2018 Canadian Cardiovascular Society (CCS)/Canadian Association of Interventional Cardiology (CAIC) Focused Update of the Guidelines for the use of Antiplatelet Therapy

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(on behalf of CCS Guideline Group)

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Disclosures

• Simon Robinson
  – Consulting Fees / Honoraria: AstraZeneca, Bayer
  – Clinical Trials: AstraZeneca, Bayer, Novartis, Sanofi, Esperion, Medinol
2018 APT Guideline Authors

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2018 Anti-Platelet Therapy Update
Overview Of Presentation

• Optimal duration of dual antiplatelet therapy (DAPT) following PCI
  • stable coronary disease and elective PCI
  • acute coronary syndromes and high risk elective PCI

• Management of DAPT in patients requiring surgery
  • Coronary Artery Bypass Grafting and Non-Cardiac Surgery

• Switching between antiplatelet agents

• Antiplatelet therapy in PCI patients who also require oral anticoagulation (OAC)
  • AF, valvular disease, LV thrombus, venous thromboembolism
## 2011 CCS Antiplatelet Therapy Guideline Topics

**Antiplatelet Therapy (APT)**
- Post MI
- Post PCI (aspirin and clopidogrel dose)
- Beyond 1yr post MI/PCI
- Following CABG
- Symptomatic cerebrovascular disease
- Primary prevention CV events
- Patients with diabetes mellitus
- Patients with heart failure
- Patients with CKD
- Women who are pregnant
- APT management during surgery
- APT management following bleeding
- APT in combination with warfarin
- APT and proton pump inhibitors
- APT in combination with NSAIDs

### Figures

**Figure 1.** Recommendations for non-ST-elevation acute coronary syndrome (NSTEACS)

- ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes.

**2012 Update of the CCS Antiplatelet Guidelines**

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<table>
<thead>
<tr>
<th>Recommendations for NSTEMI</th>
<th>Patient ineligible for ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early treatment with P2Y&lt;sub&gt;12&lt;/sub&gt; inhibitor in moderate- to high-risk NSTEMI patient*</td>
<td>Add clopidogrel for 12 months (consider 150 mg/day for 6 days if PCI performed)</td>
</tr>
</tbody>
</table>

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* ASA 81 mg daily indefinite therapy

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<table>
<thead>
<tr>
<th>PCI</th>
<th>CABG Surgery</th>
<th>Medical Therapy (no CABG, no PCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Add ticagrelor for 12 months</td>
<td>Add ticagrelor for 12 months</td>
<td>Add ticagrelor for 12 months</td>
</tr>
</tbody>
</table>

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* Moderate to high-risk NSTEACS as defined in PLATO 16:
  - 2 of: (1) ischemic ST changes on electrocardiogram; (2) positive biomarkers; and (3) 1 of the following: 60 years of age or greater, previous MI or CABG, CAD >50% stenosis in 2 vessels, previous ischemic stroke, diabetes, peripheral arterial disease, or chronic renal dysfunction.

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* Tanguay et al. 1339
New Since Last CCS Antiplatelet Therapy Guidelines
Trends in Percutaneous Coronary Intervention (PCI) and Contemporary Antiplatelet Therapies

• Ongoing evolution in PCI use
• PCI more commonly used in ACS including STEMI
• PCI used in more complex patients and lesions e.g. CABG ineligible pts
• Drug eluting stents (DES) predominantly used now
  – DES vs BMS ≈ 1:1 in 2011
  – DES vs BMS ≈ 9:1 in 2017

Baseline and procedural characteristics. The mean age of the PCI patients increased over the year cohorts, from a mean age of 60.1/1006 9.9 years in the cohort 1990 to 1995, to 67.1/1006 11.2 years in the cohort 2009 to 2010 (Table 1). The proportion of patients ages ≥75 years increased from 5.8% to 28.4%. The indication for PCI changed over time, with a majority of patients treated for stable coronary artery disease (66.4%) in 1990 to 1995, and a majority treated for unstable coronary artery disease (47.7%) or STEMI (32.5%) in 2009 to 2010 (Fig. 2). The proportion of smokers was between 19.7% and 21.8% in the different year cohorts. Diabetes and hypertension increased while hyperlipidemia decreased, and a lower proportion of patients had a history of myocardial infarction over time. Three-vessel disease increased from 3.8% in the cohort 1990 to 1995, to 17.3% to 19.0% in the cohorts from 2003 to 2010 (Table 2). In addition, stent use increased from nearly no stent usage (0.8%) to approximately 93% from the cohort 2003 to 2004 and later. Among the patients treated with a stent, the proportion receiving DES varied between 17.2% and 48.0% after its introduction in 2002.

Mortality. Figure 3A shows the mortality for the different year cohorts, with a median follow-up of 2,082 days (interquartile range: 1,105 to 3,335 days), and up to 21 years of total follow-up. The mortality rate was higher in the later year cohorts compared to the earlier year cohorts. Mortality at 1 year after PCI increased from 2.2% in 1990 to 1995, to 5.9% in 2009 to 2010 (Table 3). After adjustment for age and indication, a modest decrease in the mortality risk was seen over time (Fig. 3B). That was mainly due to a decrease in the risk of mortality in the subgroup of STEMI patients, with an age-adjusted HR up to approximately 2 in the earlier year cohorts, compared to the reference cohort 2009 to 2010 (Table 3, Fig. 4). Furthermore, the unadjusted mortality rate was lower in males compared to females in the long term after PCI (HR: 0.82 [95% CI: 0.80 to 0.84]). However, after adjustment for age, indication, and year cohort, no sex difference was seen at 1 year after PCI (HR: 1.00 [95% CI: 0.95 to 1.06]), whereas males had a slightly higher risk of mortality in the long term (HR: 1.12 [95% CI: 1.09 to 1.15]). When we performed the analyses in all PCI procedures, including repeated PCI procedures, the results were consistent.

