Coagulation Conundrums:
The Challenge of Managing Multiple Antithrombotics

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ND Family Medicine Conference, Big Sky MT
January, 2019

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Disclosures

- Speaker's Bureau: Bristol Myers Squib and Pfizer
- Direct Oral Anticoagulant (DOAC)→ Apixaban
  - Only as its use pertains to VTE and NOT Atrial Fibrillation
  - Should not effect the content of today's talk
    - You will be the judge!
- PI: Apixaban in Malignancy

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Talk Objectives

- Recognize the frequency with which patients have strong indications for both antithrombotic and antiplatelet agents
- Appreciate the changing anticoagulation landscape with the advent of new(er) antithrombotic and antiplatelet agents
- Appreciate the inherent bleeding risk with combination therapy (and why we should care)
- Gain knowledge on how to maximize benefit and minimize risk in these situations
- Become familiar with novel approaches for those requiring combination antithrombotic therapy

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Epidemiologic Perspectives

- Both Afib and CAD are exceedingly common!
  - Afib: Most common cardiac arrythmia
    - 1-2% general population with significant increase with age
      - ~6% over age 65
  - Concomitant afib = most common indication for AC in those undergoing PCI
    - ~ 7% of pt. with ACS will have concomitant Afib!
- Other indications for AC therapy→ mechanical heart valves, "strong" thrombophilias, LV thrombus, LVAD, etc.
  - Scant data on how to appropriately manage these patients….
- Thus, 20-30% of those requiring AC, ALSO have concomitant ischemic heart disease

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- **Afib = AntiCoagulation (AC)**
  - Several studies definitively showing marked decrease in stroke risk when most treated with AC
    - Net benefit increases with higher CHA_2DS_2 VASc Score
      - All with PCI *already* have a score of 1…
    - Benefit persists even in the elderly.
  - Antiplatelet agents clearly inferior for stroke prevention in Afib
    - Only marginal benefit over placebo
- **Arterial Stents = Dual AntiPlatelet Therapy (DAPT)**
  - Several RCTs showing significantly decreased MACE (Major Adverse Cardiac Events) and stent thrombosis
  - Superior to ASA alone OR VKA + ASA*
  - Class I recommendation in American/European guidelines to prevent stent thrombosis

*Leon et al. NEJM 1998

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Differing Patho-mechanisms of clot generation

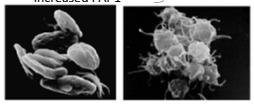
Atrial Fibrillation

- "Fibrin rich" clots
  - Platelets: smaller role
- Loss Atrial contraction
  - Stasis (particularly the LAA)
- Unhealthy atrial endothelium
  - Increased prothrombotic molecules
    - TF, VWF

Coronary art/arterial stent occlusion

- Milieu of platelet activation
  - Endothelial superficial erosions-->
    - Reduced NO
    - Reduced Prostacyclin
    - Increased VWR
    - Increased PAI-1

Platelet activation



Resting platelets | Activated platelets

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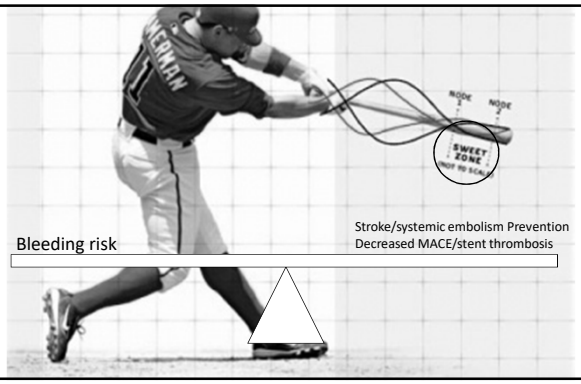

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Why is getting this right so important?

- Although CHD prevalence is stable with declining mortality, *the opposite* is true of afib
  - Likely reflective of an aging population, OSA, Obesity, hypertension
- Afib ="Marker" of adverse outcome
  - Framingham study: afib doubled CAD mortality rate*
  - Large South Korean registry: concomitant Afib = higher risk of BOTH ischemic events AND bleeding events regardless of the Rx.
- In post coronary stent pts, even "Nuisance" bleeding is BAD.
  - Older, more comorbidities….Thus
  - Higher likelihood to stop antiplatelet Rx--> Higher potential for stent thrombosis/MACE

*Kannel WB et al. NEJM 1982;306(17):1018-22.

