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:	Clopidogrel **+** ASA or Prasugrel **+** ASA or Ticagrelor **+** ASA x 12 months	Warfarin **+** Clopidogrel **+** ASA x 1 to 6 months rarely up to 12 months	Clopidogrel **+** ASA (single antiplatelet therapy also still an option) x 21 days for ischemic stroke x 90 days for intracranial stent
Phase II: Step Down **Once the intended duration is complete, therapy should be stepped down as directed by the specialist.**	ASA x life-long DAPT may be extended up to 30 months see inside	Warfarin **+** Clopidogrel (warfarin + ASA or DAPT also an option) up to 12 months post stent then Warfarin x life-long	single antiplatelet x life-long
Tipping Point for Benefit vs Harm: **When DAPT or TRIPLE THERAPY extends beyond the recommended duration, the balance between benefit & harm shifts.**	**8** fewer **myocardial infarctions** **6** more **major bleeds** per **1,000 patients** treated/year with potentially 2 more deaths [1]		**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)

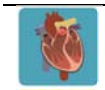
ENCOURAGE PATIENT ADHERENCE TO THE INTENDED DURATION

- ☑ 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 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 $CHADS_2$ 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.

DURATION of DUAL ANTIPLATELET THERAPY (DAPT) & TRIPLE THERAPY (TT)

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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 need compelling reason	STANDARD DURATION	COMMENTS Reset the clock with any new ACS event. ASA indefinitely once DAPT complete.
Coronary Stent + Stable CAD / Elective PCI	ASA 81mg po daily + Clopidogrel 75mg po daily	**BMS:** 2-4 weeks **DES:** 3-6 months	6-12 months, then ASA	- Stent thrombosis (ST) can lead to MI &/or death. DAPT ↓ risk of recurrent MI & ST after stent placement. - The majority of patients will receive a standard duration of DAPT x 12 months after a coronary stent.
Coronary Stent + NSTEACS (UA or NSTEMI)	ASA 81mg po daily + Clopidogrel* 75mg po daily *may be given as 150mg daily for first 6 days CURRENT-OASIS or ASA 81mg po daily + Prasugrel 10mg po daily or ASA 81mg po daily + Ticagrelor 90mg po BID	**BMS:** 1 month **DES:** 3-6 months	12 months, then ASA	**BARE-METAL (BMS) vs DRUG-ELUTING (DES) STENTS:** - Compared to BMS, DES ↓ the risk of in-stent restenosis & the need for target vessel revascularization procedures. ▪ 1st generation DES (G_1DES, e.g. paclitaxel) ↑ risk of very late ST (VL-ST, i.e. >1 year post procedure) with a comparable rate of MI & potential ↓ death. G_1DES are no longer used in Canada. ▪ Newer generation DES (new-DES, e.g. everolimus) have less risk of VL-ST vs G_1DES, with a similar rate to BMS. **RISK OF STENT THROMBOSIS:** (rare after 1 year, but potentially fatal) - Incidence: at 1 year: ~1% similar across stent types; between 1 & 3 years: BMS 0.05%, new-DES 0.04%, & G_1DES 0.3%. - Premature discontinuation of DAPT, especially within the first 6 months, ↑ risk of stent thrombosis. **BALANCING the RISK of THROMBOSIS with the RISK of MAJOR BLEEDING** **Duration of DAPT <12 Months:** would be considered by the cardiologist if there is a compelling reason, e.g.: ▪ high bleed risk/low thrombosis risk (e.g. BMS) ▪ surgery requiring tx interruption (see Perioperative Chart) ▪ bleed while on DAPT (resume DAPT/SAPT when safe) ▪ need for an oral anticoagulant (see TT section on next pg) - 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). **Duration of DAPT >12 Months** evidence is primarily with **DES** and **ASA + clopidogrel** DAPT, ARTIC-Interruption, DES-LATE - Guidelines suggest DAPT > 1 year in pts with a high risk of thrombosis & low risk of bleed; CCS'12 (CR/LQ), ESC (IIb,A), USA (IIb,C) but very high risk individuals were excluded from trials that assessed extended duration. DAPT, ARTIC-Interruption, DES-LATE - Several meta-analyses have compared standard DAPT (12 months) to extended DAPT (>12 months), ~50% new-DES. ▪ **Benefit:** ↓ risk of MI ARR 1-1.4%, NNT=71-100, ↓ risk of ST ARR 0.6-0.7%, NNT=143-167 ▪ **Harm:** ↑ major bleed risk ARI 0.7-1.1% NNH=91-143, may ↑ all-cause mortality ARI 0.4% NNH=250 see RxFiles Q&A ▪ DAPT did not show a reduction in the risk of CV mortality or stroke. ▪ Longer DAPT 12-36mos, vs shorter 3-12mos: 8 fewer MIs, 6 more major bleeds, & potentially 2 more deaths/1000 pts. - After 1 year of DAPT, a cardiologist may decide to extend DAPT up to 30 months in those who received a **DES**, were compliant & were **event-free after 12 months of DAPT** (i.e. no MI, ST, stroke, repeat revascularization, or major bleed), based on the **DAPT** study (12 vs 30 months of DAPT, see RxFiles Trial Summary). **DAPT-BMS**: no benefit. ▪ **DAPT** Score Calculator: validated tool to help identify those who may benefit for DAPT >1 year. See Online Extras.
Coronary Stent + STEMI		12 months, then ASA		

Clopidogrel vs Prasugrel vs Ticagrelor: why might a cardiologist select one over the other for patients with coronary stents?

CCS'12 recommend ticagrelor or prasugrel over clopidogrel, based on:

- **PLATO**: **Ticagrelor** vs **clopidogrel** in ACS (~60% coronary stent) x 12 months
  - Ticagrelor ↓ risk of vascular death/MI/stroke NNT=53, ↑risk of bleeding (non-CABG major bleeding NNH=167, & fatal bleeding [non-intracranial NNH=500, intracranial NNH=1112]), ↑risk of dyspnea NNH=17
- **TRITON**: **Prasugrel** vs **clopidogrel** in ACS+PCI (~95% coronary stent) x 14.5mos
  - Prasugrel ↓risk of vascular death/MI/stroke NNT=46, ↑risk of bleeding (major NNH=167, life-threatening NNH=200 or fatal NNH=334 bleed).
- **Prasugrel:** only indicated in **ACS patients who undergo PCI**. It is contraindicated in patients with a history of stroke/TIA. For patients <60kg or ≥75 years old, could consider 5mg once daily,CCS'12 however this dose has never been studied & the 10mg tablet is not scored.
- **Cost:** DAPT x 1 month with clopidogrel $30, prasugrel $104, ticagrelor $113

ACS + CABG ± Coronary Stent	ASA 81mg po daily + clopidogrel 75mg po daily or ASA 81mg po daily + ticagrelor 90mg po BID	No stent: 6 - 12 months, then ASA Stent: 12 months, then ASA		- **Ticagrelor** preferred over **clopidogrel**, CCS'12 (SR/ HQ) based on **PLATO** (10% underwent CABG). - **Prasugrel not** recommended due to very little evidence.
ACS Medically Managed (i.e. no PCI or CABG)		**If using clopidogrel:** **NSTEACS:** 1 month **STEMI:** 14 to 30 days	12 months then ASA	- **Ticagrelor** preferred over **clopidogrel**, CCS'12 (SR/ HQ) based on **PLATO** (~25% were medically managed). - **Prasugrel not** recommended; **TRILOGY** failed to show a benefit in this population, vs clopidogrel. - **Use of fibrinolytics:** clopidogrel is recommended. CLARITY
Peripheral Artery Disease no stent	ASA 81mg po daily ± clopidogrel 75mg po daily	Long-term therapy with single antiplatelet preferred, or DAPT		- **No stent:** ASA, or clopidogrel, preferred. Limited evidence with DAPT. CHARISMA May consider in individuals who are high vascular risk (e.g. DM, diabetic nephropathy, ABI <0.9, asymptomatic carotid stenosis ≥70%) & low bleed risk. - **Below knee bypass with prosthetic graft:** may consider DAPT with clopidogrel x 1 year. CASPAR

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 ⅔ 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: ESC'15 NSTEACS (IB)
  - history of GI ulcer/bleed, or
  - anticoagulant therapy (i.e. TT), or
  - chronic NSAID or corticosteroid use, 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. DAPT-DES Unclear if rebound ischemic or unmasking delayed endothelialization.