Discussion
We evaluated the clinical characteristics of all consecutive patients undergoing a first PCI procedure in Sweden in the last 2 decades. The mean age of the PCI treated population increased, and patients were more often treated for unstable coronary artery disease or STEMI over time. As a consequence of the older population, the proportion of patients with comorbidities increased. Mortality after PCI was influenced by the increasing age and the changing indication for PCI.
Superior Safety and Efficacy of Modern DES vs 1st Generation DES

Adjusted HR=0.70, 95% CI: 0.58-0.84, p<0.001
Stratified log-rank test p<0.001

Mortality in a propensity matched cohort of unselected patients undergoing PCI in BC from 2008 to 2014.
Iqbal et al, Am J Cardiol 2015

Paclitaxel-Eluting versus Everolimus-Eluting Coronary Stents in Diabetes. TUXEDO-India Investigators; NEJM 2015
Antiplatelet Strategies Following PCI

• Prior 1 year recommendation for DAPT post MI and PCI based on CURE and PCI-CURE trials

• More complex and extensive CAD now treated with PCI with higher risk of recurrent ischemic (thrombotic) events

• 5 x increase patients aged >75yrs treated by PCI since 1990
  – higher risk of bleeding, higher prevalence of AF requiring OAC
  – multiple co-morbidities, greater risk of recurrent MI

• Major bleeding higher on DAPT than aspirin monotherapy
  – Hazard ratio for (non-fatal) bleeding 1.5[CHARISMA] - 2.7[PEAGUSUS]

• Stent thrombosis rate ≈0.6% with modern generation DES
Optimal Duration of DAPT ‘Shorter vs Longer’ After PCI with DES

- 6 RCTs including 11,473 pts
  - Second generation DES
- 59% patients stable CAD
- 3 or 6 months or 1 year Clopidogrel based DAPT\(^c\)
- 1 year DAPT\(^c\) gave lower MI/stent thrombosis in ACS patients
- Shorter DAPT\(^c\) similar risk reduction in stable CAD
- Bleeding events lower with shorter DAPT in all patients

Palmerini et al. EHJ 2017
Extended DAPT vs Aspirin Beyond 1 year in Patients with Prior Myocardial Infarction

- Meta-analysis of 6 RCTs post MI involving 33,000 pts
- Extended DAPT (mean 31 months) compared to 1 year DAPT followed by aspirin alone

![Graph showing risk ratios for various endpoints](image)

- Major adverse cardiovascular events: Risk Ratio (95% CI) 0.78 (0.67 - 0.90), P = 0.001, 22% ↓ MACE
- Cardiovascular death: Risk Ratio (95% CI) 0.85 (0.74 - 0.98), P = 0.03, 15% ↓ CV death
- Myocardial infarction: Risk Ratio (95% CI) 0.70 (0.55 - 0.88), P = 0.003
- Stroke: Risk Ratio (95% CI) 0.81 (0.68 - 0.97), P = 0.02
- Stent Thrombosis (Definite/Probable): Risk Ratio (95% CI) 0.50 (0.28 - 0.89), P = 0.02
- Major Bleeding: Risk Ratio (95% CI) 1.73 (1.19 - 2.50), P = 0.004, 50% ↓ ST
- Non-cardiovascular death: Risk Ratio (95% CI) 1.03 (0.86 - 1.23), P = 0.76
- All-cause death: Risk Ratio (95% CI) 0.92 (0.83 - 1.03), P = 0.13, 70% ↑ major bleeding
Patients aged ≥50 years with a history of spontaneous MI 1–3 years prior to enrolment AND at least one additional atherothrombosis risk factor* (N=21,162)

- Ticagrelor 60 mg bid + ASA 75–150 mg/day
- Placebo + ASA 75–150 mg/day
- Ticagrelor 90 mg bid + ASA 75–150 mg/day

Minimum of 12 months’ follow up:
Every 4 months in Year 1, then semi-annually

Primary efficacy endpoint: CV death, MI or stroke
Primary safety endpoint: TIMI-defined major bleeding

*Age ≥65 years, diabetes mellitus, second prior MI, multivessel CAD or chronic non-end stage renal disease

Enhanced Efficacy of Extended Ticagrelor in Patients With Multivessel Disease

93% of patients with MVD had undergone prior PCI
69% of patients without MVD had undergone prior PCI

Event rates for patients in the placebo arm of the PEGASUS-TIMI 54 trial according to the severity of coronary artery disease

KM curves for death/MI/definite stent thrombosis in patients with multivessel disease in the PEGASUS-TIMI 54 trial.

Bansilal et al, JACC 2018
Temporal Differences For Efficacy and Bleeding Events During Extended DAPT

Consistent Efficacy Reduction Across Treatment Period

Early Bleeding Hazard

Bonaca MP et al. J Am Coll Cardiol. 2017
2018 Guideline Update on DAPT Duration PCI for a non-ACS indication

Recommendations

• We **recommend** 6 months (and up to 1 year) of DAPT with ASA and clopidogrel (**Strong Recommendation, Moderate Quality Evidence**).

• We **suggest** that in patients who have additional high-risk clinical or angiographic features for thrombotic cardiovascular events and who are at low risk of bleeding, it is reasonable to extend the duration of DAPT to greater than 1 year (**Weak Recommendation, Moderate Quality Evidence for up to 3 years of treatment**).