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Don't fret…You only have 3 possible choices!!

- Gone are the days of Warfarin, ASA and Clopidogrel…
- If your afib pt. undergoes a coronary "stent" in 2018, there are:
- 3 choices to ASA Rx
  - None
  - Low dose
  - Higher dose

  } Varying durations…
- 3 choices for P2Y12 receptor antagonist
  - Clopidogrel
  - Ticagrelor
  - Prasugrel

  } Varying durations…
- 5 AC choices for afib at different doses
- Hopefully, we can wash "away the mud"

Endless combination!!

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The "rub" with Triple Therapy

- Warfarin based "triple" therapy:
  - 3-4 fold increased risk of bleeding complications
  - 2.2% major bleed rate 1st 30 d
  - 4-12% major bleed rate 1st yr
  - Recent studies ~ 25% all bleeding
- Full-dose DOACs + DAPT:
  - Higher DOAC dose, higher bleed risk AND no difference in efficacy
    - APPRAISE-2: Apixaban
    - ATLAS ACS TIMI 46: Rivaroxaban
    - Dabigatran also with increased bleeding and no sig efficacy

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DAPT alone (No Anticoagulant)

- Is this "enough" to prevent systemic thromboembolism in AFIB?
- ACTIVE-W study*→DAPT vs. Warfarin monotherapy…
  - Significantly increased RR stroke, sys. embolus, MI, or vascular death in those with afib.
- Bottomline:
  - Proven less effective for thromboembolic prophylaxis in AFib
  - Think of Afib as a "Hypercoagulable" state

*Connolly S et al. *Lancet* 2006;367(9526):1903-1912

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- Among AF pts requiring a "stent", are there options resulting in less bleeding risk without sacrificing efficacy?

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Dual (AC) vs triple Rx

- Many studies→ RCT, observational, retrospective, registries
  - At least 16 studies b/t 2009 and 2017 (most in past 5 years)
- Most studies AFIB exclusive; few with other indications for long term AC
  - Heart valves, cardiac thrombus most common
- Most "Triple" Rx regimens Warfarin-based
- Clopidogrel most common P2Y12 inhibitor
- Most with year f/u.
- Key trends:
  - Bleeding clearly less with DT over triple Rx
  - Efficacy best with either DT including clopidogrel (over ASA) or with triple Rx
  - The losers: DAPT and OAC + ASA
    - Higher incidence of stroke, MI, stent thrombosis

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TABLE 2: Outcomes with dual therapy compared with triple therapy after PCI.

Study/author	MACE (%) [p value]	Mortality (%) [p value]	Stent thrombosis (%) [p value]	Total bleeding (%) [p value]	Major bleeding (%) [p value]
RE-DUAL PCI [31]	NR	4.9/5.6 [0.56]* 4.6/3.9 [0.44]**	0.8/1.5 [0.15] 0.9/0.9 [0.98]	42.9/27.1 [<0.001] 41.4/33.3 [<0.001]	9.2/5.0 [<0.001] 8.4/5.6 [0.02]
De Vecchis et al. [33]	27.1/12.9 [0.32]	8.3/0 [0.26]	2/0 [0.59]	16.7/19.4 [0.90]	8.3/6.5 [0.89]
PIONEER [12]	6.0/6.5 [0.75]	1.9/2.4 [0.52]	0.7/0.8 [0.79]	26.7/16.8 [<0.01]	3.3/2.1 [0.23]
ORBIT-AF [34]	NR	4.1/5.4 [0.57]	NR	NR	5.68/5.85 [0.66]
AFCAS [24]	22/18 [0.72]	11/7 [0.54]	1/3 [0.60]	18/16 [0.66]	10/7 [0.43]
WARSTENT [25]	16/15 [0.98]	5/0 [0.45]	1/0 [0.76]	11/5 [0.34]	4/5 [0.84]
Braun et al. [35]	NR	3.2/3.8 [NS]	0/0 [NS]	NR	7/7.5 [NS]
Lamberts et al. [36]	NR	8.9/7.1 [NS]	NR	14.3/10.9 [NS]	0.9/0.5 [NS]
WOEST [9]	NR	6.3/3.5 [0.03]	3.2/1.4 [0.17]	44.4/19.4 [<0.01]	5.6/3.2 [0.16]
Rubboli et al. [37]	32/24.6 [0.19]	9.9/10.2 [0.78]	2.7/2.0 [0.77]	NR	5.0/2.6 [0.32]
Persson et al. [38]	NR	3.0/4.2 [0.43]	NR	4.7/1.3 [0.02]	2.7/0.3 [0.03]
Gao et al. [39]	8.8/14.9 [0.01]	4.4/5.8 [0.17]	0.7/1.7 [0.73]	11.8/7.4 [0.038]	2.9/2.5 [0.73]
MUSICA [40]	23.7/26.1 [0.001]	6.8/10.9 [0.06]	4.0/8.7 [0.04]	15.5/13 [0.02]	4.3/6.5 [0.29]
Sørensen et al. [41]	NR	[NS]	NR	3.2/1.6 [NS]	NR
GRACE [26]	NR	5.1/6.5 [0.47]	NR	NR	5.9/4.6 [0.46]
Karjalainen et al. [42]	21.9/11 [0.003]	8.7/1.8 [0.003]	4.1/1.3 [0.09]	NR	8.2/2.6 [0.01]

