhibitors
- **Warnings**
 - Patients at risk of bradycardic events
 - Patients reporting new, prolonged or worsened dyspnea this should be investigated fully and if not tolerated, treatment should be stopped

Ticagrelor Product Monograph

- Clopidogrel 75 mg/d for 12 months (I B)
 - May be continued beyond 12 months in patients with high risk of thrombosis and a low risk of bleeding (IIa C)
- Prasugrel 10 mg/d for 12 months in patients who undergo stent implementation and have an increased risk of thrombosis (STEMI, DM, prior stent thrombosis) (I B)
 - Avoid to patients at high risk of bleeding, likely to undergo CABG within 7 days, hx of stroke/TIA, age ≥ 75 yrs or weight < 60 kg (IIb C)
- Ticagrelor 90 mg BID for 12 months (I B)

First Year Post ACS STEMI Post PCI

- **Question:** In combination with ASA, does prasugrel, in comparison to clopidogrel, change the rate of death, MI and stroke, in patients with ACS undergoing PCI?

TRITON-TIMI 38

NEJM 2007;357:2001-15.

- **Design:** Randomized, double-blind trial
- **Follow-up:** total of 6 to 15 months with 14 patients (0.1%) lost to follow-up
- **Setting:** 707 sites and 30 countries
- **Patients:** ACS patients - scheduled PCI
 - Moderate to high-risk UA and NSTEMI
 - STEMI within 12 h if primary PCI or within 14 days of medical treatment
- **Exclusions:** an increased risk of bleeding, anemia, thrombocytopenia, any thienopyridine use within 5 days

TRITON-TIMI 38

NEJM 2007;357:2001-15.

- **Intervention:** Clopidogrel 300mg LD then 75mg daily vs Prasugrel 60mg LD then 10mg daily on background therapy of ASA 75-162mg daily
- **Outcomes:** Primary endpoint of rate of death from CV causes, nonfatal MI or nonfatal stroke at 6 to 15 months
- **Safety –** TIMI major bleeding
- **Endpoint adjudication** by blinded committee

TRITON-TIMI 38

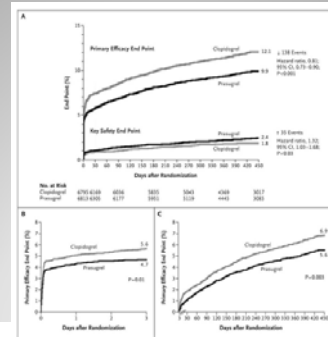
NEJM 2007;357:2001-15.

- **Patients:** 13,608 patients (10,074 UA/NSTEMI and 3534 STEMI)
- Median age 61 years, ¾ male
- HTN 64%; ↑ lipids 56%; DM 23%; smoking 38%; previous MI 18%

TRITON-TIMI 38

NEJM 2007;357:2001-15.

TRITON-TIMI 38



NNT = 45

NNH = 167

NEJM 2007;357:2001-15.

TRITON TIMI-38

| Endpoint | Pras | Clopid | HR |
|---------------|------|--------|------------------|
| Primary | 9.9 | 12.1 | 0.81 (0.73-0.90) |
| Mortality | 3.0 | 3.2 | 0.95 (0.78-1.16) |
| Stent thromb | 1.1 | 2.4 | 0.48 (0.36-0.64) |
| TIMI major | 2.4 | 1.8 | 1.32 (1.03-1.68) |
| Life threaten | 1.4 | 0.9 | 1.52 (1.08-2.13) |
| DC / hemm | 2.5 | 1.4 | P<0.001 |

NEJM 2007;357:2001-15.

TRITON-TIMI 38

| Patient | HR (95% CI) | Clinical |
|---------------------------|------------------|----------------|
| Previous stroke or TIA | 1.54 (1.02-2.32) | Net harm |
| 75 years of age and older | 0.99 (0.81-1.21) | No net benefit |
| Weighing less than 60 kg | 1.03 (0.69-1.53) | No net benefit |

NEJM 2007;357:2001-15.

