



# Making Goldilocks Happy

## Not too short, not too long, but JUST RIGHT

Duration of Dual Antiplatelet Therapy (DAPT) & Triple Therapy for Cardiovascular & Cerebrovascular Indications

March 2016

- 1) ANTITHROMBOTICS are sometimes COMBINED to reduce risk of thrombosis.
- 2) Combination antithrombotic use should be for a DEFINITE DURATION.
- 3) If therapy is TOO SHORT or TOO LONG, there is increased risk of HARM.
- 4) ALL health care providers have a role in ACHIEVING the duration that's JUST RIGHT.



DAPT coronary stent



TRIPLE THERAPY AF + stent\*



DAPT cerebrovascular

### Phase I: Initial Therapy

The specialist will select the intended duration of therapy, & will specify if therapy is to be extended.

Initial prescription is usually for:

### Phase II: Step Down

Once the intended duration is complete, therapy should be stepped down as directed by the specialist.

### Tipping Point for

**Benefit vs Harm:**

When DAPT or TRIPLE THERAPY extends beyond the recommended duration, the balance between benefit & harm shifts.

Clopidogrel + ASA  
or  
Prasugrel + ASA  
or  
Ticagrelor + ASA

x 12 months

ASA x life-long  
DAPT may be extended up to 30 months see inside

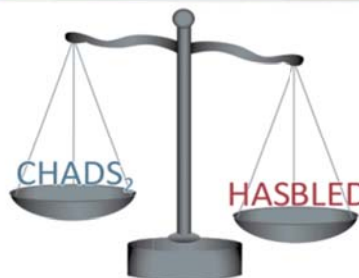
**8** fewer myocardial infarctions  
**6** more major bleeds  
per 1,000 patients treated/year  
with potentially 2 more deaths<sup>1</sup>

Warfarin + Clopidogrel + ASA

x 1 to 6 months rarely up to 12 months

Warfarin + Clopidogrel  
(warfarin + ASA or DAPT also an option)  
up to 12 months post stent

then Warfarin x life-long



Clopidogrel + ASA  
(single antiplatelet therapy also still an option)

x 21 days for ischemic stroke  
x 90 days for intracranial stent

single antiplatelet x life-long

**ISCHEMIC STROKE**  
**21** days of DAPT ↓ risk of stroke in a Chinese population CHANCE

DAPT **>90** days ↑ risk of major bleeds & all-cause mortality MATCH, SPS3

\*Preferred agents for triple therapy are listed. See inside chart for other options.

## SUGGESTED SYSTEM CHANGES TO PROMOTE ADHERENCE & APPROPRIATE DURATION

- ✓ **Specialist:** write the indication, intended duration & directions for step-down therapy on the original prescription & consult note
- ✓ **Primary Care Prescriber:** enter the indication, intended duration & step-down therapy into the patient chart paper/electronic medical record
- ✓ **Pharmacist:**
  - enter indication, intended duration & step-down therapy into the patient profile
  - add the intended duration to the prescription label
  - may send refill requests to the primary care prescriber if the specialist indicated life-long therapy (rare, see below)



## ENCOURAGE PATIENT ADHERENCE TO THE INTENDED DURATION

- ✓ identify & address reversible causes of non-adherence
- ✓ ensure the patient is taking ASA as part of the **DAPT** or **TRIPLE THERAPY** regimen
- ✓ use a **proton-pump inhibitor** for patients at high risk of a GI bleed: (potential drug interaction between clopidogrel & (es)omeprazole; conflicting evidence)
  - all patients while on **TRIPLE THERAPY**
  - those on **DAPT** with a high risk of a GI bleed
  - reassess need for the PPI when therapy is stepped down

Harms of starting too late / stopping too early for patients who are on **DAPT** after a coronary stent is inserted:

- a delay in filling the initial **DAPT** prescription even >1 day after discharge ↑ the risk of **mortality & MI**  $NNH=16^2$
- premature discontinuation of **DAPT** ↑ the risk of **stent thrombosis**, especially within the first 6 months of therapy



## IF YOU IDENTIFY PATIENTS WHO HAVE BEEN ON:



### CARDIAC:

**DAPT** for > 12 months or **TRIPLE THERAPY** > 6 months



### CEREBROVASCULAR:

**DAPT** for >21 days after ischemic stroke or >90 days intracranial stent



### Find out:

- What is the indication?
- How long has the patient been on **DAPT** or **TRIPLE THERAPY**?
- What was the intended duration? Has the specialist extended therapy or indicated it was life-long?
- Has a new event occurred since therapy was started?

Primary care prescribers should consider discontinuing **DAPT** or **TRIPLE THERAPY** if therapy is beyond the intended duration, & the specialist has not extended treatment. Too long may do more harm than good (see front cover).



In select cases, **DAPT** may be prescribed as life-long therapy. For example:

- Atrial fibrillation patients with a CHADS<sub>2</sub> score ≤1 (risk factors change over time), or who are unable to take an oral anticoagulant e.g. warfarin, apixaban, dabigatran, rivaroxaban
- Patients with a history of recurrent cardiovascular or cerebrovascular events
- Patients with peripheral artery disease who are at high vascular risk & low bleed risk (ASA or clopidogrel preferred over DAPT)

1. Spencer FA, Prasad M, Vandvik PO, et al. Longer- Versus Shorter-Duration Dual-Antiplatelet Therapy After Drug-Eluting Stent Placement: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2015 Jul 21;163(2):118-26.  
 2. Ho PM, Tsai TT, Maddox TM, et al. Delays in filling clopidogrel prescription after hospital discharge and adverse outcomes after drug-eluting stent implantation: implications for transitions of care. *Circ Cardiovasc Qual Outcomes.* 2010 May;3(3):261-6.

The focus of this chart is the duration of therapy. A specialist will select the intended duration of therapy when initiating treatment. If the duration of therapy is unclear/unknown, the specialist should be consulted. Optimize risk factor management (e.g. weight loss, smoking cessation, healthy eating, exercise, BP/BG/lipid control) to help ↓ the risk of subsequent cardiac &/or cerebrovascular events.