NR = not reported; NS = statistically nonsignificant; number preceding "/" denotes TT (triple therapy) and number proceeding "/" denotes DT (dual therapy), TT/DT; for RE-DUAL PCI: TT/DT* = Therapy with Dabigatran 110 mg BID; TT/DT** = Therapy with Dabigatran 150 mg BID

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WOEST trial

- Landmark RCT, first to examine an alternative to triple therapy (Circa 2013)
- 573 patients randomized to:
  - 1. Warfarin + clopidogrel vs. 2. Warfarin + clopidogrel + low dose ASA
- Followed for one year
- *Much less* total bleeding in Warfarin + Clopidogrel group→ 44% vs. 19%
  - No difference in major bleeding
- *No difference* in ischemic event rate
  - MI, stent thrombosis, stroke, target vessel revascularization
- Mortality reduction (though underpowered) in Warfarin/Clopidogrel group
- Many, many caveats:
  - Small number events, open label design, low PPI use, femoral access, 70% stable (non ACS) CAD, simple lesions, full year of triple therapy with DES
- Bottomline:
  - Warfarin + clopidogrel likely viable in patients at low risk for ischemic events…
  - Caution in applying to those with high thrombotic/ischemic risk→ ACS pts, complex coronary anatomy

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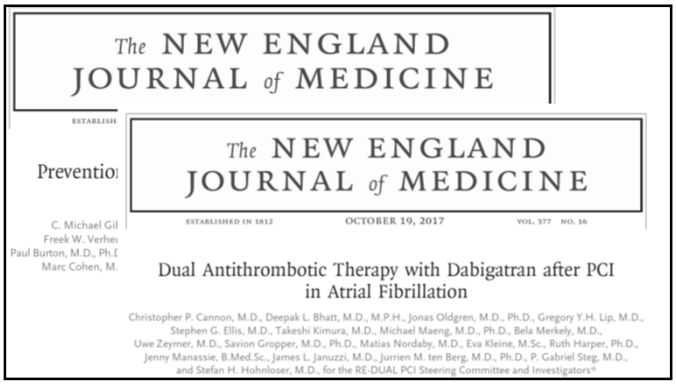
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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 19, 2017 VOL. 377 NO. 16

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Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation

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PIONEER AF-PCI

- Open-Label, Randomized, Controlled, Multicenter
- 2124 AF pts s/p stent placement randomized to 3 groups:
  - 1. Low dose rivaroxaban (15 mg po daily) + P2Y12 inhibitor
  - 2. very low dose rivaroxaban (2.5 mg PO BID) + P2Y12 inhibitor + low dose ASA
  - 3. Traditional "triple" Rx: Dose-adjusted VKA + P2Y12 inhibitor + low dose ASA
- Pts in group 2 and 3 further stratified according to the duration of DAPT
  - 1, 6, 12 months

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PIONEER Results…

- Compared to VKA-based triple Rx, Rivaroxaban-based Rx a/w reduced rates of clinically significant bleeding
  - 16-18% vs 27%
- In all 3 groups, the rates of CV death, MI, and Stroke were comparable
  - 5.6-6.5%
  - Study underpowered for efficacy..
    - Would have taken 13.5K in each group (> 40K pts total)
      - Study with ~ 700 in each group
    - As recruitment > 3 ys in 431 sites across the globe, simply unfeasible
      - 60 years to recruit!!