- Prasugrel decreased primary endpoint (NNT=45) and stent thrombosis
- Prasugrel increased rates of major bleeding (NNH=167), including life-threatening bleeding
- Post hoc analysis identified "at risk" patients – previous stroke or TIA, age ≥75 years, weight <60kg

TRITON TIMI-38 SUMMARY

NEJM 2007;357:2001-15.

- LD administered anytime between randomization and one hour after leaving the cardiac cath lab
 - PCI trial and coronary anatomy needed to be known for UA/NSTEMI or following medical tx of STEMI
 - If coronary anatomy previously known or primary PCI, pretx was permitted for up to 24h
- ¾ of study drug starts were after guidewire or within 1 hour of patient leaving lab

TRITON-TIMI 38 ISSUES

NEJM 2007;357:2001-15.

- Use of 300mg LD for clopidogrel rather than 600mg
- Higher rate of colonic cancer with prasugrel – potentially due to ↑ detection
- Data submitted to FDA showed decreased mortality in STEMI patients but no such benefit in NSTEMI patients

TRITON-TIMI 38 ISSUES

NEJM 2007;357:2001-15.

- **Contraindications**
 - Patients with a known history of transient ischemic attack (TIA) or stroke
 - Patients with severe hepatic impairment (Child-Pugh Class C)
- **Warnings**
 - In patients ≥75 years of age, prasugrel is not recommended because of the increased risk of fatal and intracranial bleeding
 - In patients with body weight <60 kg, prasugrel is not recommended because of increased risk of major bleeding. This is due to an increase in exposure to the active metabolite of prasugrel.

Prasugrel Product Monograph

- Clopidogrel 75 mg/d for a minimum 1 month (I A)
 - May be continued for 12 months in absence of excessive bleeding risk (I B)
- Prasugrel – no recommendations
- Ticagrelor 90 mg BID for 12 months (I B)

First Year Post ACS Medically Managed NSTEMI/ACS

- Clopidogrel 75 mg/d for 12 months (IA)
 - May be continued beyond 12 months in patients with high risk of thrombosis and a low risk of bleeding (IIb C)
- Prasugrel 10 mg/d for 12 months in patients who undergo stent implementation and have an increased risk of thrombosis (STEMI, DM, prior stent thrombosis) (IIa B)
 - Avoid to patients at high risk of bleeding, likely to undergo CABG within 7 days, hx of stroke/TIA, age ≥75 yrs or weight <60 kg (III B)
- Ticagrelor 90 mg BID for 12 months (I B)

First Year Post ACS NSTEMI/ACS Post PCI

- Clopidogrel 75 mg/d for a minimum of 1 month and up to 12 months (I B)
- Prasugrel – no recommendation
- Ticagrelor – no recommendation

First Year Post ACS Post CABG

- ASA 75-162 mg/d indefinitely (I A)
- Post BMS
 - Clopidogrel 75 mg/d for ≥1 month (I B)
 - Clopidogrel 75 mg/d for up to 12 months in absence of an excessive risk of bleeding (I B)
 - Minimum of 2 weeks for patients with high risk of bleeding (I B)
 - Beyond 1 year may be considered if risk of stent thrombosis high and risk of bleeding low (IIb C)
- Post DES
 - Clopidogrel 75 mg/d for 12 months (I A)
 - Beyond 1 year if risk of stent thrombosis is high and risk of bleeding is low (IIb C)
- Evidence for prasugrel post ACS
- Evidence for ticagrelor post ACS

Post Non-Acute PCI

- Issue of extrapolation and 'indefinite' therapy
- Need to balance efficacy, safety, cost-effectiveness and affordability
- Medically managed ACS
 - Clopidogrel 75 mg/d may be continued beyond 1 year provided the risk of bleeding is low (IIB C)
- Post PCI
 - Clopidogrel 75 mg/d may be considered beyond 1 year in patients with ACS who receive a BMS or DES provided their risk of bleeding is low (IIB C)