• We **suggest** that in patients who are at high risk of bleeding, the duration of DAPT be shortened to a minimum of 1 month (if a BMS was used) or 3 months (if a DES was used); (**Weak Recommendation, Low Quality Evidence**).
**Elective PCI**

**Not at high risk of bleeding**

- **DAPT for 6 months**
  - ASA + clopidogrel

**High risk of bleeding**

- **DAPT for 1 month if BMS, or 3 months if DES**

**High-risk clinical or angiographic features for thrombotic cardiovascular events**, and not at high risk of bleeding?

- **YES**
  - **Extend DAPT up to 3 years**
    - ASA 81 mg daily + Clopidogrel 75 mg daily

- **NO**
  - **SAPT**
    - ASA 81 mg daily or Clopidogrel 75 mg daily

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1 Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (> 75 years), frailty, anemia with hemoglobin < 110 g/dL, chronic renal failure (creatinine clearance < 40 mL/min), low body weight (< 60 kg), hospitalization for bleeding within last year, prior stroke/intracranial bleed, regular need for NSAIDS or prednisone.

2 Clinical and angiographic features associated with increased risk of thrombotic events include: age > 65, diabetes mellitus, prior myocardial infarction, chronic renal dysfunction (creatinine clearance < 60 mL/min), multi-vessel disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention or bioabsorbable vascular scaffold (BVS) implantation.

DAPT=dual antiplatelet therapy SAPT=single antiplatelet therapy BMS=bare metal stent DES=drug eluting stent
# 2018 CCS Guideline Update

## Variables Predicting Increased Risk For Thrombotic Events

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Angiographic</th>
</tr>
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<tbody>
<tr>
<td>Prior myocardial infarction or troponin positive acute coronary syndrome</td>
<td>Multiple stents (≥ 3 stents implanted, ≥ 3 lesions stented)</td>
</tr>
<tr>
<td>Diabetes Mellitus treated with oral hypoglycemics or insulin +</td>
<td>Long lesion length (&gt; 60 mm total stent length)</td>
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<tr>
<td>Chronic kidney disease (creatinine clearance ≤ 60 ml/min)</td>
<td>Complex lesions (bifurcation treated with 2 stents, stenting of chronic occlusion)</td>
</tr>
<tr>
<td>Prior stent thrombosis</td>
<td>Left main or proximal LAD stenting</td>
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<td>MultivesSEL PCI</td>
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## 2018 Guideline Update on DAPT Duration
### PCI For ACS (STEMI or NSTEMI)

### Recommendations

1. **We recommend** dual antiplatelet therapy (DAPT) with ASA 81 mg daily plus either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily over clopidogrel 75 mg once daily for 1 year *(Strong Recommendation, High Quality Evidence)*.

2. **We recommend** that in patients who tolerate 1 year of DAPT without a major bleeding event and who are not at high risk of bleeding, DAPT should be extended beyond 1 year *(Strong Recommendation, High Quality Evidence for up to 3 years of treatment)*. After 1 year, we **recommend** a DAPT regimen of ASA 81 mg daily plus either ticagrelor 60 mg twice daily or clopidogrel 75 mg once daily *(Strong Recommendation, High Quality Evidence)* or prasugrel 10 mg once daily *(Weak Recommendation, Moderate Quality Evidence)*.

### Values and Preferences:*
These recommendations place greater emphasis on reduction of major cardiovascular events and stent thrombosis versus an increase in bleeding complications.
PCI for STEMI or NSTEMI

DAPT for 1 year

ASA 81 mg OD +
Ticagrelor 90 mg BID or Prasugrel 10 mg OD
preferred over
Clopidogrel 75 mg OD

At 1 year, determine bleeding risk

Not at high risk of bleeding¹

Continue DAPT for up to 3 years
ASA 81 mg OD +
Ticagrelor 60 mg BID (strong
or Clopidogrel 75 mg OD² (weak recommendation)

High risk of bleeding¹

SAPT
ASA 81 mg OD
or
Clopidogrel 75 mg OD

¹ Factors associated with increased bleeding risk include: need for OAC in addition to DAPT, advanced age (> 75 years), frailty, anemia with hemoglobin < 110 g/dL, chronic renal failure (creatinine clearance < 40 mL/min), low body weight (< 60 kg), hospitalization for bleeding within last year, prior stroke/intracranial bleed, regular need for NSAIDS or prednisone
² Instead of ticagrelor or clopidogrel, prasugrel 5–10 mg daily is also an option (weak recommendation)

DAPT=dual antiplatelet therapy SAPT=single antiplatelet therapy STEMI=ST segment elevation myocardial infarction NSTEMI=non–ST segment elevation myocardial infarction OD=once daily BID=twice daily
Risk Scores may help clinicians decide *who should, and who should not* be treated with extended DAPT

<table>
<thead>
<tr>
<th>Risk Scores</th>
<th>Variables</th>
<th>Predicted outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAPT ¹</td>
<td>Age, MI at presentation, prior MI or PCI, diabetes, stent diameter &lt;3 mm, smoking, paclitaxel-eluting stent, CHF/low EF, SVG PCI</td>
<td>Trade-off between ischemic/bleeding outcomes &gt;1 year after PCI</td>
</tr>
<tr>
<td>PRECISE-DAPT ²</td>
<td>Age, previous bleeding, WBC, hemoglobin, creatinine clearance</td>
<td>Trade-off between ischemic/bleeding outcomes with 3-6 versus 12-24 months of DAPT</td>
</tr>
<tr>
<td>CALIBER ³</td>
<td>Ischemic score: 20 variables Bleeding score: 18 variables</td>
<td>Ischemic and bleeding events 2-6 years post-MI, with or without DAPT</td>
</tr>
</tbody>
</table>