**DAPT: CARDIOVASCULAR INDICATIONS**

see Online Extras for Strength of Recommendations/Levels of Evidence

INDICATION	THERAPEUTIC OPTIONS & MAINTENANCE DOSES	MINIMUM DURATION <small>need compelling reason</small>	STANDARD DURATION	COMMENTS
<b>Coronary Stent + Stable CAD / Elective PCI</b>	ASA 81mg po daily + Clopidogrel 75mg po daily	<b>BMS:</b> 2-4 weeks <b>DES:</b> 3-6 months	6-12 months, then ASA	<p><b>Reset the clock with any new ACS event. ASA indefinitely once DAPT complete.</b></p> <ul style="list-style-type: none"> <li>- Stent thrombosis (ST) can lead to MI &amp;/or death. DAPT ↓ risk of recurrent MI &amp; ST after stent placement.</li> <li>- The majority of patients will receive a standard duration of DAPT x 12 months after a coronary stent.</li> </ul>
<b>Coronary Stent + NSTEACS (UA or NSTEMI)</b>	ASA 81mg po daily + Clopidogrel* 75mg po daily <small>*may be given as 150mg daily for first 6 days <sup>CURRENT-OASIS</sup></small>	<b>BMS:</b> 1 month <b>DES:</b> 3-6 months	12 months, then ASA	<p><b>BARE-METAL (BMS) vs DRUG-ELUTING (DES) STENTS:</b></p> <ul style="list-style-type: none"> <li>- Compared to BMS, DES ↓ the risk of in-stent restenosis &amp; the need for target vessel revascularization procedures.                             <ul style="list-style-type: none"> <li>▪ 1<sup>st</sup> generation DES (G<sub>1</sub>DES, e.g. paclitaxel) ↑ risk of very late ST (VL-ST, i.e. &gt;1 year post procedure) with a comparable rate of MI &amp; potential ↓ death. G<sub>1</sub>DES are no longer used in Canada.</li> <li>▪ Newer generation DES (new-DES, e.g. everolimus) have less risk of VL-ST vs G<sub>1</sub>DES, with a similar rate to BMS.</li> </ul> </li> </ul> <p><b>RISK OF STENT THROMBOSIS:</b> (rare after 1 year, but potentially fatal)</p> <ul style="list-style-type: none"> <li>- Incidence: at 1 year: ~1% similar across stent types; between 1 &amp; 3 years: BMS 0.05%, new-DES 0.04%, &amp; G<sub>1</sub>DES 0.3%.</li> <li>- Premature discontinuation of DAPT, especially within the first 6 months, ↑ risk of stent thrombosis.</li> </ul> <p><b>BALANCING the RISK of THROMBOSIS with the RISK of MAJOR BLEEDING</b></p> <p><b>Duration of DAPT &lt;12 Months:</b> would be considered by the cardiologist if there is a compelling reason, e.g.:</p> <ul style="list-style-type: none"> <li>▪ high bleed risk/low thrombosis risk (e.g. BMS)</li> <li>▪ surgery requiring tx interruption (see Perioperative Chart)</li> <li>▪ bleed while on DAPT (resume DAPT/SAPT when safe)</li> <li>▪ need for an oral anticoagulant (see TT section on next pg)</li> </ul> <p>- If the cardiologist reduces the duration of DAPT, reassure the patient the risk outweighed the benefit. A meta-analysis comparing 3-6 vs 12 months of DAPT (majority new-DES) found no difference in benefits (MI, ST, all-cause mortality) or major bleeds (OR 0.61, 95% CI 0.35-1.03). Shorter DAPT ↓ all bleeding (OR 0.59, 95% CI 0.44-0.79).</p> <p><b>Duration of DAPT &gt;12 Months</b> evidence is primarily with <b>DES and ASA + clopidogrel</b></p> <ul style="list-style-type: none"> <li>- Guidelines suggest DAPT &gt; 1 year in pts with a high risk of thrombosis &amp; low risk of bleed; <sup>CCS'12 (CR/LQ), ESC (IIB,A), USA (IIB,C)</sup> but very high risk individuals were excluded from trials that assessed extended duration. <sup>DAPT, ARTIC-Interruption, DES-LATE</sup></li> <li>- Several meta-analyses have compared standard DAPT (12 months) to extended DAPT (&gt;12 months), ~50% new-DES.                             <ul style="list-style-type: none"> <li>▪ <b>Benefit:</b> ↓ risk of MI ARR 1-1.4%, NNT=71-100, ↓ risk of ST ARR 0.6-0.7%, NNT=143-167</li> <li>▪ <b>Harm:</b> ↑ major bleed risk ARI 0.7-1.1% NNH=91-143, may ↑ all-cause mortality ARI 0.4% NNH=250 <sup>see RxFiles Q&amp;A</sup></li> <li>▪ DAPT did <u>not</u> show a reduction in the risk of CV mortality or stroke.</li> <li>▪ Longer DAPT 12-36mos, vs shorter 3-12mos: 8 fewer MIs, 6 more major bleeds, &amp; potentially 2 more deaths/1000 pts.</li> </ul> </li> <li>- After 1 year of DAPT, a cardiologist may decide to extend DAPT up to 30 months in those who received a <b>DES</b>, were compliant &amp; were <b>event-free after 12 months of DAPT</b> (i.e. no MI, ST, stroke, repeat revascularization, or major bleed), based on the <b>DAPT</b> study (12 vs 30 months of DAPT, see <a href="#">RxFiles Trial Summary</a>). <b>DAPT-BMS:</b> no benefit.                             <ul style="list-style-type: none"> <li>▪ <b>DAPT</b> Score Calculator: validated tool to help identify those who may benefit for DAPT &gt;1 year. See Online Extras.</li> </ul> </li> </ul>
<b>Coronary Stent + STEMI</b>	ASA 81mg po daily + Prasugrel 10mg po daily or ASA 81mg po daily + Ticagrelor 90mg po BID	12 months, then ASA		
<p><b>Clopidogrel vs Prasugrel vs Ticagrelor: why might a cardiologist select one over the other for patients with coronary stents?</b></p> <p>CCS'12 recommend ticagrelor or prasugrel over clopidogrel, based on:</p> <ul style="list-style-type: none"> <li>- <b>PLATO</b> : Ticagrelor vs clopidogrel in ACS (~60% coronary stent) x 12 months                             <ul style="list-style-type: none"> <li>▪ Ticagrelor ↓ risk of vascular death/MI/stroke NNT=53, ↑ risk of bleeding (non-CABG major bleeding NNH=167, &amp; fatal bleeding [non-intracranial NNH=500, intracranial NNH=1112]), ↑ risk of dyspnea NNH=17</li> </ul> </li> <li>- <b>TRITON</b> : Prasugrel vs clopidogrel in ACS+PCI (~95% coronary stent) x 14.5mos                             <ul style="list-style-type: none"> <li>▪ Prasugrel ↓ risk of vascular death/MI/stroke NNT=46, ↑ risk of bleeding (major NNH=167, life-threatening NNH=200 or fatal NNH=334 bleed).</li> </ul> </li> <li>- <b>Prasugrel:</b> only indicated in <b>ACS patients who undergo PCI</b>. It is contraindicated in patients with a history of stroke/TIA. For patients &lt;60kg or ≥75 years old, could consider 5mg once daily, <sup>CCS'12</sup> however this dose has never been studied &amp; the 10mg tablet is not scored.</li> <li>- <b>Cost:</b> DAPT x 1 month with clopidogrel \$30, prasugrel \$104, ticagrelor \$113</li> </ul>				
<b>ACS + CABG ± Coronary Stent</b>	ASA 81mg po daily + clopidogrel 75mg po daily or	No stent: 6 - 12 months, then ASA Stent: 12 months, then ASA		<ul style="list-style-type: none"> <li>- <b>Ticagrelor</b> preferred over <b>clopidogrel</b>, <sup>CCS'12 (SR/ HQ)</sup> based on <b>PLATO</b> (10% underwent CABG).</li> <li>- <b>Prasugrel</b> <u>not</u> recommended due to very little evidence.</li> </ul>
<b>ACS Medically Managed (i.e. no PCI or CABG)</b>	ASA 81mg po daily + ticagrelor 90mg po BID	<b>If using clopidogrel:</b> <b>NSTEACS:</b> 1 month <b>STEMI:</b> 14 to 30 days	12 months then ASA	<ul style="list-style-type: none"> <li>- <b>Ticagrelor</b> preferred over <b>clopidogrel</b>, <sup>CCS'12 (SR/ HQ)</sup> based on <b>PLATO</b> (~25% were medically managed).</li> <li>- <b>Prasugrel</b> <u>not</u> recommended; <b>TRILigy</b> failed to show a benefit in this population, vs clopidogrel. <sup>CLARITY</sup></li> <li>- <b>Use of fibrinolytics:</b> clopidogrel is recommended.</li> </ul>
<b>Peripheral Artery Disease</b> no stent	ASA 81mg po daily ± clopidogrel 75mg po daily	Long-term therapy with single antiplatelet preferred, or DAPT		<ul style="list-style-type: none"> <li>- <b>No stent:</b> ASA, or clopidogrel, preferred. Limited evidence with DAPT. <sup>CHARISMA</sup> May consider in individuals who are high vascular risk (e.g. DM, diabetic nephropathy, ABI &lt;0.9, asymptomatic carotid stenosis ≥70%) &amp; low bleed risk.</li> <li>- <b>Below knee bypass with prosthetic graft:</b> may consider DAPT with clopidogrel x 1 year. <sup>CASPAR</sup></li> </ul>