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PIONEER Take-aways…

- In afib pts who undergo stenting, they bleed much less on modified dose Rivaroxaban when compared to VKA-based "Triple" Rx"
- Though underpowered, rates of bad outcomes (MACE) hovered around 5-6% in all 3 groups.
- Practical Caveats:
  - 1. Rivaroxaban doses studied NOT substantiated in AFIB.
    - Typical dose is 20 mg po daily
  - 2. No reversal agent practically available at this time

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Re-Dual

- Comparison of DTI + P2y12 inhibitor vs. VKA + P2y12 inhibitor + ASA
  - 2725 Afib pts all undergoing PCI
    - Exclusions: mechanical heart valves, severe renal impairment (GFR< 30)
- All pts randomly assigned to 1 of 3 groups:
  - Dabigatran 110 BID + clopidogrel (or ticagrelor)
    - Choice of P2y12 up to investigator
  - Dabigatran 150 BID + clopidogrel (or ticagrelor)
    - Outside US, all pts > 80→ only 110 mg option…
  - Warfarin, low dose ASA, and clopidogrel (or ticagrelor)
    - BMS → ASA stopped after 1 month
    - DES → ASA stopped after 3 months

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Re-dual
End points

- Primary end point:
  - major or CRNM bleeding
- Efficacy end point:
  - thromboembolic events, death, unplanned revascularization*

*Underpowered

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Re-dual
Results…

- Bleeding:
  - Dual (110 mg) vs triple Rx: 15.4% vs 26.9% (HR 0.52; 95% CI 0.42-0.63) P<0.001 for noninferiority and also for superiority.
  - Dual (150 mg) vs triple Rx: 20.2% vs 25.7% (HR 0.72; 95% CI 0.58-0.88) P< 0.001 for noninferiority
- Efficacy:
  - Dual Rx (both groups) vs triple Rx: 13.7% vs 13.4% (HR 1.04; 95% CI 0.84-1.29) p = 0.005 for noninferiority
    - 15.2% in 110 mg group
  - Results "held true" for various subgroups such as ACS and DES pts…
  - Absolute rates of definite stent thrombosis low in all 3 groups:
    - 1.5% in 110 mg dual Rx group vs. 0.8% in corresponding triple Rx group
    - 0.9% in 150 mg dual Rx group vs. 0.9% in corresponding triple Rx group

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Re-Dual Take-aways

- Bleeding risk is essentially ½ (110 mg) to 3/4 (150 mg) when compared head to head with traditional triple Rx.
  - This interval level of risk gives clinicians more choices in choosing an antithrombotic regimen that strikes the right balance b/t bleeding risk and thromboembolic risk.
- Efficacy similar to traditional triple therapy
  - Underpowered
- Both DTI doses *have been* previously proven to prevent thromboembolic events in nonvalvular afib
  - Vs. Rivaroxaban dose in PIONEER
- There *is* readily available reversal agent for Dabigatran
  - Unlike Rivaroxaban…

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Down the Pipe…

- AUGUSTUS (Apixaban) and ENTRUST (edoxaban)
  - Two other Xa inhibitors going head to head against Warfarin based dual or triple Rx.
  - Both studies will focus on primary safety outcomes and again, underpowered to evaluate efficacy outcomes.
  - Estimated completion date Jan 1, 2019 for AUGUSTUS and no estimation yet for ENTRUST

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What about "Potent" P2Y12 inhibitors?