DAPT Duration Following PCI

Some Of The Unresolved Issues in 2018

• No prospective validation of risk scores so residual uncertainty about how to best identify patients
  – At risk of bleeding events with prolonged DAPT
  – At risk of thrombotic events with shorter DAPT

• Scores combining bleeding and thrombotic risk assume equal clinical importance of each type of event

• Very low dose NOAC+ASA vs prolonged DAPT therapy?
  – Limited discussion of COMPASS trial as Rivaroxaban 2.5mg BID yet approved in Canada and outcome of PPI arm not yet known

• Abbreviating aspirin duration vs $P_2Y_{12}$ inhibitor duration? (GLOBAL Leaders)
Switching Anti-Platelet Therapies – When and How?
### Examples of some common clinical scenarios for P2Y$_{12}$ inhibitor switching

<table>
<thead>
<tr>
<th>Intensification from clopidogrel to prasugrel or ticagrelor</th>
<th>Switching between prasugrel and ticagrelor</th>
<th>De-escalation from prasugrel or ticagrelor to clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In patients:</strong></td>
<td><strong>In patients:</strong></td>
<td><strong>In patients with:</strong></td>
</tr>
<tr>
<td>- with ACS, who are initially treated with clopidogrel at presentation</td>
<td>-with intolerance or side effects, who have additional high-risk clinical or angiographic features for thrombotic events warranting completion of the prescribed course of DAPT</td>
<td>-major bleeding complication that has resolved, who have additional high-risk clinical or angiographic features for thrombotic events, warranting completion of the prescribed course of DAPT</td>
</tr>
<tr>
<td>- admitted with thrombotic event (e.g., stent thrombosis or ACS), who have been treated with clopidogrel</td>
<td>-admitted with thrombotic event (e.g., stent thrombosis or ACS), who have been treated with the initial P2Y12 receptor inhibitor agent</td>
<td>-clinically relevant nuisance bleeding and patient unwilling to continue agent</td>
</tr>
<tr>
<td>- who are known poor metabolizer of clopidogrel (e.g., CYP2C19 loss-of-function)</td>
<td>-Interactions between CYP3A inducers which affect pharmacodynamics of one specific agent</td>
<td>-intolerance or side effects to prasugrel / ticagrelor in patients who do not have additional high-risk clinical or angiographic features for thrombotic events</td>
</tr>
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<td></td>
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<td>-a new indication for requiring concurrent treatment with an oral anticoagulant</td>
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2018 CCS Recommended APT Regimen vs ‘Approved’ Public Drug Reimbursement

National Public Reimbursement Status
BRILINTA (ticagrelor)

<table>
<thead>
<tr>
<th>BC</th>
<th>AB</th>
<th>SK</th>
<th>MB</th>
<th>ON</th>
<th>QC</th>
<th>NB</th>
<th>NS</th>
<th>PEI</th>
<th>NL</th>
<th>NIH</th>
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Legend:
- **Full ACS criteria**
- **STEMI w/PCI + high-risk NSTEMI/UA**
- **STEMI w/PCI + NSTEMI/UA w/PCI**
- **STEMI w/PCI + high-risk NSTEMI/UA w/PCI**

Note: Limited to 12 months on most plans

- No public plans cover ticagrelor 60mg BID for extended duration as yet
- 84% of people with private insurance have access to ticagrelor 60mg BID though only ½ of these have unrestricted coverage

Data courtesy of Astra Zeneca
CCS 2018 Guideline Update
Recommendations For Intensification strategies

**Ticagrelor**
- **Loading dose:** 180 mg
- **Maintenance dose:** 90 mg twice daily
- **Timing:** regardless of the timing of the last clopidogrel dose

**Clopidogrel**
- **Loading dose:** 60 mg
- **Maintenance dose:** 10 mg daily
- **Timing:** regardless of the timing of the last clopidogrel dose

**Prasugrel**
CCS 2018 Guideline Update
De-escalation strategies

**Loading dose:** Optional loading 300-600 mg *
**Maintenance dose:** 75 mg daily
**Timing:** At next scheduled ticagrelor dose †

- **Clopidogrel**
  - **Loading dose:** None
  - **Maintenance dose:** 75 mg daily
  - **Timing:** At next scheduled dose

ASA 80 mg daily**

- **Ticagrelor**
- **Prasugrel**

* Short-term (48h) PD advantage, might be relevant in the early post-ACS/PCI period, if no bleeding risk
† Extending to 24h post last ticagrelor dose may also be reasonable
** Consider monotherapy with ASA if switch because of bleeding
Management of DAPT in Patients Undergoing CABG Undergoing Non-cardiac Surgery
2018 CCS Update Recommendations
CABG surgery after ACS

• Continuation of ASA in all patients with ACS who require CABG
  (Strong Recommendation, Moderate Quality Evidence).