**BLEEDING RISK**

- Bleeding ↑ risk of morbidity & mortality, from fatal bleeds to nuisance bleeding which can lead to premature discontinuation of DAPT resulting in ↑ risk of harm (e.g. ↑ risk of ST post-coronary stent).
- Unfortunately, there are no validated risk scores for estimating bleeding when DAPT is initiated.
  - **DAPT for coronary stents:** the DAPT Score Calculator is a validated tool which compares risk of thrombosis to bleeding, if considering therapy >1 year. The HASBLED & REACH scores may provide perspective on bleeding risk factors, but limitations exist. See Online Extras.
- ↑ risk of bleeding with prasugrel & ticagrelor (ticagrelor **CI** if history of intracranial bleed).

**GASTROPROTECTION** ½ to ¾ of bleeds caused by DAPT are GI bleeds

- Consider a PPI for those on DAPT with a higher than average risk of a GI bleed: <sup>ESC'15 NSTEACS (IB)</sup>
  - history of GI ulcer/bleed, or
  - ≥2 of the following risk factors: age ≥65 years old, dyspepsia, GERD, *H.pylori* infection, or chronic alcohol use (others: SSRI use, smoking)
- Omeprazole (& esomeprazole) may prevent CYP 2C19 conversion of clopidogrel to its active form. Some evidence suggests this is not clinically significant. Consider **pantoprazole**, rabeprazole or lansoprazole. **Reassess need for PPI when DAPT is stopped.**

There may be a small ↑ risk in ischemic events when DAPT d/c; risk of ST ↑ 0.4% to 0.7% & MI ↑ 2% to 3% 3 months after DAPT stopped. <sup>DAPT-DES</sup> Unclear if rebound ischemic or unmasking delayed endothelialization.

**Restarting DAPT after initial tx complete:** Clopidogrel + ASA: no benefit. <sup>CHARISMA</sup> Ticagrelor 60mg BID (not available in Canada) vs placebo x3yrs ↓ death/ MI/stroke NNT=77 but ↑ major bleed NNH=84. <sup>PEGASUS</sup>

COST & FORMULARY STATUS	
DAPT = P2Y <sub>12</sub> Inhibitor + ASA formulary coverage is limited to 1 year in SK	\$/30days
Clopidogrel <b>PLAVIX</b> , g ☞ ▼75mg daily + ASA <b>ASPIRIN</b> , g 81mg daily	\$30
Prasugrel <b>EFFIENT</b> ☞ ⊗ 5-10mg daily + ASA <b>ASPIRIN</b> , g 81mg daily	\$104
Ticagrelor <b>BRILINTA</b> ☞ ▼90mg BID + ASA <b>ASPIRIN</b> , g 81mg daily	\$113
<b>Warfarin + Antiplatelet</b>	
Warfarin <b>COUMADIN</b> , g + Clopidogrel <b>PLAVIX</b> , g ☞ ▼75mg daily (preferred)	\$41
Warfarin <b>COUMADIN</b> , g + ASA <b>ASPIRIN</b> , g 81mg daily	\$19
<b>Triple Therapy = Warfarin + ASA + Clopidogrel</b>	
Warfarin <b>COUMADIN</b> , g + ASA 81mg + Clopidogrel <b>PLAVIX</b> , g ☞ ▼75mg daily	\$45

SWITCHING BETWEEN CLOPIDOGREL vs TICAGRELOR vs PRASUGREL
- CCS'12 Antiplatelet Guidelines suggest against switching the P2Y <sub>12</sub> inhibitor initially selected at discharge unless there is a compelling reason e.g. ST, bleed, CV event. <sup>CR/VLQ</sup>
- Information on switching is primarily based on pharmacodynamic & registry studies.
- The risk of ST is greatest during the 1 <sup>st</sup> month.
- <b>Most likely reason for switching from:</b> (see Online Extras for a summary of all options) <ul style="list-style-type: none"> <li>▪ <b>Clopidogrel</b> → <b>ticagrelor</b> or <b>prasugrel</b>: clinical failure (e.g. stent thrombosis despite adherence to therapy). A loading dose (LD) would likely be administered, in the hospital.</li> <li>▪ <b>Ticagrelor</b> → <b>clopidogrel</b>: dyspnea (rule out HF) or cost concerns. Suggested to give a LD 24hrs after the last ticagrelor dose (pharmacodynamic study showed a residual effect 12hrs after the last dose).</li> </ul>
- <b>Loading Doses for switching:</b> clopidogrel 300mg x1; ticagrelor 180mg x1; prasugrel 60mg x1

DAPT: CEREBROVASCULAR INDICATIONS (not comprehensive)			
Indication	Antiplatelet Options & Maintenance Doses	Duration of DAPT	Comments
<b>Cardioembolic Stroke in AF</b> OAC preferred over DAPT	ASA 75-325mg po daily + Clopidogrel 75mg po daily  <b>Note:</b> - Prasugrel <b>Cl</b> in patients with a history of stroke/TIA <sup>TRITON</sup> - Ticagrelor: no benefit <sup>SOCRATES</sup>	lifelong	- DAPT may be considered if CHADS <sub>2</sub> or CHA <sub>2</sub> DS <sub>2</sub> VASC score <2 or unable to take OAC. See AF chart page 18. - <b>ACTIVE-W</b> : DAPT vs warfarin x 1.3 years, <b>NNH=47</b> for stroke/non-CNS embolus/vascular death & <b>NNH=37</b> minor bleeds.
<b>Intracranial Artery Stenosis (Secondary Prevention)</b>		90 days	- Indicated for severe stenosis (70-99%) of a major intracranial artery. <sup>CSBPR 2014 (B), AHA/ASA 2014 (IIb,B)</sup> - <b>SAMMPRIS</b> : DAPT x 90 days ± stent, then ASA 81-325mg daily. DAPT was started within 30 days of stroke/TIA.
<b>Non-Cardioembolic Stroke (Secondary Prevention)</b>		21 days	- If started ≤ 24hr of minor ischemic stroke/TIA, may consider DAPT x 21 days, <sup>CSBPR'14 (C), AHA/ASA'14 (IIb,B), CHANCE</sup> then single antiplatelet (agent depends on if the patient was on an antiplatelet prior to their event, and if yes, which one) - Avoid DAPT >90 days: <sup>CSBPR'14 (A), AHA/ASA'14 (IIIA)</sup> <b>MATCH</b> (DAPT vs clopidogrel x 18 mos): DAPT no benefit; ↑ bleed risk >90 days (e.g. life-threatening <b>NNH=50</b> ). <b>SPS3</b> (DAPT vs ASA x 3.4yr): no benefit; ↑ all-cause mortality ( <b>NNH=44</b> ) & major bleed risk ( <b>NNH=32</b> ).

**TRIPLE THERAPY (TT = Warfarin + ASA + Clopidogrel)** consult with cardiologist see Online Extras for Strength of Recommendations/Levels of Evidence

- **TT should only be used in consultation with a cardiologist.**

- The efficacy & safety data for TT is primarily based on observational studies & a few small open-label RCTs (good evidence lacking).