Dual Antiplatelet Therapy Beyond One Year Post ACS or PCI

- EXCELLENT 2x2 factorial randomizing 1443 patients with CAD and DES to DAPT for 6 months vs one year
- Event rates of 4.7% for 6 months vs 4.4% for 12 months met non-inferiority criteria for primary endpoint of TVF (target vessel failure) defined as cardiac death, MI or TVR at 12 months
- No difference in bleeds
- Significantly increased risk of TVR in DM with 6 months of therapy

Beyond One Year

ACC 2011.

- PRODIGY randomized 2013 stented pts to 6 or 24 months of clopidogrel plus ASA
- Results not dependent upon randomized stent type (incl BMS)
- Can not rule out a benefit smaller than 30% reduction
- Awaiting DAPT trial of 20,000 patients tx 12 vs 30 months

| Endpoint | 6 month DAPT | 24 month DAPT | HR (95% CI)/ p value |
|-------------------|--------------|---------------|----------------------|
| Death/MI/stroke | 10.0 | 10.1 | 0.98 (0.74-1.29) |
| BARC bleeding | 3.5 | 7.4 | 0.00018 |
| TIMI major bleeds | 0.6 | 1.6 | 0.041 |

Beyond One Year

ESC 2011.

- Prasugrel not listed
 - Risk benefit
 - Trilogy ACS to prospectively collect cancer data
- Ticagrelor under review

Common Drug Review

- Major bleeding in NSTEMI patients is associated with a 5-fold increase in 30 day mortality
- Most common non-access site of hemorrhage among ACS patients is GIB
 - Associated with significant mortality risk
- ACS patients in the National Cardiovascular Data Registry, GIB rates increased significantly from 0.54 to 0.67% between 2005 and 2009

Bleed Risk

Circ 2009;119:1873-1882.

- Can Rapid risk stratification of Unstable angina patients Suppress Adverse outcomes with Early implementation of the ACC/AHA guidelines
- Developed and validated a scoring system to estimate baseline risk of **in-hospital** major bleeding in NSTEMI patients
- A tool to consider safety outcomes when making treatment decisions

CRUSADE

Circ 2009;119:1873-1882.

- High risk patients with NSTEMI admitted to 485 US hospitals 2003 to 2006
- Excluded those who died within 48 hours of admission, unstable angina, those taking warfarin at home (too bad ☹) and transfers
- N=87,214

CRUSADE Database

Circ 2009;119:1873-1882.

- ICH
- Documented retroperitoneal bleed
- Hematocrit drop $\geq 12\%$
- Any red blood cell transfusion when hematocrit was $\geq 28\%$
- Any red blood cell transfusion when hematocrit was $< 28\%$ with witnessed bleed
- Bleeds during or after surgery were excluded

Crusade Major Bleeding

Circ 2009;119:1873-1882.

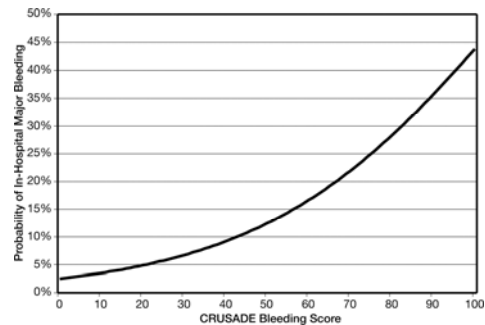
Table 5. Algorithm Used to Determine the Risk Score of CRUSADE In-Hospital Major Bleeding