• We suggest a minimum interruption of
  ✓ ticagrelor for 48-72 hours prior to semi-urgent CABG and 5 days prior to elective CABG
  ✓ clopidogrel for 48-72 hours prior to semi-urgent CABG and 5 days prior to elective CABG
  ✓ prasugrel for 5 days prior to semi-urgent CABG and an ideal interruption period of 7 days prior to elective CABG
2018 CCS Update Recommendations
Interrupting DAPT for non-cardiac surgery

• In patients who require elective non-cardiac surgery we recommend
  ✓ delaying surgery for at least 1 month after BMS implantation
  ✓ delaying surgery for at least 3 months after DES implantation
    (Strong Recommendation, Moderate Quality Evidence)
  ✓ Restarting when deemed safe to complete recommended period
    of DAPT (Weak Recommendation, Very Low Quality Evidence)

• If there is a need for semi-urgent non-cardiac surgery, we suggest
  delaying surgery for at least 1 month after PCI (Weak Recommendation,
  Low Quality Evidence)

• Following PCI with stenting, we suggest continuing ASA
  perioperatively if possible (Weak Recommendation, Low Quality Evidence)
Management of Antiplatelet Therapy in Patients Requiring OAC Following PCI

• **Atrial Fibrillation**
  – Approx 20% of patients with AF will require PCI at some time\(^c\)
  – Approx 21% of ACS patients will new or established AF\(^d\)
  – Dual antiplatelet therapy is less effective than warfarin in patients with AF\(^a\)
  – Aspirin and thienopyridine more effective than warfarin post stenting\(^b\)
  – >2 million permutations of OAC+APT in ACS patient with AF undergoing PCI\(^e\)

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• Prosthetic heart valves (PHV)
  – Vitamin K antagonists and/or antiplatelet therapy is indicated to prevent thrombotic complications of surgically implanted prosthetic heart valves (PHV).

• Established or suspected left ventricular thrombus
  – OAC recommended if confirmed LV thrombus to reduce systemic embolism
  – Currently Class IIb recommendation for patients with apical dyskinesis even in absence of clinical benefit of OAC\(^f,g\)

• Patients with venous thromboembolism

### Randomized Trials of OAC Following PCI

<table>
<thead>
<tr>
<th>Trials</th>
<th>Studied regimens</th>
<th>Primary endpoint</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WOEST</strong> (n=573)</td>
<td>Warfarin (target INR 2.0) + clopidogrel 75 mg daily Versus Warfarin (target INR 2.0) + clopidogrel 75 mg daily + ASA 80-100 mg daily</td>
<td>Any bleeding episode at 12 months</td>
<td>Prevalence of AF/flutter: 69% Use of PPI: &lt;40% Stents used 65% DES, 35% BMS 10% patients prosthetic heart valve Clopidogrel 100%</td>
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<tr>
<td>Lancet 2008</td>
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<td>Warfarin + clopidogrel: 19.4%</td>
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<td>Warfarin + clopidogrel + ASA: 44.4% (p&lt;0.0001)</td>
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<tr>
<td>ISAR-TRIPLE (n=614)</td>
<td>ASA 75-200 mg daily + clopidogrel 75 mg daily + warfarin (lowest recommended target INR) for 6 weeks versus 6 months</td>
<td>Composite of death, MI, definite stent thrombosis, stroke, or major bleeding at 9 months</td>
<td>Prevalence of AF: 84% Use of PPI: 37.2% Stents used 99% DES INR therapeutic range 64% 7% patients prosthetic heart valve Clopidogrel 100%</td>
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<tr>
<td>JACC 2015</td>
<td></td>
<td>• 6 weeks triple therapy: 9.8%</td>
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<td>• 6 months triple therapy: 8.8% (p=0.63)</td>
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<tr>
<td><strong>PIONEER-AF</strong> (n=2124)</td>
<td>Rivaroxaban 15 mg daily + P2Y12 inhibitor (group 1) vs Rivaroxaban 2.5 mg twice daily + DAPT (group 2) vs Warfarin (INR 2.0-3.0) + DAPT (group 3)</td>
<td>Clinically significant bleeding at 12 months</td>
<td>Prevalence of AF: 100% Clopidogrel used in 93% of patients Use of PPI: &lt;40% Stents used 65% DES, 32% BMS INR therapeutic range 65% Clopidogrel 94% Ticagrelor 5% Prasugrel 1%</td>
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<tr>
<td>NEJM 2016</td>
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<td>Group 1: 16.8%</td>
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<td>Group 2: 18.0%</td>
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<td>Group 3: 26.7% (p&lt;0.001 versus both groups 1 and 2)</td>
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<tr>
<td><strong>RE-DUAL PCI</strong> (n=2725)</td>
<td>Dabigatran 110 mg twice daily + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) vs Dabigatran 150 mg twice daily + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) vs Warfarin (INR 2.0-3.0) + P2Y12 inhibitor (clopidogrel 75 mg daily or ticagrelor 90 mg twice daily) + aspirin ≤100 mg daily</td>
<td>Time to first major or clinically relevant non-major bleeding event</td>
<td>Prevalence of AF: 100% Clopidogrel used in 88% of patients Stents used 83% DES, 35% BMS Use of PPI: unknown INR therapeutic range 64% Clopidogrel 88% Ticagrelor 12%</td>
</tr>
<tr>
<td>NEJM 2017</td>
<td></td>
<td>15.4% in 110mg dual therapy vs 26.9% comparable triple therapy group (P&lt;0.001 for noninferiority; P&lt;0.001 for superiority)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>20.2% in 150mg dual therapy vs 25.7% comparable triple therapy group (P&lt;0.001 for noninferiority)</td>
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</tr>
</tbody>
</table>
Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI
Rivaroxaban vs Warfarin Based OAC

- 2100 patients with NVAF
- Coronary stenting
- No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