**WHEN MIGHT TRIPLE THERAPY BE USED**

- Patients who require DAPT (i.e. coronary stent) + an OAC, e.g.:

- AF with CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VASC score ≥2. If CHADS<sub>2</sub> <2, DAPT may be sufficient for both ST & AF stroke prevention.
- Non-AF indications: hypercoagulable disorder, LV mural thrombus, mechanical valve prosthesis, VTE [recent or recurrent], & potentially anterior apical akinesis/dyskinesis

**HOW LONG WILL TRIPLE THERAPY BE PRESCRIBED**

- The cardiologist will consider indication for TT, risk of bleed, risk of thrombosis & stent type (if applicable) when determining the duration of therapy. A few examples:

- **AF (CHADS<sub>2</sub> score ≥2) + coronary stent examples:**

- TT may be as short as 1 month if: HASBLED ≥3, with a BMS.
- TT may be 3 to 6 months if: HASBLED ≤2, with a DES.
- Although rare, TT may be up to 12 months (e.g. very high risk of thrombosis with a low bleed risk).
- **ISAR-TRIPLE**: 6 weeks vs 6 months of TT in AF + DES patients; no difference in death/MI/ST/stroke/major bleeding, or major bleeding on its own. ⅓ stable CAD, majority new-DES.

- **Anterior MI with/high risk of LV thrombus + coronary stent:**

- TT may be used for 3 months, then warfarin is stopped

**WHICH MEDICATIONS SHOULD BE USED IN TRIPLE THERAPY**

- The evidence for TT is primarily with **warfarin, ASA + clopidogrel.**

- **Oral Anticoagulants (OAC) for TT:**

- **Warfarin**: the preferred OAC, regardless of indication for TT.
- **Dabigatran**: if warfarin cannot be used, there is a small amount of evidence for **dabigatran 110mg BID in AF patients.** **RELY sub-study**: n=812 (4.5%) on DAPT & dabigatran or warfarin at *some time* during the study; underpowered. Dabigatran has also been evaluated in a TT regimen for ACS secondary prevention; ↑ risk of bleed with no benefit. <sup>REDEEM</sup> ? ↑ risk of MI with dabigatran, <sup>RELY</sup> see [RxFiles Q&A](#). PPI may ↓ dabigatran serum levels (clinical significance unknown).
- **Apixaban**: studied as part of TT for ACS secondary prevention. Trial terminated early as ↑ bleed risk with no benefit. <sup>APPRAISE-2</sup>
- **Rivaroxaban**: 2.5mg BID as part of a TT for ACS secondary prevention. ↓ composite of CV death, MI, stroke **NNT=63** but ↑ risk of bleeding **NNH=83** over 2 years. <sup>ATLAS</sup> In Canada, this is not an approved indication & 2.5mg tablet is not available.

- **Dual Antiplatelets for TT:**

- **ASA 75-100mg/day plus clopidogrel 75mg/day** are the preferred antiplatelets, regardless of indication for TT.
- **Prasugrel**: avoid due to ↑ risk of bleeding, compared to clopidogrel in DAPT <sup>TRITON</sup> & TT studies. <sup>Sarafoff, TRANSLATE-ACS</sup>
- **Ticagrelor**: avoid due to ↑ risk of bleeding (more potent than clopidogrel) <sup>PLATO</sup> & very limited (n=27) evidence in TT. <sup>CAPITAL</sup>

**STEPPING DOWN FROM TRIPLE THERAPY**

- The cardiologist will provide instructions on which medications should be used once TT is complete.

- For example, step-down therapy for AF + coronary stent may be:

- DAPT or “warfarin plus clopidogrel” until 1 year post-stent, followed by life-long OAC (warfarin preferred)

- **WOEST**: warfarin + clopidogrel vs TT x 1 year in 573 patients with an indication for OAC + coronary stent (~27% ACS). Any bleeding **NNT=4**, major bleeding NS, ischemic events NS.

**RISK OF BLEEDING WITH TRIPLE THERAPY**

- Annual rate of major bleeds on TT is 10%. Nose, skin & GI bleeds are most common. 1 in 10 bleeds are fatal (½ intracranial, ½ GI).

- After a bleed, antithrombotics should be reassessed / restarted when safe to do so.

- **Strategies to ↓ the risk of bleeding with Triple Therapy:**

- Limit TT to recommended definite duration.
- Correct reversible HASBLED risk factors (e.g. uncontrolled HTN, labile INRs, concomitant NSAID use, & alcohol excess/abuse).
- Consider target INR of 2-2.5 (unless mechanical valve) & TTR >70%. Monitor INR q2weeks.
- Use ASA <100mg/day.
- Use a PPI for gastroprotection (e.g. pantoprazole 40mg po daily).
- Avoid prasugrel & ticagrelor as ↑ bleed risk vs clopidogrel.
- Avoid apixaban & rivaroxaban. If dabigatran is used (warfarin preferred), use lowest AF dose (110mg BID).

See AF Chart (page 18, <http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Atrial-Fibrillation.pdf>) for CHADS<sub>2</sub>, CHA<sub>2</sub>DS<sub>2</sub>VASC & HASBLED scores. See [www.rxfiles.ca](http://www.rxfiles.ca) for trial summaries on DAPT, PLATO, TRITON, PCI-CURE, & PCI-CLARITY.

☞ = EDS in SK ☞ =not covered by NIHB ▼ =covered by NIHB 2° =secondary ABI=ankle-brachial index ACS=acute coronary syndrome (i.e. UA, NSTEMI & STEMI) AF=atrial fibrillation BMS=bare-metal stent CABG=coronary artery bypass graft DAPT=dual antiplatelet therapy d/c=discontinue DES=drug-eluting stent g=generic G<sub>1</sub>DES=1<sup>st</sup> generation DES INR=international normalization ratio LD=loading dose MI=myocardial infarction NA=not applicable new-DES=newer drug-eluting stent NS=non-statistically significant NSTEACS=non-ST elevated ACS (UA or NSTEMI) OAC=oral anticoagulant PCI=percutaneous coronary intervention SAPT=single antiplatelet therapy ST=stent thrombosis TIA=transient ischemic attack TT=triple therapy TTR=time in therapeutic range UA=unstable angina VKA=vitamin K antagonist VL-ST=very late stent thrombosis

## ACKNOWLEDGEMENTS

**Contributors & Reviewers: Interventional Cardiologists (Saskatoon):** Dr. Colin Pearce, Dr. Paul Basran, & Dr. Jason Orvold. **Neurologist:** Dr Gary Hunter. **Neurosurgeon:** Dr. Michael Kelly (Saskatoon).

**Family Medicine:** Dr. Tessa Laubscher (Saskatoon). **Pharmacists:** Dr. Arden Barry (British Columbia), Dr. Margaret Jin (Hamilton), Dr. Patrick Robertson (Saskatoon), Alex Crawley (Prince Albert), Dr. Jennifer Bolt (Regina), Dr. Roland Halil (Ottawa), Lori Albers (Regina), Marlys LeBras (British Columbia), Trish Rawn (Toronto), Dr. Sarah Jennings (Ottawa).

**Chart Prepared by:** K Koziol BSP, A Martens BSP, D Shmyr BSP, L Kosar MSc, B Jensen BSP, L Regier BSP. **Newsletter Prepared by:** L Kosar, D Bunka, L Regier, B Jensen.