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

COST & FORMULARY STATUS	$/30days
DAPT = $P2Y_{12}$ Inhibitor + ASA formulary coverage is limited to 1 year in SK	
Clopidogrel PLAVIX, g ☎▼75mg daily + ASA ASPIRIN, g 81mg daily	$30
Prasugrel EFFIENT ☎⊗ 5-10mg daily + ASA ASPIRIN, g 81mg daily	$104
Ticagrelor BRILINTA ☎▼90mg BID + ASA ASPIRIN, g 81mg daily	$113
Warfarin + Antiplatelet	
Warfarin COUMADIN, g + Clopidogrel PLAVIX, g ☎▼75mg daily (preferred)	$41
Warfarin COUMADIN, g + ASA ASPIRIN, g 81mg daily	$19
Triple Therapy = Warfarin + ASA + Clopidogrel	
Warfarin COUMADIN, g + ASA 81mg + Clopidogrel PLAVIX, g ☎▼75mg daily	$45

SWITCHING BETWEEN CLOPIDOGREL vs TICAGRELOR vs PRASUGREL

- CCS'12 Antiplatelet Guidelines suggest against switching the $P2Y_{12}$ inhibitor initially selected at discharge unless there is a compelling reason e.g. ST, bleed, CV event. CR/VLQ
- Information on switching is primarily based on pharmacodynamic & registry studies.
- The risk of ST is greatest during the 1st month.
- **Most likely reason for switching from:** (see Online Extras for a summary of all options)
  - **Clopidogrel → ticagrelor or prasugrel:** clinical failure (e.g. stent thrombosis despite adherence to therapy). A loading dose (LD) would likely be administered, in the hospital.
  - **Ticagrelor → clopidogrel:** 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).
- **Loading Doses for switching:** clopidogrel 300mg x1; ticagrelor 180mg x1; prasugrel 60mg x1

DAPT: CEREBROVASCULAR INDICATIONS (not comprehensive)

Indication	Antiplatelet Options & Maintenance Doses	Duration of DAPT	Comments
Cardioembolic Stroke in AF OAC preferred over DAPT	ASA 75-325mg po daily + Clopidogrel 75mg po daily Note: - Prasugrel CI in patients with a history of stroke/TIA TRITON - Ticagrelor: no benefit SOCRATES	lifelong	- DAPT may be considered if $CHADS_2$ or CHA_2DS_2VASC score <2 or unable to take OAC. See AF chart page 18. - **ACTIVE-W**: DAPT vs warfarin x 1.3 years, NNH=47 for stroke/non-CNS embolus/vascular death & NNH=37 minor bleeds.
Intracranial Artery Stenosis (Secondary Prevention)		90 days	- Indicated for severe stenosis (70-99%) of a major intracranial artery. CSBPR 2014 (B), AHA/ASA 2014 (IIb,B) - **SAMMPRIS**: DAPT x 90 days ± stent, then ASA 81-325mg daily. DAPT was started within 30 days of stroke/TIA.
Non-Cardioembolic Stroke (Secondary Prevention)		21 days	- If started ≤ 24hr of minor ischemic stroke/TIA, may consider DAPT x 21 days, CSBPR'14 (C), AHA/ASA'14 (IIb,B), CHANCE 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: CSBPR'14 (A), AHA/ASA'14 (IIIA) **MATCH** (DAPT vs clopidogrel x 18 mos): DAPT no benefit; ↑ bleed risk >90 days (e.g.life-threatening NNH=50). **SPS3** (DAPT vs ASA x 3.4yr): no benefit; ↑ all-cause mortality (NNH=44) & major bleed risk (NNH=32).

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 $CHADS_2$ or CHA_2DS_2-VASc score **≥2**. If $CHADS_2$ <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 ($CHADS_2$ 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. ⅔ 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. REDEEM ? ↑ risk of MI with dabigatran, RELY 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. APPRAISE-2
  - **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. ATLAS 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 TRITON & TT studies. Saraforf, TRANSLATE-ACS
  - **Ticagrelor:** avoid due to ↑ risk of bleeding (more potent than clopidogrel) PLATO & very limited (n=27) evidence in TT. CAPITAL

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 **$CHADS_2$, CHA_2DS_2VASc & HASBLED** scores. See 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_1DES**=1st 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

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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**=acetylsalicyclic 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_1DES**=1st 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)
- 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 Apr 2016

DAPT SCORE CALCULATOR (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
Patient Characteristics	
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
Index Procedure Characteristic	
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 $P2Y_{12}$ INHIBITORS (Clopidogrel vs Prasugrel vs Ticagrelor)

- The Canadian Cardiovascular Society 2012 Antiplatelet Guidelines suggest against switching the $P2Y_{12}$ inhibitor initially selected at discharge unless there is a compelling reason e.g. stent thrombosis, bleed, cardiovascular event. [CR/VLQ]
- 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 $P2Y_{12}$ receptors at the same site where ADP binds – thus blocking ADP. Ticagrelor, on the other hand, binds to the P2Y12 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 "$P2Y_{12}$ 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.

$P2Y_{12}$ 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 [ESC/EACTS'14 (IB), ACA/AHA'16 (IB-R)] to 12 months [ACC/AHA'16 (IIb,A), CCS'12 (SR/HQ), ESC/EACTS'14 (IIb, C), ACCF/AHA/SCAI'11 (IB), CHEST'12 (2C)]
- Minimum Durations:
  - **BMS:** ↑ risk of bleeding, scheduled for non-cardiac surgery: minimum DAPT x 1 month [ACC/AHA'16 (IA), CCS'12 (SR/HQ), ESC/EACTS'14 (IA), ACCF/AHA/SCAI'11 (IB), CHEST'12 (IA)]
  - **BMS:** very high risk of bleeding – minimum DAPT x 2 weeks [CCS'12 (CR/LQ), ACCF/AHA/SCAI'11 (IB)]
  - **DES:** ↑ risk of bleeding, scheduled for non-cardiac surgery, OAC: minimum 3 [ACC/AHA'16 (IIb,C-LD), CCS'12 (CR/LQ)] to 6 months [ACC/AHA'16 (IB-R), ESC/EACTS'14 (IIb, A), CHEST'12 (IA)]
- ASA 81mg [ACC/AHA'16 (IB-NR), ACCF/AHA/SCAI'11 (IIa, B)] po daily indefinitely [ESC/EACTS'14 (IA), ACCF/AHA/SCAI'11 (IA)]

NSTEACS & PCI

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

STRENGTH OF RECOMMENDATIONS & LEVELS OF EVIDENCE continued

CARDIOVASCULAR INDICATIONS – DAPT continued

STEMI & PCI

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

MEDICALLY MANAGED ACS

- Ideally, DAPT with ASA 81mg po daily + clopidogrel 75mg po daily [CURE, CURRENT-OASIS] or ticagrelor 90mg po BID [PLATO, PLATO (non-invasive management subgroup analysis)] x 12 months. [ACC/AHA'16(IB-R), CCS'12(NSTEACS – SR/HQ, STEMI – CR/LQ), ESC'15 (IA), AHA/ACC'14 (IB), CHEST'12 (IB)]
- Preference for ticagrelor over clopidogrel, [ACC/AHA'16(IIa,B-R), CCS'12 (SR,HQ)] 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. [CLARITY]
- Minimum Durations with clopidogrel: **STEMI:** 14 days [ACC/AHA'16(IA), CCS'10(IB), ACCF/AHA'13(IA)] to 1 month; [CCS'12(SR/HQ), COMMIT, CLARITY] **NSTEACS:** 1 month [CCS'10(IA), CURE]
- May be reasonable to continue DAPT longer than 12 months in ACS patients who were medically managed/STEMI with fibrinolytic. [ACC/AHA'16(IIb,A)]