Rivaroxaban 15 mg qd*
Clopidogrel 75 mg qd†

1,6, or 12 months –
Pre randomization MD Choice

Rivaroxaban 2.5 mg bid
Clopidogrel 75 mg qd†
Aspirin 75-100 mg qd‡

Rivaroxaban 15mg QD
Aspirin 75-100 mg qd

WOEST
Like

VKA† (target INR 2.0-3.0)
Clopidogrel 75 mg qd†
Aspirin 75-100 mg qd

VKA (target INR 2.0-3.0)
Aspirin 75-100 mg qd

ATLAS
Like

Triple
Therapy

≤72 hours
After Sheath removal

≤72 hours
After Sheath removal

16% OAC+DAPT 1 month; 35% OAC+DAPT 6 months; 49% OAC+DAPT 12 months

1° endpoint: TIMI major + minor + bleeding requiring medical attention
2° endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative P2Y₁₂ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d). △ Open label VKA
**Both Rivaroxaban Strategies Were Associated With Significant Reductions in the Primary Bleeding Endpoint**

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); p<0.001

Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); p<0.001

Approx 16% OAC+DAPT 1 month; 35% OAC+DAPT 6 months; 49% OAC+DAPT 12 months

All subgroups analyzed were consistent with overall results

Non-inferior, open label trial design

Comparable Efficacy Between All Three Treatment Strategies*

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); p=0.750
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); p=0.765

*Trial not powered to detect moderate differences in MI, stroke or stent thrombosis

Dabigatran and Antiplatelet Therapy in Patients Undergoing PCI

In comparison to PIONEER-AF patients receiving dabigatran did not receive aspirin therapy beyond randomization

*Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable). PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent. ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016

Exclusion criteria included CVA within 1 month, CrCl <30mL/min
Dual Pathway Approach Associated with Lower Bleeding Than Warfarin Based Triple Therapy

Primary Endpoint: Time to First Bleeding Event

Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified model is used, elderly patients outside the USA are excluded. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

Primary end-point: time to first ISTH major or clinically relevant bleeding event

ISTH Major Bleed: Bleeding into critical organ, Hgb<2g/dL or transfusion >2units RBC or fatal bleeding.
## Secondary Thrombotic Endpoints
**Dabigatran vs Warfarin in AF Patients Undergoing PCI**

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran 110 mg dual therapy (n=981)</th>
<th>Warfarin triple therapy (n=981)</th>
<th>D110 DT vs warfarin TT (HR (95% CI) P value)</th>
<th>Dabigatran 150 mg dual therapy (n=763)</th>
<th>Warfarin triple therapy (n=764)</th>
<th>D150 DT vs warfarin TT (HR (95% CI) P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All-cause death</strong></td>
<td>55 (5.6)</td>
<td>48 (4.9)</td>
<td>1.12 (0.76–1.65) 0.56</td>
<td>30 (3.9)</td>
<td>35 (4.6)</td>
<td>0.83 (0.51–1.34) 0.44</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>17 (1.7)</td>
<td>13 (1.3)</td>
<td>1.30 (0.63–2.67) 0.48</td>
<td>9 (1.2)</td>
<td>8 (1.0)</td>
<td>1.09 (0.42–2.83) 0.85</td>
</tr>
<tr>
<td><strong>Unplanned revascularization</strong></td>
<td>76 (7.7)</td>
<td>69 (7.0)</td>
<td>1.09 (0.79–1.51) 0.61</td>
<td>51 (6.7)</td>
<td>52 (6.8)</td>
<td>0.96 (0.65–1.41) 0.83</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>44 (4.5)</td>
<td>29 (3.0)</td>
<td>1.51 (0.94–2.41) 0.09</td>
<td>26 (3.4)</td>
<td>22 (2.9)</td>
<td>1.16 (0.66–2.04) 0.61</td>
</tr>
<tr>
<td><strong>Stent thrombosis</strong></td>
<td>15 (1.5)</td>
<td>8 (0.8)</td>
<td>1.86 (0.79–4.40) 0.15</td>
<td>7 (0.9)</td>
<td>7 (0.9)</td>
<td>0.99 (0.35–2.81) 0.98</td>
</tr>
</tbody>
</table>

110 mg BID dabigatran dose associated with trend to higher risk of death/thrombotic events (11% vs 8.5%, HR 1.30, 95% CI 0.98–1.73, P=0.07)

No signal for excess thrombotic events seen with 150 mg BID dose (7.9% vs 7.9%, HR 0.97, 95% CI 0.68–1.39, P=0.44).
Efficacy of NOACs in PCI Patients

• Modest numbers of high thrombotic risk patients enrolled in RCTs
  – Few STEMI patients included
  – Patients with recent CVA/TIA excluded from both PIONEER-AF and RE-DUAL PCI

• PIONEER-AF and Re-DUAL PCI not powered to assess efficacy of NOAC vs warfarin based strategies

• Use of NOAC will more easily facilitate initiation or restoration of therapeutic anticoagulation post PCI

• No trial data as yet with apixaban or edoxaban

• Analyses from the NOAC AF trials suggest a 30-60% increased bleeding risk in patients receiving a NOAC plus an antiplatelet agent so careful assessment of risk/benefit if consideration of longterm APT with NOAC

• Imbalance between clinical guidelines recommending NOAC use and provincial drug reimbursement criteria across Canada
  – special access if failed trial of warfarin, drug intolerance, inability to monitor INRs
AF and elective PCI without high-risk features

1. Age < 65 and CHADS$_2$ = 0
   - ASA + Clopidogrel
     - Duration: at least 1 month for BMS and at least 3 months for DES (and up to 12 months)
   - ASA +/- P$_2$Y$_{12}$ inhibitor

2. Age ≥ 65 or CHADS$_2$ ≥ 1
   - OAC$^2$ + Clopidogrel
     - Duration: at least 1 month for BMS and at least 3 months for DES (and up to 12 months)
   - OAC$^4$ +/- SAPT

---

1. A PCI is considered high-risk based on clinical and angiographic features such as: diabetes mellitus, prior ACS, chronic renal dysfunction (creatinine clearance < 60 mL/min), prior stent thrombosis, current smoker, multi-vessel disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention or bioabsorbable vascular scaffold (BVS) implantation.