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## COMPLETE LIST OF ABBREVIATIONS

☐ = EDS in SK ☒ = not covered by NIHB 2° = secondary **ABI**=ankle-brachial index **ACS**=acute coronary syndrome **AF**=atrial fibrillation **ARI**=absolute risk increase **ARR**=absolute risk reduction **ASA**=acetylsalicylic acid **BG**=blood glucose **BMS**=bare-metal stent **BP**=blood pressure **CABG**=coronary artery bypass graft **CAD**=coronary artery disease **CI**=contraindication **CNS**=central nervous system **CV**=cardiovascular **DAPT**=dual antiplatelet therapy **d/c**=discontinue **DES**=drug-eluting stent **DM**=diabetes **g**=generic **G<sub>1</sub>DES**=1<sup>st</sup> generation drug-eluting stent **GERD**=gastroesophageal reflux disease **GI**=gastrointestinal bleed **HF**=heart failure **hr**=hour **HTN**=hypertension **INR**=international normalization ratio **LD**=loading dose **LV**=left ventricular **MI**=myocardial infarction **new-DES**=newer drug-eluting stent **mos**=months **NA**=not applicable **NNH**=number needed to harm **NNT**=number needed to treat **NS**=non-statistically significant **NSAID**=non-steroidal anti-inflammatory drug **NSTEACS**=non-ST elevated ACS **OAC**=oral anticoagulant **PAD**=peripheral artery disease **PCI**=percutaneous coronary intervention **PPI**=proton-pump inhibitor **pt**=patient **RCT**=randomized controlled trial **SAPT**=single antiplatelet therapy **SK**=Saskatchewan **SSRI**=selective serotonin reuptake inhibitor **ST**=stent thrombosis **TIA**=transient ischemic attack **TT**=triple therapy **TTR**=time in therapeutic range **tx**=treatment **VKA**=vitamin K antagonist **VL-ST**=very late stent thrombosis **VTE**=venous thromboembolism **yr**=year **yo**=years old

## RXFILES RELATED DOCUMENTS

- Perioperative Antithrombotic Management Chart (<http://www.rxfiles.ca/rxfiles/uploads/documents/members/Cht-Perioperative.pdf>)
- Oral Antiplatelet & Antithrombotic Agents Chart (<http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-AntiThrombotics.pdf>)
- Atrial Fibrillation – Selection of Thromboembolic Therapy Chart (<http://www.rxfiles.ca/rxfiles/uploads/documents/members/cht-Atrial-Fibrillation.pdf>)
- Oral Acid Suppression Chart (<http://www.rxfiles.ca/rxfiles/uploads/documents/members/CHT-AcidSuppression.pdf>)
- Q&A Does Clopidogrel + ASA Impact Mortality ([http://www.rxfiles.ca/rxfiles/uploads/documents/QandA\\_Clopidogrel\\_and\\_Mortality.pdf](http://www.rxfiles.ca/rxfiles/uploads/documents/QandA_Clopidogrel_and_Mortality.pdf))
- **ACTIVE-W** (DAPT vs warfarin in AF) Trial Summary (<http://www.rxfiles.ca/rxfiles/uploads/documents/ACTIVE-A-Trial-Summary.pdf>)
- **DAPT** (DAPT 12 vs 30 months) Trial Summary (<http://www.rxfiles.ca/rxfiles/uploads/documents/DAPT-Trial-12vs30months.pdf>)
- **PCI-CLARITY** (ASA vs clopidogrel post STEMI + PCI) Trial Summary (<http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CLARITY%20Trial%20Summary.pdf>)
- **PCI-CURE** (ASA vs clopidogrel post NSTEACS + PCI) Trial Summary (<http://www.rxfiles.ca/rxfiles/uploads/documents/PCI-CURE%20Trial%20Summary.pdf>)
- **PLATO** (ticagrelor vs clopidogrel in ACS+PCI) Trial Summary (<http://www.rxfiles.ca/rxfiles/uploads/documents/PLATO%20Trial%20Summary.pdf>)
- **TRITON** (prasugrel vs clopidogrel ACS) Trial Summary (<http://www.rxfiles.ca/rxfiles/uploads/documents/TRITON-TIMI%2038%20Trial%20Summary.pdf>)

## RxFiles Duration of DAPT & TT Online Extras:

L Kosar MSc, K Koziol BSP, A Martens BSP, D Shmyr BSP © [www.RxFiles.ca](http://www.RxFiles.ca) Apr 2016

### DAPT SCORE CALCULATOR ([www.daptstudy.org](http://www.daptstudy.org))

- The DAPT Score Calculator is a validated tool to help identify patients who may benefit from extended DAPT (i.e. beyond 1 year after a drug-eluting stent [**not** for those with a bare-metal stent]).
- The calculator should not be used at the time of coronary stent insertion. Instead, it may be used by a **cardiologist after the patient has been on DAPT for 12 months.**
- The score is based on the **DAPT** study – i.e. DAPT x 12 vs 30 months in patients with drug-eluting stent who were compliant & **event-free after 12 months of DAPT** (i.e. no MI, stent thrombosis, stroke, repeat revascularization, or major bleed).
- Balances risk of thrombosis (i.e. MI or stent thrombosis) vs bleeding.
- Risk of bleeding for the calculator was based solely on age.
- Variables that were risk factors for both thrombosis & bleeding were excluded from the calculator (e.g. HTN, CKD, & PAD).
- The score ranges from -2 to 10:
  - **Score <2:** bleed **NNH=64** > ischemic risk **NNT=153**, DAPT x 12 months then stop.
  - **Score ≥2:** ischemic **NNT=34** > bleeding risk **NNH=272**. May consider DAPT >12 months

VARIABLE	POINTS
<b>Patient Characteristics</b>	
Age: ≥75 years of age	-2
65-74 years of age	-1
<65 years of age	0
Diabetes Mellitus	1
Cigarette smoker within past 2 years	1
Prior PCI or Prior MI	1
History of HF or LVEF <30%	2
<b>Index Procedure Characteristic</b>	
MI at presentation	1
Vein graft PCI	2
Stent diameter <3mm	1

paclitaxel stent =1 point

**CKD**=chronic kidney disease **DAPT**=dual antiplatelet therapy **HTN**=hypertension **HF**=heart failure **LVEF**=left ventricular ejection fraction **MI**=myocardial infarction **NNH**=number needed to harm **NNT**=number needed to treat **PAD**=peripheral artery disease **PCI**=percutaneous coronary intervention