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. [IIb,B for both] 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. [CHEST 2012 (2C), ESC 2011 (IIb,B), CASPAR]

CARDIOVASCULAR INDICATIONS – TRIPLE THERAPY

GENERAL RECOMMENDATIONS

- Ensure there is a compelling indication for triple therapy: LV thrombus, [ACCF/AHA'13 (IIa,C)] anterior apical akinesis or dyskinesis; [ACCF/AHA'13 (IIb,C)] AF with CHA_2DS_2-VASc score ≥2, [recent or recurrent] VTE, mechanical valve prosthesis; [ESC'15 (IC), ESC/EACTS'14 (IC), ACCF/AHA'13 (IC)] or hypercoagulable disorder [ACCF/AHA'13 (IC)]
- In patients with AF, use the $CHADS_2$ or CHA_2DS_2-VASc score to estimate stroke risk & the HASBLED to estimate bleed risk. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IC), CCS'12 (CR/LQ)]
- New-generation DES are preferred over BMS, especially when HASBLED ≤2. [ESC'15 (IIa,B), ESC/EACTS'1 4 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)]
- Implement strategies to reduce bleeding: aim for a TTR>70%, [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IA)] target an INR 2-2.5, [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C), AHA/ACC'14 (IIb,C), ACCF/AHA'13 (IIb,C)] Avoid novel P2Y12 inhibitors (i.e. prasugrel or ticagrelor). [ESC'15 (III,C), ESC/EACTS'1 4 (III,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (III,C)] Use a PPI. [ESC'15 (IB), ESC/EACTS'1 4 (IA), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C), AHA/ACC'14 (IIa,C – IC)] Minimize duration.[AHA/ACC'14 (IC), ACCF/AHA'13 (IC)]

STABLE CAD + PCI & AF

- **CHA_2DS_2-VASc score ≤1:** consider using DAPT as an alternative to TT. [ESC/EACTS'1 4 (IIa,C)]
  - **HAS-BLED ≤2:** consider using DAPT or dual therapy (OAC + clopidogrel [or ASA]), as alternatives to TT. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)]
  - **HASBLED >3:** consider using DAPT, or dual therapy (OAC + clopidogrel [or ASA]) x 12 months, as alternatives to TT. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)]
- **CHA_2DS_2-VASc score ≥2:**
  - **HAS-BLED ≤2:** TT x 1 month, [ESC/EACTS'1 4 (IIb,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)] (maximum 6 months) [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)] regardless of stent type, followed by dual therapy (OAC + SAPT) up to 12 months.[ESC/EACTS'1 4 (IIb,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)] May consider dual therapy x 1 year as an alternative. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C), AHA/ACC/HRS'14 (IIb,B)]
  - **HASBLED >3:** TT [ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)] or dual therapy (OAC + clopidogrel [or ASA]) [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)] x 1 month, followed by dual therapy x 11 months. [ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)]
- After 1 year post-PCI, long-term OAC. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IB)] 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. [ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)]

STRENGTH OF RECOMMENDATIONS & LEVELS OF EVIDENCE continued

CARDIOVASCULAR INDICATIONS – TRIPLE THERAPY continued

NSTEACS + PCI & AF

- **CHA_2DS_2-VASc score of 1 (in males) or 2 (in females):** consider using DAPT as an alternative to TT. ESC'15 (IIa,C)
- **HASBLED 0-2:** TT x 6 months, then dual therapy (OAC + SAPT) x 6 months, ESC'15 (IIa,C), ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C) regardless of stent type. ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)
  - **CHA_2DS_2-VASc ≥2:** may continue TT or dual therapy (OAC + SAPT) between 6 and 12 months. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)
- **HASBLED ≥3:** TT x 1 month, then dual therapy (OAC + SAPT) x 11 months, regardless of stent type. ESC'15 (IIa,C), ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C) May consider dual therapy (OAC + SAPT) as an alternative to TT if low risk of stent thrombosis or high bleed risk. ESC'15 (IIb,B), ESC/EACTS'14 (IIb,B), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)
- After 1 year post-PCI, long-term OAC. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IB) May use dual therapy (OAC + clopidogrel [or ASA]) in very selected cases e.g. stenting of left main, proximal bifuraction, recurrent MIs, etc. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,B)
- **Medically Managed or CABG:** dual therapy (OAC + SAPT) preferred x 12 months. ESC'15 (IIa,C)
- Avoid TT with novel P2Y12 inhibitors, ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (III,B) however may consider one of these agents if the patient has a stent thrombosis while on TT with clopidogrel. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)

STEMI + PCI & AF

- **HASBLED 0-2:** TT x 6 months, regardless of stent type, then dual therapy (OAC + clopidogrel [or ASA]). ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C)
  - **CHA_2DS_2-VASc score ≥2:** may continue TT or dual therapy (OAC + SAPT) between 6 and 12 months. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)
- **HASBLED ≥3:** TT x 1 month, regardless of stent type, followed by dual therapy (OAC + clopidogrel [or ASA]). ESC/EACTS'14 (IIa,C), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIa,C) May consider dual therapy (OAC + SAPT) as an alternative to TT if low risk of recurrent ischemic events & high bleed risk. ESC/EACTS'14 (IIb,B), ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,B)
- After 1 year post-PCI, long-term OAC. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IB) May use dual therapy (OAC + clopidogrel [or ASA]) in very selected cases e.g. stenting of left main, proximal bifuraction, recurrent MIs, etc. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,B)
- Avoid TT with novel P2Y12 inhibitors, ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (III,B) however may consider one of these agents if the patient has a stent thrombosis while on TT with clopidogrel. ESC/EHRA/EAPCI/ACCA/HRS/APHRS'14 (IIb,C)

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. ESC'15 (IIb,B), ESC/EACTS'14(IIb,B), CCS'12 (CR/VLQ) 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. CCS'12 (SR/HQ), APPRAISE, REDEEM

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 CSBPR'14 (C), AHA/ASA'14 (IIb,B), CHANCE
- Long-term DAPT started days to years after a stroke/TIA is not recommended due to the increased risk of bleeding and mortality CSBPR'14 (A), AHA/ASA'14 (IIIA), SPS3, MATCH
- 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, CSBPR 2014 (B), AHA/ASA 2014 (IIb,B) with aggressive risk factor management (e.g. SBP<140mmHg or <130mmHg in DM, LDL-C < 1.81mmol/L, lifestyle modification) SAMMPRIS
- 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% SAMMPRIS

SUMMARY OF ISCHEMIC STROKE DAPT TRIALS (NON-CARDIOEMBOLIC): SECONDARY PREVENTION					
Study	**Regimen ***	**Start of Treatment in Relation to Event**	**DAPT Duration**	**Benefit**	**Harm**
CHANCE (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 NNT=29/90 days	- NS for bleeding & all-cause mortality
SPS3 (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 NNH=44 (or 143/year) - ↑ risk of major bleeding NNH=32 (or 100/year) - discontinuation rates NNH=34
FASTER (2007)	DAPT vs ASA 81mg	within 24 hours	90 days	NS for primary endpoint (stroke)	- ↑ risk of symptomatic bleeding NNH=34 & bruising NNH=6
MATCH (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 NNH=50, major NNH=100) - 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.