- Not recommended in standard full dose warfarin based "triple" Rx
  - Observational studies: 3x higher bleed risk vs. clopidogrel*
  - Most Guidelines: "Class III" recommendation (causes harm)
    - Suggest clopidogrel *over* Ticagrelor and Prasugrel
- However in PIONEER (6%) and RE-DUAL (12%); no increase bleeding/MACE
- Essentially half in GEMINI ACS trial received ticagrelor
  - Post ACS trial: P2Y12 inhibitor + ASA OR P2Y12 + very low dose rivaroxaban BID
    - Both groups with similar efficacy and bleeding
- Thus, small body of evidence suggesting can be safely implemented in a multidrug antithrombotic regimen…especially in those with previous stent thrombosis while on Clopidogrel

- Sarafoff N et al. *J Am Coll Cardiol* 2013;61(20):2060-2066
- Jackson LR et al. *JACC Cardiovasc Interv* 2015;8(14):1880-89

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Strategies to minimize bleeding risk…

- Radial over femoral access
  - Guideline recommended over femoral particularly in high bleed risk patients
  - Lower rates of access site complications→ hematoma, pseudo-aneurysm, bleeding
    - Caveat: possibly longer door to balloon time
  - Several large meta analysis* 12 randomized trails, 5000+ pt. with MI→ lower mortality, MACE and major bleeding
- Use lowest proven dose of ASA (typically 81 mg)
  - Especially lessens GIB risk
  - ATC trial***→ low dose no less effective than higher dose in secondary prevention of MACE

***Baigent C at al. Lancet. 2009;373(9678):1849-60.

* Karrowni W et al. JACC Cardiovasc Interv. 2013;6(8):814-23.

**Ando G. et al. JACC Cardiovasc Interv. 2016;9:660-670

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Strategies (continued…)

- Add PPI with > 1 antithrombotic…
  - Non Cyt P450 2C19-interfering PPI preferred→ pantoprazole/dexlansoprazole
    - Avoid omeprazole and esomeprazole
- Avoid NSAIDs→ GIB risk; possible interference with ASA efficacy.
  - Alarming common in my experience
- Ensuring optimal AC targeting (VKA)
  - Targeting INR 2-2.5→ supported by registry data only
  - Consider dedicated anticoagulation clinic→ supported by evidence; more TTR and less adverse events
  - Self monitoring, "point of care" device
  - Computer-assisted dosing algorithms

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What about VTE?

- "Small Potatoes" when compared to AFIB
  - For every one newly diagnosed case of VTE there are 4 newly diagnosed cases of afib in USA (all commers)
  - Afib ~ 3 million vs DVT ~ 900K
- VTE more transient (at least provoked)
  - Afib mainly a chronic, persistent disease
- Recurrent VTE rarely deadly vs. Afib where event likely to cause significant morbidity at very least.

*Lam D et al. *Current atherosclerosis reports* 2018; 20(4):1-10

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VTE + CHD/Stenting/DAPT

- Generally, more willing to decrease/stop AC
- Consider "modified" dose DOAC
  - Apixaban 2.5 BID
  - Rivaroxaban 10 QD
- Unprovoked DVT, more apt to stop AC
- Unprovoked PE, more apt to continue AC
- Remember, guidelines suggest long term AC *NOT* needed much of the time….
  - Provoked DVT(proximal or distal) or PE
  - Unprovoked 1st distal DVT

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Practical Management Strategies

- **OAC**
  - First, don't skip it!
  - if it ain't broke, don't fix it!
    - Working well, no bleeding, good compliance.
    - Consider lower target INR 2-2.5
  - DOACs preferred if…
    - labile INR
    - Close INR checks not feasible…
- **Antiplatelet Rx**
  - More complex
  - Triple Rx for first month
  - Dropping ASA favored
  - Consider removing ASA at 1-3 m depending on risk/benefit ratio
  - Triple Rx discouraged after 6 m
  - No Society recommending *ANY* antiplatelet agent after 12 months

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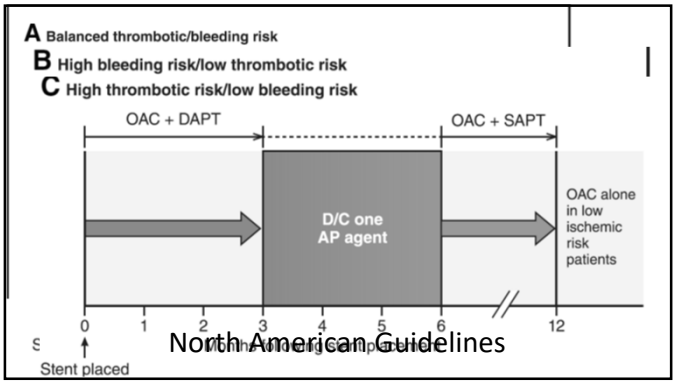