**SWITCHING P2Y<sub>12</sub> INHIBITORS (Clopidogrel vs Prasugrel vs Ticagrelor)**

- The Canadian Cardiovascular Society 2012 Antiplatelet Guidelines suggest against switching the P2Y<sub>12</sub> inhibitor initially selected at discharge unless there is a compelling reason e.g. stent thrombosis, bleed, cardiovascular event.<sup>CR/VLQ</sup>
- The following information is based primarily on pharmacodynamics studies & registries. Unfortunately, the timeframe for “acute phase” and “chronic phase” was not defined in the publications. Of note, **the risk of stent thrombosis is greatest during the first month.**
- Clopidogrel & prasugrel bind to the P2Y<sub>12</sub> receptors at the same site where ADP binds – thus blocking ADP. Ticagrelor, on the other hand, binds to the P2Y<sub>12</sub> receptor at a different site than ADP & induces a conformational change making the receptor inactive. As such, when switching between clopidogrel & prasugrel, it is a saturable process. Once all of the receptor sites are blocked, any additional drug is eliminated from the systemic circulation.
- **Loading Doses for Switching:** clopidogrel 300mg x1; ticagrelor 180mg x1; prasugrel 60mg x 1
- **Switching from clopidogrel → ticagrelor or prasugrel:** (e.g. clinical failure [e.g. stent thrombosis] despite adherence to therapy)
  - **Acute Phase:** administer loading dose (unless active bleeding) regardless of clopidogrel timing/dose
  - **Chronic Phase:** omit loading dose, start maintenance dose 24 hours after last clopidogrel dose.
  - In the **PLATO** trial (**ticagrelor** vs clopidogrel in ACS), 46% of the patients in the ticagrelor arm received a dose of clopidogrel prior to randomization. The loading dose of ticagrelor (180mg x 1) was administered to all of these patients.
  - In the **TRITON-TIMI** trial (**prasugrel** vs clopidogrel in ACS + PCI), all of the patients in the prasugrel arm were “P2Y<sub>12</sub> inhibitor naïve”.
- **Switching from ticagrelor → clopidogrel or prasugrel:** (e.g. dyspnea or cost concerns)
  - Administer loading dose 24 hours after the last ticagrelor dose (pharmacodynamic study showed a residual effect 12 hours after the last dose).
  - If the patient presents with dyspnea, it is important to rule out heart failure before switching agents.
- **Switching from prasugrel → clopidogrel:** (e.g. history of stroke or TIA not known at time of stent insertion or cost concerns)
  - **Acute Phase:** administer loading dose (unless active bleeding) 24 hours after the last dose of prasugrel.
  - **Chronic Phase:** omit loading dose, start maintenance dose 24 hours after last prasugrel dose.
- **Switching from prasugrel → ticagrelor:** (e.g. history of stroke or TIA not known at time of stent insertion)
  - Administer loading dose unless active bleeding 24 hours after the last prasugrel dose.

P2Y<sub>12</sub> inhibitor=clopidogrel, prasugrel or ticagrelor TIA=transient ischemic stroke

**STRENGTH OF RECOMMENDATIONS & LEVELS OF EVIDENCE****CARDIOVASCULAR INDICATIONS – DAPT****Stable CAD / Non-ACS / Stable Ischemic Heart Disease / Established CAD & Elective PCI**

- Ideally, DAPT with ASA 81mg po daily + **clopidogrel** 75mg po daily 6 months<sup>ESC/EACTS'14 (IB), ACA/AHA'16 (IB-R)</sup> to 12 months<sup>ACC/AHA'16 (IIb,A), CCS'12 (SR/HQ), ESC/EACTS'14 (IIb, C), ACCF/AHA/SCAI'11 (IB), CHEST'12 (2C)</sup>
- Minimum Durations:
  - **BMS:** ↑ risk of bleeding, scheduled for non-cardiac surgery: minimum DAPT x 1 month<sup>ACC/AHA'16 (IA), CCS'12 (SR/HQ), ESC/EACTS'14 (IA), ACCF/AHA/SCAI'11 (IB), CHEST'12 (IA)</sup>
  - **BMS:** very high risk of bleeding – minimum DAPT x 2 weeks<sup>CCS'12 (CR/LQ), ACCF/AHA/SCAI'11 (IB)</sup>
  - **DES:** ↑ risk of bleeding, scheduled for non-cardiac surgery, OAC: minimum 3<sup>ACC/AHA'16 (IIb,C-LD), CCS'12 (CR/LQ)</sup> to 6 months<sup>ACC/AHA'16 (IB-R), ESC/EACTS'14 (IIb, A), CHEST'12 (IA)</sup>
- ASA 81mg<sup>ACC/AHA'16 (IB-NR), ACCF/AHA/SCAI'11 (IIa, B)</sup> po daily indefinitely<sup>ESC/EACTS'14 (IA), ACCF/AHA/SCAI'11 (IA)</sup>

**NSTEACS & PCI**

- Ideally, DAPT x 12 months<sup>ACC/AHA'16(IIb-R), ESC'15 (IA), AHA/ACC'14 , CCS'12 (SR/HQ), CHEST'12(IIb)</sup> Options listed alphabetically:
  - Clopidogrel<sup>ESC'15 (IB), AHA/ACC'14 (IB), CCS'12 (SR/HQ)</sup> which is preferred for those requiring oral anticoagulation<sup>ESC'15 (IB)</sup>
  - Prasugrel preferred over clopidogrel if PCI planned<sup>ACC/AHA'16(IIa, B-R), ESC'15 (IB), AHA/ACC'14 (IB), CCS'12 (SR/HQ)</sup>. Not recommended if coronary anatomy is unknown, not treated with PCI, high bleed risk, or history of stroke/TIA.<sup>ESC'15 (IIIB), AHA/ACC'14 (IB, IIIB), CCS'12 (SR/HQ)</sup>
  - Ticagrelor, which is preferred over clopidogrel in those with moderate-to-high risk of ischemic events<sup>ACC/AHA'16(IIa, B-R), ESC'15 (IB), AHA/ACC'14 (IB), CCS'12 (SR/HQ), CHEST'12 (2B)</sup>
- Longer DAPT >12 months (balance ischemic & bleeding risks)<sup>ACC/AHA'16 (IIb,A), ESC'15 (IIb,A), AHA/ACC'14 (IIb,C), CCS'12 (CR/LQ)</sup>
- Shorter DAPT of 3 to 6 months after DES if high bleeding risk<sup>ESC'15 (IIb,A), AHA/ACC'14 (IIa,C)</sup>
- Minimum DAPT: BMS x 1 month, new-generation DES 3 to 6 months<sup>ESC'15 (IIb,C)</sup>
- ASA 81mg<sup>ACC/AHA'16(I, B-NR), CCS'12 (SR/HQ), AHA/ACC'14 (IIa,B)</sup> po daily indefinitely;<sup>ESC'15 (IA), AHA/ACC'14 (IA)</sup> ensure 81mg po daily if using ticagrelor.<sup>AHA/ACC'14 (IA)</sup> If ASA allergy or intolerance, use clopidogrel indefinitely.<sup>CCS'12 (SR/HQ)</sup>

## STRENGTH OF RECOMMENDATIONS &amp; LEVELS OF EVIDENCE continued

## CARDIOVASCULAR INDICATIONS – DAPT continued

## STEMI &amp; PCI

- Ideally, DAPT x 12 months <sup>ACC/AHA'16(IIb-R), ESC/EACTS'14 (IA), ACCF/AHA'13, CCS'12 (SR/HQ), CHEST'12(IIb)</sup> Options listed alphabetically:
  - Clopidogrel <sup>ESC/EACTS'14 (IB), ACCF/AHA'13 (IB), CCS'12 (SR/MQ)</sup>
  - Prasugrel <sup>ESC/EACTS'14 (IB), ACCF/AHA'13 (IB), CCS'12 (SR/HQ)</sup> avoid if a history of stroke/TIA, <sup>ACC/AHA'16(III, B-R), ACCF/AHA'13 (IIIB)</sup> high bleed risk <sup>ACC/AHA'16(IIa, B-R)</sup> & use 5mg daily if ≥75 years or weigh ≤60kg. <sup>CCS'12 (SR/LQ)</sup> Preferred over clopidogrel <sup>ACC/AHA'16(IIa, B-R), CCS'12 (SR/HQ)</sup> if not a high bleed risk. <sup>ACC/AHA'16 (IIb,A)</sup>
  - Ticagrelor <sup>ESC/EACTS'14 (IB), ACCF/AHA'13 (IB), CCS'12 (SR/HQ)</sup> is preferred over clopidogrel <sup>ACC/AHA'16(IIa, B-R), CCS'12 (SR/HQ), CHEST'12(2B)</sup>
- Longer DAPT beyond 12 months may be considered if DES <sup>ACC/AHA'16 (IIb,A), ACCF/AHA'13 (IIb,C), CCS'12 (CR/LQ)</sup>
- If high bleed risk & DES: may consider a minimum 6 months of DAPT. <sup>ACC/AHA'16(IIb,C-LD)</sup>
- ASA 81mg po <sup>ACC/AHA'16(I, B-NR), ACCF/AHA'13 (IIa,B)</sup> daily indefinitely. <sup>ESC/EACTS'14 (IA), ACCF/AHA'13 (IA)</sup> If ASA allergy or intolerance, use clopidogrel indefinitely. <sup>CCS'12 (SR/HQ)</sup>