HASBLED	
HASBLED RISK CRITERIA	**POINTS**
Hypertension (SBP>160mmHg)	1
Abnormal renal or liver function (1 point each)	1 to 2
Stroke (caused by a bleed)	1
Bleeding (hospitalization, ↓ Hgb >20g/L, transfusion)	1
Labile INRs (TTR<60%)	1
Elderly (age >65 years)	1
Drugs (ASA/NSAID) or alcohol (≥8 drinks/week) (1 point each)	1 to 2
TOTAL	
HASBLED score of ≥3 indicates ↑ risk of bleeding	

REACH	
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
TOTAL	
REACH score >10 indicates ↑ risk of bleeding	

REFERENCES: DURATION OF DAPT & TT

CARDIOVASCULAR GUIDELINES:

CANADIAN CARDIOVASCULAR GUIDELINES

Ackman ML, Bucci C, Callaghan M, et al. A pharmacist's guide to the 2012 update of the Canadian Cardiovascular Society Guidelines for the Use of Antiplatelet Therapy. Can Pharm J (Ott).2015 Mar;148(2):71-81.

Tanguay JF, Bell AD, Ackman ML et al; **Canadian Cardiovascular Society**. Focused **2012** update of the Canadian Cardiovascular Society guidelines for the use of antiplatelet therapy. Can J Cardiol. 2013 Nov;29(11):1334-45.

Skanes AC, Healey JS, Cairns JA, et al; **Canadian Cardiovascular Society Atrial Fibrillation Guidelines** Committee. Focused **2012** update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol. 2012 Mar-Apr;28(2):125-36.

Bell AD, Roussin A, Cartier R, et al; **Canadian Cardiovascular Society**. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society guidelines. Can J Cardiol. **2011** May-Jun;27 Suppl A:S1-59.

EUROPEAN CARDIOVASCULAR GUIDELINES

Roffi M, Patrono C, Collet JP, et al. **2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-segment Elevation**. Rev Esp Cardiol (Engl Ed). 2015 Dec;68(12):1125.

Authors/Task Force members, Windecker S, Kolh P, Alfonso F, et al. **2014 ESC/EACTS Guidelines on myocardial revascularization**: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014 Oct 1;35(37):2541-619.

Lip GY, Windecker S, Huber K, et al. **Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions**: a joint consensus document of the **European Society of Cardiology Working Group on Thrombosis**, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J. **2014** Dec 1;35(45):3155-79.

Montalescot G, Sechtem U, Achenbach S, et al. **2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology**. Eur Heart J. 2013 Oct;34(38):2949-3003.

European Stroke Organisation, Tendera M, Aboyans V, Bartelink ML, et al; ESC Committee for Practice Guidelines. ESC Guidelines on the diagnosis and treatment of **peripheral artery diseases**: Document covering atherosclerotic disease of extracranial carotid and vertebral,mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2011 Nov;32(22):2851-906.

USA CARDIOVASCULAR GUIDELINES

Levine GN, Bates ER, Bittl JA, et al. **2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease**: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation. 2016 Mar 29. pii: CIR.0000000000000404. [Epub ahead of print] PubMed PMID: 27026020.

Bittl JA, Baber U, Bradley SM, Wijeysundera DN. Duration of Dual Antiplatelet Therapy: A **Systematic Review for the 2016 ACC/AHA Guideline** Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2016 Mar 29. pii: CIR.0000000000000405. [Epub ahead of print] PubMed PMID: 27026019.

Kulik A, Ruel M, Jneid H et al; **American Heart Association** Council on Cardiovascular Surgery and Anesthesia. Secondary prevention after **coronary artery bypass graft** surgery: a scientific statement from the American Heart Association. Circulation. **2015** Mar 10;131(10):927-64.

Amsterdam EA, Wenger NK, Brindis RG, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association for Clinical Chemistry. **2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes:** a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014 Dec 23;64(24):e139-228.

January CT, Wann LS, Alpert JS, et al; ACC/AHA Task Force Members. **2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation**: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014 Dec 2;130(23):e199-267.

O'Gara PT, Kushner FG, Ascheim DD, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Emergency Physicians; Society for Cardiovascular Angiography and Interventions. **2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction**: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv. 2013 Jul 1;82(1):E1-27.

Vandvik PO, Lincoff AM, Gore JM, et al; American College of Chest Physicians. Primary and secondary prevention of cardiovascular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: **American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**. Chest. 2012 Feb;141(2 Suppl):e637S-68S. doi: 10.1378/chest.11-2306. Erratum in: Chest. 2012 Apr;141(4):1129.

Alonso-Coello P, Bellmunt S, McGorrian C, et al; American College of Chest Physicians. Antithrombotic therapy in **peripheral artery disease**: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012 Feb;141(2Suppl):e669S-90S.

Hillis LD, Smith PK, Anderson JL, et al; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. **2011 ACCF/AHA guideline for coronary artery bypass graft surgery: executive summary**: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2012 Jan; 143(1):4-34.

Levine GN, Bates ER, Blankenship JC et al; ACCF; AHA; SCAI. **2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention**: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Catheter Cardiovasc Interv. 2012 Feb 15;79(3):453-95.

American College of Cardiology Foundation; American Heart Association Task Force; Society for Cardiovascular Angiography and Interventions; Society of Interventional Radiology; Society for Vascular Medicine; Society for Vascular Surgery, Rooke TW, Hirsch AT, Misra S, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with **peripheral artery disease** (updating the 2005 guideline). Vasc Med. 2011 Dec;16(6):452-76.

Grines CL, Bonow RO, Casey DE Jr, et al; American Heart Association; American College of Cardiology; Society for Cardiovascular Angiography and Interventions; American College of Surgeons; American Dental Association; American College of Physicians. **Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents**: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. J Am Dent Assoc. **2007** May;138(5):652-5.

Laskey WK, Yancy CW, Maisel WH. Thrombosis in coronary drug-eluting stents: report from the meeting of the Circulatory System Medical Devices Advisory Panel of the Food and Drug Administration Center for Devices and Radiologic Health, December 7-8, 2006. Circulation. **2007** May 1;115(17):2352-7.

Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines; ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention. **ACC/AHA/SCAI 2005 guideline update for percutaneous coronary intervention**: a report of the AmericanCollege of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to Update 2001 Guidelines for Percutaneous Coronary Intervention). Circulation. 2006 Feb 21;113(7):e166-286.

DAPT POST-PCI META-ANALYSES

Abo-Salem E, Alsidawi S, Jamali H, et al. Optimal Duration of Dual Antiplatelet Therapy after Drug-Eluting Stents: Meta-Analysis of Randomized Trials. Cardiovasc Ther. 2015 Oct;33(5):253-63.

Basaraba J, Barry A. Short- versus standard-term dual antiplatelet therapy after percutaneous coronary intervention with drug-eluting stent implantation: a meta-analysis. Abstract CSHP PPC 2016. CJHP 2016; 69(1).

Cassese S, Byrne RA, Ndrepepa G, et al. Prolonged dual antiplatelet therapy after drug-eluting stenting: meta-analysis of randomized trials. Clin Res Cardiol. 2015 Oct;104(10):887-901.

Giustino G, Baber U, Sartori S, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Cardiol. 2015 Apr 7;65(13):1298-310.

Navarese EP, Andreotti F, Schulze V, et al. Optimal duration of dual antiplatelet therapy after percutaneous coronary intervention with drug eluting stents: meta-analysis of randomised controlled trials. BMJ. 2015 Apr 16;350:h1618.

Palmerini T, Benedetto U, Bacchi-Reggiani L, et al. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. Lancet. 2015 Jun 13;385(9985):2371-82.