North American Guidelines

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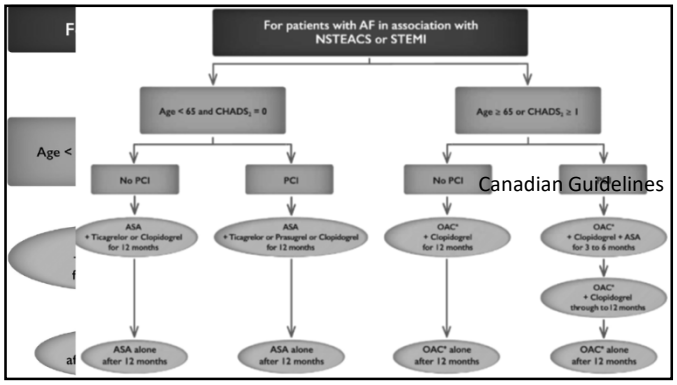

Canadian Guidelines

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Summary

- Those with an indication for both AC and Antiplatelet therapy *will arise* in your practice!
  - Most commonly afib + CAD (stent)
- *Any* bleeding in this population is potentially harmful
  - Especially post ACS
- Prolonged Triple Rx (VKA or full dose DOAC) fallen out of favor
  - Certainly more bleeding with no proven efficacy
- DAPT alone *not* "enough" (to prevent sys embolism in afib)
- OAC + Clopidogrel or DOAC + clopidogrel seems to be favored
  - Unequivocally less bleeding yet similar MACE, stent thrombosis, and mortality
  - ASA seem to have fallen out of favor

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Summary

- Communication with cardiology is key
  - Get a sense of ischemic risk based on complexity of PCI, type of stents, etc..
  - Radial access?
- Remember the basics: no NSAIDs, PPIs, lower INR target, keep ASA dose low
- More studies on the horizon→ other DOACs
  - Could assist particularly in assessing efficacy as bleed risk seems to have been "put to bed"

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Bibliography

- Agarwal N, et al. Optimal antithrombotic therapy in patients requiring long-term anticoagulation and undergoing percutaneous coronary intervention. *Biomed Research International* 2017; 2018: 0-10.
- Cannon CP, et al. Dual antithrombotic therapy with Dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;377:1513-24.
- Effron MB, et al. Dual (anticoagulant plus single antiplatelet) vs triple (anticoagulant plus dual antiplatelet) antithrombotic therapy--"real world" experience. *Progress in Cardiovascular Diseases* 2018;60:531-36.
- Macle L, et al. 2016 focused update of the Canadian cardiovascular society guidelines for the management of atrial fibrillation. *Canadian Journal of Cardiology* 2016;32:1170-1185.
- Chang KW et al. Antithrombotic regimens in patients with atrial fibrillation and coronary artery disease after percutaneous coronary intervention: a focused review. *International Journal of Cardiology* 2017;243:263-269.
- Angiolillo DJ, et al. Antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention. A north American perspective—2016 update. Circ *Cardiovasc Interv* 2016;9:1-26.
- Choi HI et al. Prevalence, management, and long-term outcomes of atrial fibrillation among patients receiving drug eluting coronary stents. *JACC Cardiovasc Interv* 2017;10(11):1075-1085.
- Thompson PL. et al. Managing antithrombotic therapy in patients with both atrial fibrillation and coronary heart disease. *Clin Therapeutics* 2014;36(9):1176-1181.
- Kerneis M, et al. Triple antithrombotic therapy for patients with atrial fibrillation undergoing percutaneous coronary intervention. *Progress in Cardiovascular Diseases* 2018;60:524-530.
- Crowther M. et al. Dual and triple antithrombotic therapies: current patterns of practice and controversies. *Polish Heart Journal* 2018; online only publication. 1-17.
- Gaist D et al. Association of antithrombotic drug use with subdural hematoma risk. *JAMA* 2017;317(8):836-846.
- Watson T. et al. Mechanisms of thrombogenesis in atrial fibrillation: virchow's triad revisited. *Lancet* 2009;373:155-166.
- Gibson CM et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;375(25):2423-2434.

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Should we use a bleeding score?