| Predictor | Score | Predictor | Score |
|------------------------------|-------|--------------------------------|-------|
| Baseline hemoglobin, % | | Sex | |
| <31 | 6 | Male | 0 |
| 31-33.0 | 7 | Female | 8 |
| 34-36.0 | 9 | Signs of CHF at presentation | |
| 37-39.0 | 2 | No | 0 |
| >40 | 0 | Yes | 7 |
| Creatinine clearance* mL/min | | Prior vascular disease | |
| <15 | 10 | No | 0 |
| >15-30 | 10 | Yes | 6 |
| >30-60 | 28 | Diabetes mellitus | |
| >60-90 | 17 | No | 0 |
| >90-120 | 7 | Yes | 6 |
| >120 | 0 | Systemic blood pressure, mm Hg | |
| Heart rate (bpm) | | <90 | 10 |
| ≤ 70 | 0 | 90-100 | 8 |
| 71-80 | 1 | 101-120 | 5 |
| 81-90 | 3 | 121-140 | 1 |
| 91-100 | 8 | 141-200 | 5 |
| 101-110 | 8 | ≥ 201 | 9 |
| 111-120 | 10 | | |
| ≥ 121 | 11 | | |

Crusade

Circ 2009;119:1873-1882.

Figure 1. Predicted probability of in-hospital major bleeding across the spectrum of CRUSADE bleeding score in the derivation cohort.



Subherwal S et al. Circulation 2009;119:1873-1882



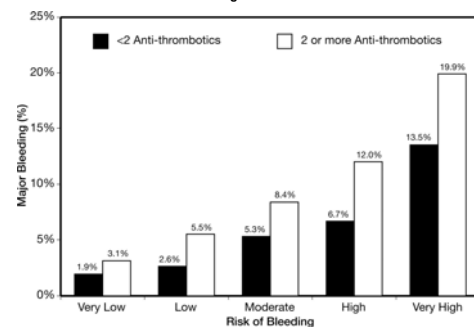
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- Treatments that increase the risk of bleeding were omitted from bleeding score
- Model has demonstrated discrimination in groups who received ≥ 2 antithrombotic medications and those who received < 2

CRUSADE and Treatment Subgroups

Circ 2009;119:1873-1882.

Figure 3. Rate of major bleeding among patients treated with < 2 vs ≥ 2 antithrombotic drugs across CRUSADE bleeding score in the derivation cohort.



Subherwal S et al. Circulation 2009;119:1873-1882



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- ASA
 - ASA at a maintenance dose of 75-100 mg daily long-term regardless of treatment strategy

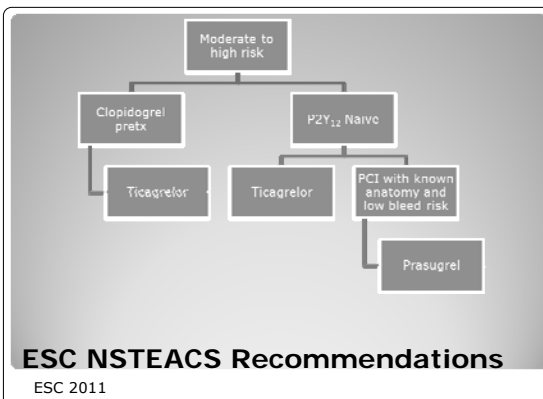
ESC NSTEMI Class I Recommendations

ESC 2011

- P2Y₁₂ inhibitor added to ASA as soon as possible and maintained for 12 months, unless there are contraindications
 - Prolonged or permanent withdrawal of P2Y₁₂ inhibitors within 12 months after the index event is discouraged unless clinically indicated (level C)

ESC NSTEMI Class I Recommendations

ESC 2011



ESC NSTEMI Recommendations

ESC 2011

- Clopidogrel is recommended for patients who can not receive ticagrelor or prasugrel

ESC NSTEMI Class I Recommendations

ESC 2011

- New Canadian guidelines include applicability – that the guidelines pertain to the likely organizational, behavioural and cost implications of applying the guidelines
- Lack of hierarchical decision making in comparison to new European guidelines, perhaps related to issues around process of care, implications of drug coverage and lack of real world experience

Summary

Questions?