## MEDICALLY MANAGED ACS

- Ideally, DAPT with ASA 81mg po daily + clopidogrel 75mg po daily <sup>CURE, CURRENT-OASIS</sup> or ticagrelor 90mg po BID <sup>PLATO, PLATO (non-invasive management subgroup analysis)</sup> x 12 months. <sup>ACC/AHA'16(IIb-R), CCS'12(INSTEACS – SR/HQ, STEMI – CR/LQ), ESC'15 (IA), AHA/ACC'14 (IB), CHEST'12 (IB)</sup>
- Preference for ticagrelor over clopidogrel, <sup>ACC/AHA'16(IIa,B-R), CCS'12 (SR,HQ)</sup> based on PLATO (~25% were medically managed), except in patients who receive fibrinolytics. Patients who received fibrinolytics were excluded from PLATO. If **fibrinolytics** are administered, clopidogrel is recommended. <sup>CLARITY</sup>
- Minimum Durations with clopidogrel: **STEMI:** 14 days <sup>ACC/AHA'16(IA), CCS'10(IIb), ACCF/AHA'13(IA)</sup> to 1 month; <sup>CCS'12(SR/HQ), COMMIT, CLARITY</sup> **NSTEMI/ACS:** 1 month <sup>CCS'10(IA), CURE</sup>
- May be reasonable to continue DAPT longer than 12 months in ACS patients who were medically managed/STEMI with fibrinolytic. <sup>ACC/AHA'16(IIb,A)</sup>

## PERIPHERAL ARTERY DISEASE

- Symptomatic PAD:** CHEST 2012 & ESC 2011 recommend *against* the use of DAPT for symptomatic PAD. ACCF/AHA 2011 & CCS 2010 state the combination may be considered in patients at high vascular risk with a low risk of bleeding. <sup>IIb,B for both</sup> This is based on CHARISMA (clopidogrel + ASA vs ASA alone), in which 25% of the patients had PAD. The primary endpoint (MI, stroke, CV death) was non-statistically significant for the whole population. However, in a subgroup of symptomatic patients (i.e. established vascular disease): clopidogrel + ASA 6.9% vs ASA alone 7.9%, RR 0.88 (95% CI 0.77-0.998), p=0.046 (underpowered).
- Below-knee bypass with a prosthetic graft:** may consider DAPT x 1 year. <sup>CHEST 2012 (2C), ESC 2011 (IIb,B), CASPAR</sup>

## CARDIOVASCULAR INDICATIONS TRIPLE THERAPY

## GENERAL RECOMMENDATIONS

- Ensure there is a compelling indication for triple therapy: LV thrombus, <sup>ACCF/AHA'13 (IIa,C)</sup> anterior apical akinesis or dyskinesia; <sup>ACCF/AHA'13 (IIb,C)</sup> AF with CHA<sub>2</sub>DS<sub>2</sub>-VAsc score ≥2, [recent or recurrent] VTE, mechanical valve prosthesis; <sup>ESC'15 (IC), ESC/EACTS'14 (IC), ACCF/AHA'13 (IC)</sup> or hypercoagulable disorder <sup>ACCF/AHA'13 (IC)</sup>
- In patients with AF, use the CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>-VAsc score to estimate stroke risk & the HASBLED to estimate bleed risk. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IC), CCS'12 (CR/LQ)</sup>
- New-generation DES are preferred over BMS, especially when HASBLED ≤2. <sup>ESC'15 (IIa,B), ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)</sup>
- Implement strategies to reduce bleeding: aim for a TTR>70%, <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IA)</sup> target an INR 2-2.5, <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C), AHA/ACC'14 (IIb,C), ACCF/AHA'13 (IIb,C)</sup> Avoid novel P2Y<sub>12</sub> inhibitors (i.e. prasugrel or ticagrelor). <sup>ESC'15 (III,C), ESC/EACTS'14 (III,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (III,C)</sup> Use a PPI. <sup>ESC'15 (IB), ESC/EACTS'14 (IA), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C), AHA/ACC'14 (IIa,C – IC)</sup>
- Minimize duration. <sup>AHA/ACC'14 (IC), ACCF/AHA'13 (IC)</sup>

## STABLE CAD + PCI &amp; AF

- CHA<sub>2</sub>DS<sub>2</sub>-VAsc score ≤1:** consider using DAPT as an alternative to TT. <sup>ESC/EACTS'14 (IIa,C)</sup>
  - HAS-BLED ≤2:** consider using DAPT or dual therapy (OAC + clopidogrel [or ASA]), as alternatives to TT. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup>
  - HASBLED >3:** consider using DAPT, or dual therapy (OAC + clopidogrel [or ASA]) x 12 months, as alternatives to TT. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup>
- CHA<sub>2</sub>DS<sub>2</sub>-VAsc score ≥2:**
  - HAS-BLED ≤2:** TT x 1 month, <sup>ESC/EACTS'14 (IIb,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup> (maximum 6 months) <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup> regardless of stent type, followed by dual therapy (OAC + SAPT) up to 12 months. <sup>ESC/EACTS'14 (IIb,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup> May consider dual therapy x 1 year as an alternative. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C), AHA/ACC/HRS'14 (IIb,B)</sup>
  - HASBLED >3:** TT <sup>ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup> or dual therapy (OAC + clopidogrel [or ASA]) <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup> x 1 month, followed by dual therapy x 11 months. <sup>ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup>
- After 1 year post-PCI, long-term OAC. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IB)</sup> May use dual therapy (OAC + clopidogrel [or ASA]) in very selected cases e.g. stenting of left main, proximal left anterior descending, proximal bifurcation, recurrent MIs, etc. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)</sup>

## STRENGTH OF RECOMMENDATIONS &amp; LEVELS OF EVIDENCE continued

## CARDIOVASCULAR INDICATIONS TRIPLE THERAPY continued

## NSTEACS + PCI &amp; AF

- **CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 1 (in males) or 2 (in females):** consider using DAPT as an alternative to TT. <sup>ESC'15 (IIa,C)</sup>
- **HASBLED 0-2:** TT x 6 months, then dual therapy (OAC + SAPT) x 6 months, <sup>ESC'15 (IIa,C), ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup> regardless of stent type. <sup>ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup>
- **CHA<sub>2</sub>DS<sub>2</sub>-VASc ≥2:** may continue TT or dual therapy (OAC + SAPT) between 6 and 12 months. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)</sup>
- **HASBLED ≥3:** TT x 1 month, then dual therapy (OAC + SAPT) x 11 months, regardless of stent type. <sup>ESC'15 (IIa,C), ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup> May consider dual therapy (OAC + SAPT) as an alternative to TT if low risk of stent thrombosis or high bleed risk. <sup>ESC'15 (IIb,B), ESC/EACTS'14 (IIb,B), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)</sup>
- After 1 year post-PCI, long-term OAC. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb)</sup> May use dual therapy (OAC + clopidogrel [or ASA]) in very selected cases e.g. stenting of left main, proximal bifurcation, recurrent MIs, etc. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,B)</sup>
- **Medically Managed or CABG:** dual therapy (OAC + SAPT) preferred x 12 months. <sup>ESC'15 (IIa,C)</sup>
- Avoid TT with novel P2Y12 inhibitors, <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (III,B)</sup> however may consider one of these agents if the patient has a stent thrombosis while on TT with clopidogrel. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)</sup>