2. OAC regimens evaluated in this context include rivaroxaban 15 mg daily (10 mg in patients with renal dysfunction), dabigatran 110 mg or 150 mg BID and warfarin. If warfarin is to be used, recommended INR target is 2.0-2.5. All patients should receive a loading dose of ASA 160 mg at the time of PCI (if previously ASA naive). Thereafter, ASA can be discontinued as early as the day following PCI.

3. Extended treatment with a P$_2$Y$_{12}$ inhibitor can be added to ASA if high-risk clinical or angiographic features of ischemic events develop and low risk of bleeding.

4. The dose of OAC beyond the initial period of antithrombotic therapy (up to a year after PCI) should be standard stroke prevention doses as per the CCS Atrial Fibrillation Guidelines. Single antiplatelet therapy with either ASA or clopidogrel may be added to OAC if high-risk clinical or angiographic features of ischemic events develop and low risk of bleeding.

AF: atrial fibrillation; ASA: acetylsalicylic acid; BMS: bare-metal stent; DES: drug-eluting stent; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; SAPT: single antiplatelet therapy.
AF and PCI for ACS or high-risk\(^1\) elective PCI

**Age < 65** and CHADS\(_2\) = 0

\[
\text{ASA + P}_2\text{Y}_{12} \text{ inhibitor}^2 \\
\text{(ticagrelor, prasugrel preferred over clopidogrel for ACS)} \\
\text{Duration after PCI: Up to 12 months}
\]

**Age ≥ 65** or CHADS\(_2\) ≥ 1\(^*\)

\[
\text{Reduced OAC}^3 + \text{ASA + clopidogrel} \\
\text{ASA: stop 1 day post PCI or any time up to 6 months}^4 \\
\text{Followed by: clopidogrel + OAC} \\
\text{Duration after PCI: Up to 12 months}
\]

**ASA +/- P\(2\)Y\(_{12}\) inhibitor\(^5\)**

**OAC\(^6\) +/- SAPT**

\*If CHADS\(_2\) = 1 and Age < 65 another option for initial treatment (especially if high-risk for ischemic events) is DAPT alone using ASA+ticagrelor or ASA+prasugrel, similar to the recommendation for the CHADS\(_2\)=0 patient

1. A PCI is considered high-risk based on clinical and angiographic features such as: diabetes, prior ACS, chronic renal dysfunction (creatinine clearance < 60 mL/min), prior stent thrombosis, current smoker, multi-vessel coronary artery disease, multiple stents implanted, complex bifurcation lesion, total stent length > 60 mm, chronic total occlusion intervention or bioabsorbable vascular scaffold implantation.

2. Ticagrelor and prasugrel are recommended in ACS patients, whereas clopidogrel is recommended for elective PCI.

3. Regimens evaluated in the context of triple therapy include rivaroxaban 2.5 mg BID or warfarin. If warfarin is to be used, recommended INR target is 2.0-2.5. OAC options evaluated in the context of a dual pathway strategy include rivaroxaban 15 mg daily (plus clopidogrel) or dabigatran 110 mg/150 mg BID (plus clopidogrel).

4. DAPT will have been started as part of ACS management or prior to high risk elective PCI. ASA may be discontinued as early as the day following PCI or it can be continued longer term (eg. 1, 3 or maximum 6 months after PCI). The timing of when to discontinue ASA will vary, depending on the individual patient’s ischemic and bleeding risk.

5. A P\(2\)Y\(_{12}\) inhibitor can be added to ASA if high-risk clinical or angiographic features of ischemic events and low risk of bleeding.

6. The dose of OAC beyond 1 year after PCI should be standard stroke prevention doses as per the CCS Atrial Fibrillation Guidelines. Single antiplatelet therapy with either ASA or clopidogrel may be added to OAC if high-risk clinical or angiographic features of ischemic events and low risk of bleeding.

AF: atrial fibrillation; ACS: acute coronary syndrome; ASA: acetylsalicylic acid; OAC: oral anticoagulant; PCI: percutaneous coronary intervention; DAPT: dual antiplatelet therapy; SAPT: single antiplatelet therapy
Practical Considerations Around Time of PCI in Patients Requiring OAC

- All patients should receive ASA 81 mg (or 160-300mg if ASA naïve) on the day of the PCI procedure. ASA may be discontinued from the day after PCI onwards up to 6 months post PCI.

- **Triple therapy regimens evaluated as part of RCTs**
  - rivaroxaban 2.5 mg BID + ASA 81 mg daily + clopidogrel 75 mg daily
  - warfarin + ASA 81 mg daily + clopidogrel 75 mg daily

- **Dual pathway regimens evaluated as part of RCTs**
  - rivaroxaban 15 mg daily (10 mg CrCl 30-50) + clopidogrel 75 mg daily
  - dabigatran 110mg BID or 150mg BID + clopidogrel 75 mg daily

- Clopidogrel suggested over ticagrelor or prasugrel in patients requiring OAC given its lower risk of bleeding complications and the relative lack of data on ticagrelor or prasugrel in combination with OAC.
Practical Considerations Around Time of PCI in Patients Requiring OAC

• Emphasis on bleeding reduction strategies in OAC pts having PCI
  – *Wide variation in clinical practice regarding holding OAC prior to angio/PCI*
  – transradial access, limit use of IIbIIIa inhibitors
  – Avoid routine peri-procedural bridging for anticoagulation
  – Routine gastroprotection using PPI along with triple therapy