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.

Tsoi MF, Cheung CL, Cheung TT, et al. Duration of dual antiplatelet therapy after drug-eluting stent implantation: Meta-analysis of large randomised controlled trials. Sci Rep. 2015 Aug 17;5:13204.

Verdoia M, Schaffer A, Barbieri L, et al. Optimal Duration of Dual Antiplatelet Therapy After DES Implantation: A Meta-Analysis of 11 Randomized Trials. Angiology. 2015 Jun 11.

DAPT-POST PCI TRIALS (>1 year)

Collet JP, Silvain J, Barthélémy O, et al; **ARCTIC** investigators. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. Lancet. 2014 Nov 1;384(9954):1577-85.

Helft G, Steg PG, Le Feuvre C, et al; OPTImal DUAL Antiplatelet Therapy Trial Investigators. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the **OPTIDUAL** randomized trial. Eur Heart J. 2016 Jan 21;37(4):365-74.

Lee CW, Ahn JM, Park DW, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial (**DES-LATE**). Circulation. 2014 Jan 21;129(3):304-12.

Mauri L, Kereiakes DJ, Yeh RW, et al; **DAPT Study Investigators**. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med. 2014 Dec 4; 371(23):2155-66.

Wallace EL, Abdel-Latif A, Charnigo R,et al. Meta-analysis of long-term outcomes for drug-eluting stents versus bare-metal stents in primary percutaneous coronary interventions for ST-segment elevation myocardial infarction. Am J Cardiol. 2012 Apr 1;109(7):932-40.

Yeh R, Secemsky E, Kereiakes J, et al. Individualizing treatment duration of dual antiplatelet therapy after percutaneous coronary intervention: an analysis from the DAPT study (**DAPT Score Calculator**). Available at: http://www.daptstudy.org/for-media/DAPT_Score_AHA_Slides.pdf. Accessed January 2016.

Yeh RW, Secemsky EA, Kereiakes DJ, et al; DAPT Study Investigators. Development and Validation of a Prediction Rule for Benefit and Harm of Dual Antiplatelet Therapy Beyond 1 Year After Percutaneous Coronary Intervention. JAMA. 2016 Mar 29.

DAPT-POST PCI TRIALS

Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, et al. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the **SECURITY** randomized clinical trial. J Am Coll Cardiol. 2014;64: 2086-97.

Feres F, Costa RA, Abizaid A, et al; **OPTIMIZE** Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. JAMA. 2013;310:2510-22.

Gilard M, Barragan P, Noryani AA, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter **ITALIC** trial. J Am Coll Cardiol. 2015;65:777-86.

Gwon HC, Hahn JY, Park KW, et al. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (**EXCELLENT**) randomized, multicenter study. Circulation. 2012;125:505-13.

Kim BK, Hong MK, Shin DH, et al; **RESET** Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). J Am Coll Cardiol. 2012;60:1340-8.

Schulz-Schupke S, Byrne RA, Ten Berg JM, et al; on behalf of the Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (**ISAR-SAFE**) trial investigators. ISAR-SAFE: a randomized, double-blind, placebo controlled trial of 6 versus 12 months of clopidogrel therapy after drug-eluting stenting. Eur Heart J. 2015.

Valgimigli M, Borghesi M, Tebaldi M, et al; PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY Investigators. Should duration of dual antiplatelet therapy depend on the type and/or potency of implanted stent? A pre-specified analysis from the PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia studY (**PRODIGY**). Eur Heart J. 2013;34:909-19.

BARE-METAL STENTS

Kereiakes DJ, Yeh RW, Massaro JM, et al; Dual Antiplatelet Therapy (**DAPT)** Study Investigators. Antiplatelet therapy duration following **bare metal** or drug-eluting coronary stents: the dual antiplatelet therapy randomized clinical trial. JAMA. 2015 Mar 17;313(11):1113-21.

Steinhubl SR, Berger PB, Mann JT et al; **CREDO** Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002 Nov 20; 288(19):2411-20.

Yamaji K, Shiomi H, Morimoto T, et al. Influence of Sex on Long-Term Outcomes After Implantation of Bare-Metal Stent: A Multicenter Report From the Coronary Revascularization Demonstrating Outcome Study-Kyoto (CREDO-Kyoto) Registry Cohort-1. Circulation. 2015 Dec 15;132(24):2323-33.

DISCONTINUATION OF THERAPY

Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. JAMA. 2007 Jan 10;297(2):159-68.

Loh JP, Torguson R, Pendyala LK, et al. Impact of early versus late clopidogrel discontinuation on stent thrombosis following percutaneous coronary intervention with first- and second-generation drug-eluting stents. Am J Cardiol. 2014 Jun 15;113(12):1968-76.

Mehran R, Baber U, Steg PG, et al. Cessation of dual antiplatelet treatment and cardiac events after percutaneous coronary intervention (**PARIS**): 2 year results from a prospective observational study. Lancet. 2013 Nov 23;382(9906):1714-22.
Moussa ID, Colombo A. Antiplatelet therapy discontinuation following drug-eluting stent placement: dangers, reasons, and management recommendations. Catheter Cardiovasc Interv. 2009 Dec 1;74(7):1047-54.
Naidu SS, Krucoff MW, Rutledge DR, et al. Contemporary incidence and predictors of stent thrombosis and other major adverse cardiac events in the year after XIENCE V implantation: results from the 8,061-patient XIENCE V United States study. JACC Cardiovasc Interv. 2012 Jun;5(6):626-35.
Pfisterer M, Brunner-La Rocca HP, Buser PT, et al; BASKET-LATE Investigators. Late clinical events after clopidogrel discontinuation may limit the benefit of drug-eluting stents: an observational study of drug-eluting versus bare-metal stents. J Am Coll Cardiol. 2006 Dec 19;48(12):2584-91.
Schulz S, Schuster T, Mehilli J, et al. Stent thrombosis after drug-eluting stent implantation: incidence, timing, and relation to discontinuation of clopidogrel therapy over a 4-year period. Eur Heart J. 2009 Nov;30(22):2714-21.
Silber S, Kirtane AJ, Belardi JA, et al. Lack of association between dual antiplatelet therapy use and stent thrombosis between 1 and 12 months following resolute zotarolimus-eluting stent implantation. Eur Heart J. 2014 Aug 1;35(29):1949-56.
Yano M, Natsuaki M, Morimoto T, Nakagawa Y, et al; j-Cypher Registry Investigators. Antiplatelet therapy discontinuation and stent thrombosis after sirolimus-eluting stent implantation: five-year outcome of the j-Cypher Registry. Int J Cardiol. 2015 Nov 15;199:296-301.