- Seems like a good idea, right?....Maybe not
- The very same pts that are at high risk of bleeding ARE ALSO the same folks that are at high risk of thrombotic stroke!!
  - In other words the CHA_2DS_2 VASc Score is about as good and HAS-BLEED score in predicting who is going to bleed!!
- A paradox of sorts:
  - high HASBLEED score: OAC reduced risk of death at 12 months
  - Use of DES (and hence, DAPT): independently predicted higher risk of major bleeding.
  - Similar observations in octogenarians
- Bottom line: use of OAC on top of DAPT improves prognosis, despite the increased risk of bleeding, even in those with high "has bled" score!

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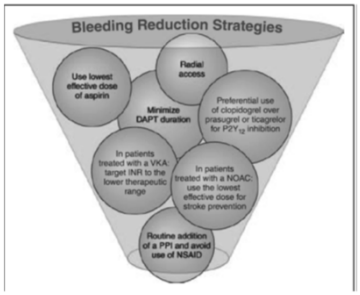
An Ounce of Prevention…



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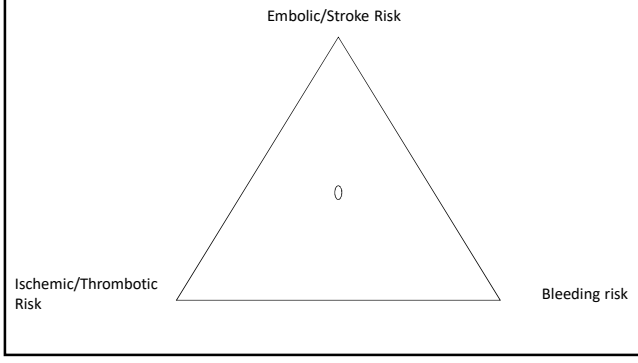

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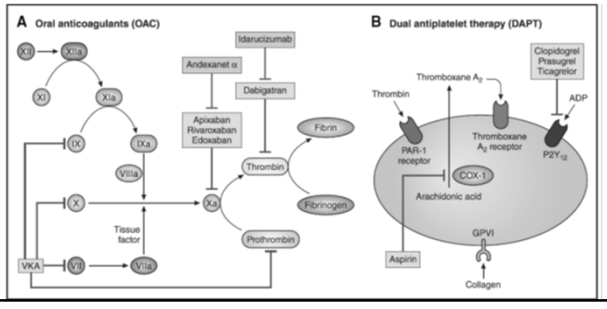
Sites of action: AC vs. Antiplatelet Rx



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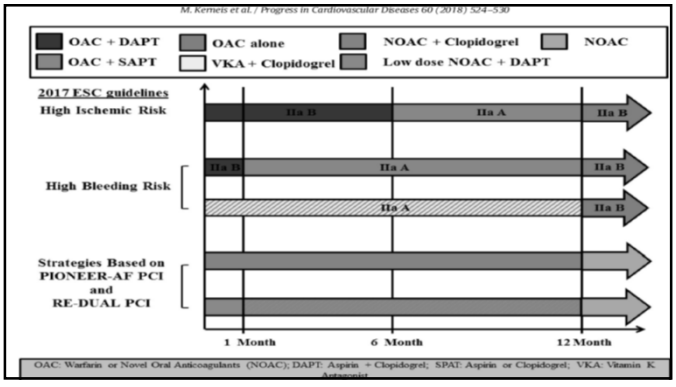

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DOACs and PCI

- In General, DAOCs display superior net clinical effect in Afib
  - Mostly d/t less ICH
  - Now the "Standard of care"
- Modified-dose DOACs have been studied in various (non-afib) cardiac populations:
  - Post ACS: GEMINI ACS-1
    - Standard DAPT vs. very low dose DOAC + baby ASA
      - No difference either from bleeding or efficacy
  - Stable CAD and PAD: COMPASS
    - Stopped early after 23 months d/t overwhelming efficacy in the very low dose DOAC + ASA
      - Composite of CV death, MI or stroke
      - An increase in major bleeding but not enough to offset the decrease in cardiac events.
- But what about DOACs in PCI + Afib?
- All Pivotal randomized clinical trials leading to approval for AFIB specifically *excluded* those on DAPT
  - Except RELY (dabigatran)→ no difference

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