• If warfarin used as part of triple therapy suggested INR is lower therapeutic range for specific indication e.g. AF 2-2.5
Following the initial period of antithrombotic therapy for patients with AF undergoing PCI for ACS or elective PCI with high-risk features:

Recommendation

29. If age < 65 and CHADS$_2$ = 0, we recommend long-term therapy with either ASA alone or, if high-risk clinical or angiographic features of ischemic events and low risk of bleeding, ASA + P2Y$_{12}$ inhibitor (Strong Recommendation, High Quality Evidence); or

If age $\geq$ 65 or CHADS$_2$ $\geq$ 1, we recommend long-term therapy with either OAC alone (Strong Recommendation, Moderate and High Quality Evidence) or, if high-risk clinical or angiographic features of ischemic events persist and low risk of bleeding, OAC plus single antiplatelet therapy with ASA or a P2Y$_{12}$ inhibitor (Weak Recommendation, Low Quality Evidence).
Other reasons for anticoagulation

In patients with established left ventricular thrombus undergoing PCI for an ACS or non-ACS indication:

37. We suggest an initial regimen of triple therapy with ASA 81 mg daily plus clopidogrel 75 mg daily plus OAC. ASA may be discontinued as early as the day following PCI or it can be continued up to 6 months of treatment, depending on the risk of recurrent coronary ischemic events versus major bleeding. Following ASA discontinuation, we suggest treatment with OAC plus clopidogrel 75 mg daily for up to 1 year. If there is evidence of LV thrombus resolution ≥ 3 months after PCI, we suggest discontinuation of OAC and treatment with ASA 81 mg daily plus a P2Y\textsubscript{12} inhibitor for up to 1 year after PCI (Weak Recommendation, Very Low Quality Evidence).

Practical tip:
- Warfarin is the only anticoagulant evaluated for the treatment of established left ventricular thrombus. While NOACS are generally safer than warfarin, they have not been evaluated specifically in this context.
Other reasons for anticoagulation

*In patients undergoing PCI for an ACS indication who are high-risk of developing LV thrombus:*

38. We **recommend** dual antiplatelet therapy (DAPT) with ASA 81 mg daily plus either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily for up to 1 year (**Strong Recommendation, Moderate Quality Evidence**).

39. We **suggest** triple therapy should be avoided given the weak evidence for prevention of LV thrombus and higher risk of bleeding events (**Weak Recommendation, Moderate Quality Evidence**).
Other reasons for anticoagulation

Recommendation

30. We **recommend** that patients who have **concomitant symptomatic CAD** and **another condition requiring OAC** receive a regimen of antithrombotic therapy that is based on a balanced assessment of their risk of (1) systemic embolism, (2) future coronary event(s) and (3) clinically significant bleeding associated with the use of antithrombotic agents (**Strong Recommendation, High Quality Evidence**).

In patients with a prior valve replacement who undergo PCI for an ACS or non-ACS indication:

31. For patients with a **mechanical valve replacement**, we **suggest** an initial regimen of ASA 81 mg daily plus clopidogrel 75 mg daily plus a vitamin K antagonist (VKA) (triple therapy). ASA may be discontinued as early as the day after PCI or it can be continued up to 6 months of treatment, depending on the risk of recurrent thrombotic events versus major bleeding (**Weak Recommendation, Very Low Quality Evidence**).
Other reasons for anticoagulation

In patients with a prior valve replacement who undergo PCI for an ACS or non-ACS indication:

32. For patients with a mechanical valve replacement, we recommend against the use of a NOAC regardless of whether it is in combination with antiplatelet therapy or used alone (Strong Recommendation, Moderate Quality Evidence).

33. For patients with a surgical bioprosthetic valve replacement, (implanted < 6 months), we suggest DAPT with ASA 81 mg daily and clopidogrel 75 mg daily for at least 6 months (and up to 12 months) (Weak Recommendation, Very Low Quality Evidence).

34. For patients with a transcatheter aortic valve replacement (TAVR) (implanted < 6 months), we suggest DAPT with ASA 81 mg daily and clopidogrel 75 mg daily for 3-6 months (Weak Recommendation, Very Low Quality Evidence).
Closing Thoughts On 2018 CCS Focused Update On APT

- More potent P2Y12 inhibitors preferred following ACS with emphasis for reducing thrombotic events whilst acknowledging some excess in non-fatal bleeding events

- For some patients ‘less may be better’ (or at least as good) than more
  - shorter duration DAPT may be ok following elective PCI
  - not all post MI patients should have prolonged DAPT
    - utilize risk scores for DAPT duration in everyday clinical practice
  - OAC+P\textsubscript{2}Y\textsubscript{12} inhibitor as good or better than OAC+DAPT in AF patients undergoing PCI (but for how long)
    - Prophylaxis against LV thrombus formation with OAC discouraged in those already on DAPT e.g. post PCI for STEMI

- NOACs generally preferred as OAC with antiplatelet therapy in those with CAD (unless severe renal impairment or metallic prosthetic valve)

- Communication vital between hospital physicians and primary care given increasing numbers of potential treatment options
Contemporary Canadian Travel Advisory February 2018

Travel advisory: Germans in Canada should exercise a high degree of empathy. Be nice, don’t gloat, give hugs, buy rounds of hot chocolate.

Just imagine how you would feel if Canada beat us in soccer 😞

Thank you @GermanyDiplo. Congrats on your first shot at gold! We remember our first gold medal in #IceHockey like it was yesterday... 1920 to be exact. #PyeongChang2018

3:52 AM - Feb 23, 2018
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