STENT THROMBOSIS

Byrne RA, Joner M, Kastrati A. Stent thrombosis and restenosis: what have we learned and where are we going? The Andreas Grüntzig Lecture ESC 2014. Eur Heart J. 2015 Dec 14;36(47):3320-31.
Eisen A, Bhatt DL. Antiplatelet therapy: Defining the optimal duration of DAPT after PCI with DES. Nat Rev Cardiol. 2015 Aug;12(8):445-6.
Daemen J, Wenaweser P, Tsuchida K, et al. Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. Lancet. 2007 Feb 24;369(9562):667-78.
Dangas GD, Claessen BE, Mehran R, et al. Development and validation of a stent thrombosis risk score in patients with acute coronary syndromes. JACC Cardiovasc Interv. 2012 Nov;5(11):1097-105.
Jeger RV, Pfisterer ME, Sørensen R, et al; BASKET and BASKET-PROVE investigators. Tradeoff between bleeding and stent thrombosis in different dual antiplatelet therapy regimes: Importance of case fatality rates and effective treatment durations. Am Heart J. 2014 Nov;168(5):698-705.
Holmes DR Jr, Kereiakes DJ, Garg S et al. Stent thrombosis. J Am Coll Cardiol. 2010 Oct 19;56(17):1357-65.
Kaul U, Bangalore S, Seth A, et al; **TUXEDO**–India Investigators. Paclitaxel-Eluting versus Everolimus-Eluting Coronary Stents in Diabetes. N Engl J Med. 2015 Oct 29;373(18):1709-19.
Naidu SS, Krucoff MW, Rutledge DR, et al. Contemporary incidence and predictors of stent thrombosis and other major adverse cardiac events in the year after XIENCE V implantation: results from the 8,061-patient XIENCE V United States study. JACC Cardiovasc Interv. 2012 Jun;5(6):626-35.
Sarno G, Lagerqvist B, Fröbert O, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Eur Heart J. 2012 Mar;33(5):606-13.
Serruys PW, Farooq V, Kalesan B, et al. Improved safety and reduction in stent thrombosis associated with biodegradable polymer-based biolimus-eluting stents versus durable polymer-based sirolimus-eluting stents in patients with coronary artery disease: final 5-year report of the LEADERS (Limus Eluted From A Durable Versus ERodable Stent Coating)randomized, noninferiority trial. JACC Cardiovasc Interv. 2013 Aug;6(8):777-89.
Tada T, Byrne RA, Simunovic I, et al. Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. JACC Cardiovasc Interv. 2013 Dec;6(12):1267-74.
van Werkum JW, Heestermans AA, Zomer AC, et al. Predictors of coronary stent thrombosis: the Dutch Stent Thrombosis Registry. J Am Coll Cardiol. 2009 Apr 21;53(16):1399-409.

REVIEWS ON THE DURATION OF DAPT AFTER CORONARY STENTING

Binder R, Luscher T. Duration of DAPT after coronary artery stenting: where is the sweet spot between ischemia and bleeding? European Heart Jouranl. 2015; (36)1207-1211.
Mehran R, Giustino G, Baber U. DAPT duration after DES: what is the "mandatory" duration? J Am Coll Cardiol. 2015 Mar 24;65(11):1103-6.
Montalescot G, Brieger D, Dalby AJ, et al. Duration of Dual Antiplatelet Therapy After Coronary Stenting: A Review of the Evidence. J Am Coll Cardiol. 2015 Aug 18;66(7):832-47.
Park SJ, Kang SM, Park DW. Dual antiplatelet therapy after drug-eluting stents: defining the proper duration. Coron Artery Dis. 2014 Jan;25(1):83-9.

ASA

Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12;324(7329):71-86.

Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009 May 30;373(9678):1849-60.

CLOPIDOGREL

Belch JJ, Dormandy J et al; CASPAR Writing Committee. Results of the randomized, placebo-controlled clopidogrel and acetylsalicylic acid in bypass surgery for peripheral arterial disease (**CASPAR**) trial. J Vasc Surg. 2010 Oct;52(4):825-33, 833.e1-2.

Bhatt DL, Fox KA, Hacke W, et al; **CHARISMA** Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006 Apr 20;354(16):1706-17.

Chen ZM, Jiang LX, Chen YP, et al; **COMMIT** (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet. 2005 Nov 5; 366(9497):1607-21.

CURE Study Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (**CURE**) trial programme. Eur Heart J 2000, 21:2033-2041.

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.

Kulik A, Le May MR, Voisine P, et al. Aspirin plus clopidogrel versus aspirin alone after coronary artery bypass grafting: the clopidogrel after surgery for coronary artery disease (**CASCADE**) Trial. Circulation. 2010 Dec 21; 122(25):2680-7.

Mehta SR, Tanguay JF, Eikelboom JW, et al; CURRENT-OASIS 7 trial investigators. Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (**CURRENT-OASIS 7**): a randomised factorial trial. Lancet. 2010 Oct 9; 376(9748):1233-43.

Mehta SR, Bassand JP, Chrolavicius S, et al. **CURRENT-OASIS 7** Investigators. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med. 2010 Sep 2;363(10):930-42.

Mehta SR, Yusuf S, Peter RJG, Bertrand ME, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the **PCI-CURE** study. Lancet 2001. 358:527-533.

Mehta SR, Yusuf S; Clopidogrel in Unstable angina to prevent Recurrent Events (**CURE**) Study Investigators. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial programme; rationale, design and baseline characteristics including a meta-analysis of the effects of thienopyridines in vascular disease. Eur Heart J. 2000 Dec; 21(24):2033-41.

Mega JL, Close SL, Wiviott SD, et al. Cytochrome p-450 polymorphisms and response to clopidogrel. N Engl J Med. 2009 Jan 22;360(4):354-62.

Sabatine MS, Cannon CP, Gibson CM, et al. Effect of Clopidogrel Pretreatment Before Percutaneous Coronary Intervention in Patients with ST-Elevation Myocardial Infarction Treated with Fibrinolytics: The **PCI-CLARITY** Study. JAMA. 2005 Sept 14; 29=4 (10): 1224-1232.

Sabatine MS, Cannon CP, Gibson CM, et al; **CLARITY-TIMI** 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005 Mar 24; 352(12):1179-89.

Sabatine MS, McCabe CH, Gibson CH & Cannon CP. Design and rationale of Clopidogrel as Adjunctive Reperfusion Therapy- Thrombolysis in Myocardial Infarction (CLARITY-TIMI) 28 trial. Am Heart J 2005 149: 227-233.

Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, Steg PG, Ferrières J, Danchin N, Becquemont L; French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators. Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med. 2009 Jan 22; 360(4):363-75.

Steinhubl SR, Berger PB, Mann JT et al; **CREDO** Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. JAMA. 2002 Nov 20; 288(19):2411-20.

CLOPIDOGREL: MORTALITY

Elmariah S, Mauri L, Doros G et al Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. Lancet. 2015 Feb 28;385(9970):792-8. FDA Drug Safety Communication: FDA review finds long-term treatment with blood-thinning medicine Plavix (clopidogrel) does not change risk of death. Available at: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM471586.pdf. Accessed February 2016.

Mauri L, Elmariah S, Yeh RW et al; DAPT Study Investigators. Causes of late mortality with dual antiplatelet therapy after coronary stents. Eur Heart J. 2016 Jan 21;37(4):378-85.

TICAGRELOR

Bonaca MP, Bhatt DL, Cohen M, et al; **PEGASUS-TIMI** 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med. 2015 May 7;372(19):1791-800.

Grima DT, Brown ST, Kamboj L, et al. Cost-effectiveness of ticagrelor versus clopidogrel in patients with acute coronary syndromes in Canada. Clinicoecon Outcomes Res. 2014 Jan 24;6:49-62.

Mahaffey KW, Wojdyla DM, Carroll K, et al; **PLATO** Investigators. Ticagrelor compared with clopidogrel by **geographic region** in the Platelet Inhibition and Patient Outcomes (PLATO) trial. Circulation. 2011 Aug 2;124(5):544-54.

Wallentin L, Becker RC, Budaj A, et al; **PLATO** Investigators, Freij A, Thorsén M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009 Sep10;361(11):1045-57.

PRASUGREL

Montalescot G, Wiviott SD, Braunwald E, et al; **TRITON-TIMI** 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for **ST-elevation myocardial infarction** (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet. 2009 Feb 28;373(9665):723-31.

Roe MT, Armstrong PW, Fox KA, et al; **TRILOGY** ACS Investigators. Prasugrel versus clopidogrel for acute coronary syndromes without revascularization. N Engl J Med. 2012 Oct 4;367(14):1297-309.

Wiviott SD, Braunwald E, McCabe CH, et al; **TRITON-TIMI** 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007 Nov 15; 357(20):2001-15.