## STEMI + PCI &amp; AF

- **HASBLED 0-2:** TT x 6 months, regardless of stent type, then dual therapy (OAC + clopidogrel [or ASA]). <sup>ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup>
- **CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥2:** may continue TT or dual therapy (OAC + SAPT) between 6 and 12 months. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)</sup>
- **HASBLED ≥3:** TT x 1 month, regardless of stent type, followed by dual therapy (OAC + clopidogrel [or ASA]). <sup>ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)</sup> May consider dual therapy (OAC + SAPT) as an alternative to TT if low risk of recurrent ischemic events & high bleed risk. <sup>ESC/EACTS'14 (IIb,B), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,B)</sup>
- After 1 year post-PCI, long-term OAC. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb)</sup> May use dual therapy (OAC + clopidogrel [or ASA]) in very selected cases e.g. stenting of left main, proximal bifurcation, recurrent MIs, etc. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,B)</sup>
- Avoid TT with novel P2Y12 inhibitors, <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (III,B)</sup> however may consider one of these agents if the patient has a stent thrombosis while on TT with clopidogrel. <sup>ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)</sup>

## Triple Therapy for Secondary Prevention

- There are conflicting guideline considerations for the use of rivaroxaban for secondary prevention of ACS. Rivaroxaban 2.5mg BID x 1 year may be considered in select patients with a low risk of bleeding, but should not be used in preference to DAPT with a novel P2Y12 inhibitor. <sup>ESC'15 (IIb,B), ESC/EACTS'14(IIb,B), CCS'12 (CR/VLQ)</sup> Note: this is not an approved indication in Canada & rivaroxaban 2.5mg **is not** commercially available.
- Dabigatran & apixaban are NOT recommended for the sole indication of secondary ACS prevention. <sup>CCS'12 (SR/HQ), APPRAISE, REDEEM</sup>

## CEREBROVASCULAR INDICATIONS

## Non-cardoembolic Ischemic Stroke

- If antiplatelet therapy is initiated within 24 hours of minor ischemic stroke/TIA, may consider DAPT x 21 days <sup>CSBPR'14 (C), AHA/ASA'14 (IIb,B), CHANCE</sup>
- Long-term DAPT started days to years after a stroke/TIA is not recommended due to the increased risk of bleeding and mortality <sup>CSBPR'14 (A), AHA/ASA'14 (IIIA), SPS3, MATCH</sup>
- See following page for a summary of the trials that formed the basis of the guideline recommendations.

## Intracranial Artery Stenosis

- **DAPT (ASA 325mg + clopidogrel 75mg po daily) x 90 days** for patients with recent stroke/TIA (within 30 days) due to severe stenosis (70-99%) of a major intracranial artery, <sup>CSBPR 2014 (B), AHA/ASA 2014 (IIb,B)</sup> with aggressive risk factor management (e.g. SBP<140mmHg or <130mmHg in DM, LDL-C < 1.81mmol/L, lifestyle modification) <sup>SAMMPRIS</sup>
- Aggressive medical management with percutaneous transluminal angioplasty and stenting (PTAS) had a NNH of 12/30 days, compared to aggressive medical management alone (rate of stroke 30 days to 1 year: NS); ARI at 30 days was 8.9% and at 3 years was 9% <sup>SAMMPRIS</sup>



**SUMMARY OF ISCHEMIC STROKE DAPT TRIALS (NON-CARDIOEMBOLIC): SECONDARY PREVENTION**

Study	Regimen *	Start of Treatment in Relation to Event	DAPT Duration	Benefit	Harm
<b>CHANCE</b> (2013, in China)	- Days 1-22: DAPT vs ASA - Days 22-90: clopidogrel vs ASA 75mg daily	within 24 hours	21 days	- ↓ risk of stroke <b>NNT=29/90</b> days	- NS for bleeding & all-cause mortality
<b>SPS3</b> (2012)	DAPT vs ASA 325mg	within 2 weeks to 180 days (mean 62 days)	3.4 years	NS for primary endpoint (stroke/MI)	- ↑ risk of all-cause mortality <b>NNH=44</b> (or 143/year) - ↑ risk of major bleeding <b>NNH=32</b> (or 100/year) - discontinuation rates <b>NNH=34</b>
<b>FASTER</b> (2007)	DAPT vs ASA 81mg	within 24 hours	90 days	NS for primary endpoint (stroke)	- ↑ risk of symptomatic bleeding <b>NNH=34</b> & bruising <b>NNH=6</b>
<b>MATCH</b> (2004)	DAPT vs clopidogrel	within 3 months (mean 26 days)	18 months	NS for primary endpoint (stroke, MI, vascular death or rehospitalization for acute ischemic event)	- ↑ risk of bleeding (life-threatening <b>NNH=50</b> , major <b>NNH=100</b> ) - GI bleeds were the most common location for life-threatening (53%) & major (58%) bleeds. - Kaplan-Meier curve for intracranial hemorrhage suggests no difference in risk for the first 90 days; ↑ risk with DAPT beyond 90 days.

\* All DAPT regimens with clopidogrel 75mg daily

**ESTIMATING BLEEDING RISK for DAPT**

- **DAPT** score calculator weighs the risk of thrombosis against the risk of bleeding... for patients who were compliant & event-free for 12 months on DAPT. As such, the DAPT score is unable to estimate the risk of bleeding in individuals whom may require less than 1 year of therapy due to bleeding risk.
- The **HASBLED** score was shown to have predictive value (score ≥3 indicated ↑ risk of bleeding) in Japanese patients who were on DAPT post-PCI. However, the HASBLED score has not been validated in this patient population (it has been validated in AF patients).
- The **REACH** registry bleeding risk score was developed & validated (CHARISMA patient population) in outpatients with/without atherothrombosis. Approximately 2/3 of the population had a history of CAD, but the authors did not report how many had undergone revascularization procedures.
- There are limitations to applying the HASBLED or REACH scores to patients who are on DAPT post-ACS; however, these tools may provide additional perspective into bleeding risk factors to consider for choice & duration of therapy.

<b>HASBLED</b>	
HASBLED RISK CRITERIA	POINTS
<u>H</u> ypertension (SBP>160mmHg)	1
<u>A</u> bnormal renal or liver function (1 point each)	1 to 2
<u>S</u> troke (caused by a bleed)	1
<u>B</u> leeding (hospitalization, ↓ Hgb >20g/L, transfusion)	1
<u>L</u> abile INRs (TTR<60%)	1
<u>E</u> lderly (age >65 years)	1
<u>D</u> rugs (ASA/NSAID) or alcohol (≥8 drinks/week) (1 point each)	1 to 2
<b>TOTAL</b>	
HASBLED score of ≥3 indicates ↑ risk of bleeding	

<b>REACH</b>	
REACH RISK FACTORS	POINTS
Age: 55-64 years	2
65-74 years	4
≥75 years	6
Peripheral Artery Disease	1
Congestive Heart Failure	2
Diabetes	1
Hypercholesterolemia	2
Hypertension	2
Smoking: Former	1
Current	2
Antiplatelet agents: ASA	1
Other	2
DAPT	4
Oral Anticoagulants	4
<b>TOTAL</b>	
REACH score >10 indicates ↑ risk of bleeding	

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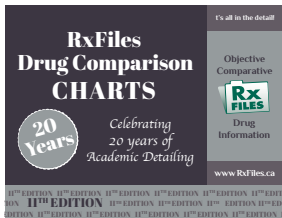
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