SWITCHING P2Y12 INHIBITORS

Bagai A, Chua D, Cohen EA, et al. Pharmacodynamic and clinical implications of switching between P2Y12 receptor antagonists: considerations for practice. Crit Pathw Cardiol. 2014 Dec;13(4):156-8.

Rollini F, Franchi F, Angiolillo DJ. Switching P2Y12-receptor inhibitors in patients with coronary artery disease. Nat Rev Cardiol. 2016 Jan;13(1):11-27.

Wallentin L, Becker RC, Budaj A, et al; **PLATO** Investigators. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009 Sep10; 361(11):1045-57.

BLEEDING RISK

Ducrocq G, Wallace JS, Baron G, et al; **REACH Investigators**. Risk score to predict serious bleeding in stable outpatients with or at risk of atherothrombosis. Eur Heart J. 2010 May;31(10):1257-65.

Généreux P, Giustino G, Witzenbichler B, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. J Am Coll Cardiol. 2015 Sep 1;66(9):1036-45.

Ko DT, Yun L, Wijeysundera HC, et al. Incidence, predictors, and prognostic implications of hospitalization for late bleeding after percutaneous coronary intervention for patients older than 65 years. Circ Cardiovasc Interv. 2010 Apr;3(2):140-7.

Konishi H, Miyauchi K, Tsuboi S, et al. Impact of the **HAS-BLED Score** on Long-Term Outcomes **After Percutaneous Coronary Intervention**. Am J Cardiol. 2015 Aug 15;116(4):527-31.

Vries MJ, van der Meijden PE, Henskens YM, et al. Assessment of bleeding risk in patients with coronary artery disease on dual antiplatelet therapy. A systematic review. Thromb Haemost. 2015 Dec 22;115(1):7-24.

GASTROINTESTINAL BLEEDING & GASTROPROTECTION

Abraham NS, Hlatky MA, Antman EM, et al; ACCF/ACG/AHA. **ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines**: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. J Am Coll Cardiol. 2010 Dec 7;56(24):2051-66.

Bhatt DL, Cryer BL, Contant CF, et al; **COGENT** Investigators. Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med. 2010 Nov 11;363(20):1909-17.

Cardoso RN, Benjo AM, DiNicolantonio JJ, et al. Incidence of cardiovascular events and gastrointestinal bleeding in patients receiving clopidogrel with and without proton pump inhibitors: an updated meta-analysis. Open Heart. 2015 Jun 30;2(1):e000248.

Moukarbel GV, Signorovitch JE, Pfeffer MA, et al. Gastrointestinal bleeding in high risk survivors of myocardial infarction: the **VALIANT** Trial. Eur Heart J. 2009 Sep;30(18):2226-32.

Roffi M, Patrono C, Collet JP, et al. **2015 ESC Guidelines for the Management of Acute Coronary Syndromes in Patients Presenting Without Persistent ST-segment Elevation**. Rev Esp Cardiol (Engl Ed). 2015 Dec;68(12):1125.

Schjerning Olsen AM, Lindhardsen J, Gislason GH, et al. Impact of proton pump inhibitor treatment on gastrointestinal bleeding associated with non-steroidal anti-inflammatory drug use among post-myocardial infarction patients taking antithrombotics: nationwide study. BMJ. 2015 Oct 19;351:h5096.

Vardi M, Cryer BL, Cohen M, et al. The effects of proton pump inhibition on patient-reported severity of dyspepsia when receiving dual anti-platelet therapy with clopidogrel and low-dose aspirin: analysis from the **Clopidogrel and the Optimization of Gastrointestinal Events Trial**. Aliment Pharmacol Ther. 2015 Aug;42(3):365-74.

DAPT + CABG

Bomb R, Oliphant CS, Khouzam RN. Dual Antiplatelet Therapy After Coronary Artery Bypass Grafting in the Setting of Acute Coronary Syndrome. Am J Cardiol. 2015 Jul 1;116(1):148-54.

Gurbuz AT, Zia AA, Vuran AC, Cui H, Aytac A. Postoperative clopidogrel improves mid-term outcome after off-pump coronary artery bypass graft surgery: a prospective study. Eur J Cardiothorac Surg. 2006 Feb;29(2):190-5.

Patel JH, Stoner JA, Owora A, Mathew ST, Thadani U. Evidence for using clopidogrel alone or in addition to aspirin in post coronary artery bypass surgery patients. Am J Cardiol. 2009 Jun 15; 103(12):1687-93. doi: 10.1016/j.amjcard.2009.02.021. Epub 2009 May 4. Review.

TRIPLE THERAPY

Alexander JH, Lopes RD, James S, et al; **APPRAISE-2** Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011 Aug 25;365(8):699-708.

Andrade JG, Deyell MW, Khoo C, et al. Risk of bleeding on triple antithrombotic therapy after percutaneous coronary intervention/stenting: a systematic review and meta-analysis. Can J Cardiol. 2013 Feb;29(2):204-12.

Barry AR, Ackman ML. Triple antithrombotic therapy in patients with atrial fibrillation who have undergone percutaneous coronary intervention with stent implantation. Am J Health Syst Pharm. 2012 Sep 1;69(17):1485-93.

Bavishi C, Koulova A, Bangalore S, et al. Evaluation of the efficacy and safety of dual antiplatelet therapy with or without warfarin in patients with a clinical indication for DAPT and chronic anticoagulation: A meta-analysis of observational studies. Catheter Cardiovasc Interv. 2015 Sep 10.

Briasoulis A, Papageorgiou N, Zacharia E, et al. Meta-Analysis of Oral Anticoagulants with Dual versus Single Antiplatelet Therapy in Patients after Percutaneous Coronary Intervention. Am J Cardiovasc Drugs. 2015 Dec 9.

Braun OÖ, Bico B, Chaudhry U, et al. Concomitant use of warfarin and **ticagrelor** as an alternative to triple antithrombotic therapy after an acute coronary syndrome. Thromb Res. 2015 Jan;135(1):26-30.

Chamberlain AM, Gersh BJ, Mills RM, et al. Antithrombotic strategies and outcomes in acute coronary syndrome with atrial fibrillation. Am J Cardiol. 2015 Apr 15;115(8):1042-8.

Chen CF, Chen B, Zhu J, Xu YZ. Antithrombotic therapy after percutaneous coronary intervention in patients requiring oral anticoagulant treatment: A meta-analysis. Herz. 2015 Dec;40(8):1070-83.

Dans AL, Connolly SJ, Wallentin L, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (**RE-LY**) trial. Circulation. 2013 Feb 5;127(5):634-40.

D'Ascenzo F, Taha S, Moretti C, et al. Meta-analysis of randomized controlled trials and adjusted observational results of use of clopidogrel, aspirin, and oral anticoagulants in patients undergoing percutaneous coronary intervention. Am J Cardiol. 2015 May 1;115(9):1185-93.

Dewilde WJ, Oirbans T, Verheugt FW, et al; **WOEST** study investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013 Mar 30; 381(9872):1107-15.

Faxon DP, Eikelboom JW, Berger PB, et al. Antithrombotic therapy in patients with atrial fibrillation undergoing coronary stenting: a North American perspective: executive summary. Circ Cardiovasc Interv. 2011 Oct 1;4(5):522-34.

Fiedler KA, Maeng M, Mehilli J, et al. Duration of Triple Therapy inPatients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation:The **ISAR-TRIPLE** Trial. J Am Coll Cardiol. 2015 Apr 28; 65 (16):1619-29.

Fu A, Singh K, Abunassar J, et al; **CAPITAL** Investigators. **Ticagrelor** in Triple Antithrombotic Therapy: Predictors of Ischemic and Bleeding Complications. Clin Cardiol. 2016 Jan;39(1):19-23.

Hansen ML, Sørensen R, Clausen MT, Fog-Petersen ML, Raunsø J, Gadsbøll N, Gislason GH, Folke F, Andersen SS, Schramm TK, Abildstrøm SZ, Poulsen HE, Køber L, Torp-Pedersen C. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. Arch Intern Med. 2010 Sep 13;170(16):1433-41

Hess CN, Peterson ED, Peng SA, et al. Use and Outcomes of Triple Therapy Among Older Patients With Acute Myocardial Infarction and Atrial Fibrillation. J Am Coll Cardiol. 2015 Aug 11;66(6):616-27.

Jackson LR 2nd, Ju C, Zettler M, et al. Outcomes of Patients With Acute Myocardial Infarction Undergoing Percutaneous Coronary Intervention Receiving an Oral Anticoagulant and Dual Antiplatelet Therapy: A Comparison of Clopidogrel Versus **Prasugrel** From the **TRANSLATE-ACS** Study. JACC Cardiovasc Interv. 2015 Dec 21;8(14):1880-9.

Lamberts M, Olesen JB, Ruwald MH, Hansen CM, Karasoy D, Kristensen SL, KøberL, Torp-Pedersen C, Gislason GH, Hansen ML. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction & coronary intervention: a nationwide cohort study. Circulation. 2012 Sep 4;126(10):1185-93.

Mega JL, Braunwald E, Wiviott SD, et al; **ATLAS ACS 2**–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012 Jan 5;366(1):9-19.

Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Schjerning Olsen AM, Mikkelsen A, Christensen CB, Lip GY, Køber L, Torp-Pedersen C, Hansen ML. Oral anticoagulation & antiplatelets in atrial fibrillation patients after myocardial infarction & coronary intervention. J Am Coll Cardiol. 2013 Sep 10;62(11):981-9.

Mennuni MG, Halperin JL, Bansilal S, et al. Balancing the Risk of Bleeding and Stroke in Patients With Atrial Fibrillation After Percutaneous Coronary Intervention (from the AVIATOR Registry). Am J Cardiol. 2015 Jul 1;116(1):37-42.

Oldgren J, Budaj A, Granger CB, et al; **RE-DEEM** Investigators. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J. 2011 Nov;32(22):2781-9.

Sambola A, Mutuberría M, García Del Blanco B, et al. Impact of Triple Therapy in Elderly Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention. PLoS One. 2016 Jan 25;11(1):e0147245.

Sambola A, Mutuberría M, García Del Blanco B, et al. Effects of Triple Therapy in Patients With Non-Valvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention Regarding Thromboembolic Risk Stratification. Circ J. 2016 Jan 25;80(2):354-62.

Sarafoff N, Martischnig A, Wealer J, et al. Triple therapy with aspirin, **prasugrel**, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. J Am Coll Cardiol. 2013 May 21;61(20):2060-6.

Valgimigli M, Patialiakas A, Thury A, et; **ZEUS** Investigators. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. J Am Coll Cardiol. 2015 Mar 3;65(8):805-15.

Zhao HJ, Zheng ZT, Wang ZH, et al. "Triple therapy" rather than "triple threat": a meta-analysis of the two antithrombotic regimens after stent implantation in patients receiving long-term oral anticoagulant treatment. Chest. 2011 Feb;139(2):260-70.

OTHERS

Udell JA, Bonaca MP, Collet JP, et al. Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with **previous myocardial infarction**: a collaborative meta-analysis of randomized trials. Eur Heart J. 2016 Jan 21;37(4):390-9.

Cutlip DE, Windecker S, Mehran R, et al; **Academic Research Consortium**. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation. 2007 May 1;115(17):2344-51.

CEREBROVASCULAR INDICATIONS

GUIDELINES

Bell AD, Roussin A, Cartier R, Chan WS, Douketis JD, Gupta A, Kraw ME, Lindsay TF, Love MP, Pannu N, Rabasa-Lhoret R, Shuaib A, Teal P, Théroux P, Turpie AG,Welsh RC, Tanguay JF; **Canadian Cardiovascular Society**. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society Guidelines. Can J Cardiol. 2011 May-Jun;27 Suppl A:S1-59

Coutts SB, Wein TH, Lindsay MP, et al; Heart, and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee. **Canadian Stroke Best Practice Recommendations**: secondary prevention of stroke guidelines, update 2014. Int J Stroke. 2015 Apr;10(3):282-91.

Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: **American College of Chest Physicians Evidence-Based Clinical Practice Guidelines**. Chest. 2012 Feb;141(2 Suppl):7S-47S.

Kernan WN, Ovbiagele B, Black HR, et al; American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the **American Heart Association/American Stroke Association**. Stroke. 2014 Jul;45(7):2160-236.

Skanes AC, Healey JS, Cairns JA, Dorian P, Gillis AM, McMurtry MS, Mitchell, LB, Verma A, Nattel S; Canadian Cardiovascular Society Atrial FibrillationGuidelines Committee. Focused 2012 update of the **Canadian Cardiovascular Society Atrial fibrillation** guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol. 2012 Mar-Apr;28(2):125-36.

TRIALS

ACTIVE Investigators, Connolly SJ, Pogue J, Hart RG, Hohnloser SH, Pfeffer M, Chrolavicius S, Yusuf S. Effect of clopidogrel added to aspirin in patients with atrial fibrillation **(ACTIVE A)**. N Engl J Med. 2009 May 14;360(20):2066-78.

ACTIVE Writing Group of the ACTIVE Investigators, Connolly S, Pogue J, Hart R, Pfeffer M, Hohnloser S, Chrolavicius S, Pfeffer M, Hohnloser S, Yusuf S. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events **(ACTIVE W)**: a randomised controlled trial. Lancet. 2006 Jun 10;367(9526):1903-12.

Bhatt DL, Fox KA, Hacke W, et al; **CHARISMA** Investigators. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. N Engl J Med. 2006 Apr 20;354(16):1706-17.

Chimowitz MI, Lynn MJ, Derdeyn CP, et al; **SAMMPRIS** Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. NEngl J Med. 2011 Sep 15;365(11):993-1003.

Chiu D, Klucznik RP, Turan TN, et al. Enrollment volume effect on risk factor control and outcomes in the **SAMMPRIS** trial. Neurology. 2015 Dec 15;85(24):2090-7.

Derdeyn CP, Chimowitz MI, Lynn MJ, et al; Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial Investigators. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis **(SAMMPRIS): the final results of a randomised trial**. Lancet. 2014 Jan 25;383(9914):333-41.

Diener HC, Bogousslavsky J, Brass LM, et al; **MATCH** investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet. 2004 Jul 24-30;364(9431):331-7.

Kennedy J, Hill MD, Ryckborst KJ, et al; **FASTER** Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. Lancet Neurol. 2007 Nov;6(11):961-9.

Kim JT, Park MS, Choi KH, et al. Different Antiplatelet Strategies in Patients With New Ischemic Stroke While Taking Aspirin. Stroke. 2016 Jan;47(1):128-34.

SPS3 Investigators, Benavente OR, Hart RG, McClure LA, et al. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. N Engl J Med. 2012 Aug 30;367(9):817-25.

Wang Y, Wang Y, Zhao X, et al; **CHANCE** Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013 Jul 4;369(1):11-9.

Wang Y, Pan Y, Zhao X, et al; CHANCE Investigators. Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack **(CHANCE) Trial: One-Year Outcomes**. Circulation. 2015 Jul 7;132(1):40-6.

Wiviott SD, Braunwald E, McCabe CH, et al; **TRITON-TIMI** 38 Investigators. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007 Nov 15; 357(20):2001-15.

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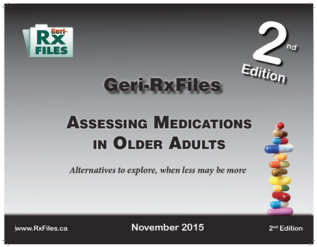

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