Venous Thromboembolism Update: Select Cases

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Housekeeping….

- I am on the "speaker's bureau" for Bristol Myers Squib and Pfizer, the makers of the DOAC, Apixaban.
- I am involved in research with Apixaban.

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Objectives

- Focus on the latest recommendations from the most recent "CHEST" guidelines
- Update on post thrombotic prevention interventions
- Update on new "standard of care" for VTE Rx
- Identify specific thrombotic situations where antithrombotic treatment may NOT be required
- Appreciate new insights on the role of "bridging" therapy

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Magnitude of VTE

- VTE = DVT and PE
- Common and becoming more common
  - #3 behind CHD and Cerebrovascular disease
  - More common with age
    - Annual incidence: all commers 0.69-2.69/1000; Age >70: 2-7/1000
- Accounts for substantial chunk of health care expenditures
  - Rate of Hospitalization circa 2001: 581/100k subjects vs. 2011: 739/100k subjects
    - Despite strong trend toward more outpatient management of VTE!!
  - Average LOS: 4.7 days DVT and 5.1 days PE.
- Mortal
  - 30 d case fatality rate after VTE 10.6% (95% CI 10.4-10.8)
  - 1 year: 23% (95% CI 22.8-23.3)

Becattini C, Agnelli. JACC vol 67 No 16 2016

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Magnitude of VTE

- Think: "chronic" disease
  - All comers, expected 10 year rate of recurrence ~ 25%
  - Recurrence peaks at 6 m then decreases slowly to stabilize after 3 years, remaining at about 2% per pt /year
  - Risk of recurrence similar whether DVT or PE but "what you had is likely what you'll get"
- Long term Sequalae:
  - Chronic thrombo-embolic pulmonary hypertension
    - 0.1-0.8 % of pts after PE
  - Post Thrombotic Syndrome
    - 20-50% of pts after DVT

Becattini C, Agnelli. JACC vol 67 No 16 2016

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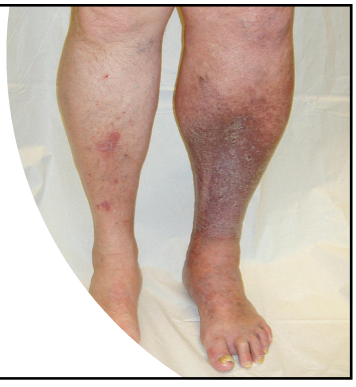
Post Thrombotic Syndrome

- Affects 25 to 50% of pts after deep vein thrombosis.
- Wide spectrum of clinical symptoms
- Reduces quality of life and imparts substantial economic burden on both patients and society.
- As treatment is limited, prevention is crucial!
- Ideally, *preventing* DVT outright is ultimate prevention
  - The rub: ~ 50% of DVTs-> unpredictable!



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Case 1

- 45-year-old m presenting with moderately swollen right lower limb, "ruddy" discoloration. No chest pain, shortness of breath, or pre-syncope.
- 6 wks prior, foot sx with cast immobilization.
  - Cast came off a week ago, thought just week but because of increasing pain and swelling sought medical attention.
- Ultrasound: thrombus in distal femoral and popliteal vein.
- Vitals WNL. Involved limb moderately swollen; somewhat discolored. Distal foot pulses easily palpated.
- Limited financial means; great difficulty with range of motion and strength in UE/hands due to severe rheumatoid arthritis.

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The following interventions are proven to *prevent* post-thrombotic syndrome…

- Lymphedema **wraps** until circumferential measurements plateau, then 30-40 mm Hg knee-high graduated compression garment x minimum of 2 years
- Skip the lymphedema wraps; simply supply 30-40 mm Hg **knee-high** graduate compression garment x minimum of 2 years
- Fit with 30-40 mm Hg **thigh-high** graduate compression garments x minimum of 2 years
- **None** of the above

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"Jumped the Gun"…

- Vascular specialists were crazy about stockings!
- Mantra: ECS halved risk of developing PTS after 2 yrs continuous use.
  - small single-center, non-placebo controlled trials
- The definitive trial→ SOX!!
  - Multicenter, randomized, placebo controlled trial to answer the question:
    - Do ECS prevent PTS after proximal DVT?
    - Also assessed effect of ECS on PTS severity, recurrent VTE, venous valvular reflux, and quality of life.
  - Eligibility:
    - First symptomatic proximal DVT (with or without concurrent distal DVT or PE)
  - 30 – 40 mm Hg ECS Vs. sham stockings with < 5 mm . N~ 400 in each group.
    - Applied within two weeks of DVT diagnosis, replaced every six months (earlier if required)
    - Patients asked to wear on affected leg from waking until retiring for two years. Encouraged to keep active
    - Follow-up visits at one, six, 12, 18, and 24 months.
      - Frequency of stocking use recorded.

Kahn SR, Shapiro S, et al. Lancet 2014, 383:880-88.

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Sox Results…

- Middle-aged white males, outpatients. Mean time after DVT dx ~ 5 d
- Most proximal extent of the DVT: typically CFV or FV.
- No serious adverse events attributable to stockings in either group.
  - Minor adverse events→ 8 pts active group vs. 7 placebo group.

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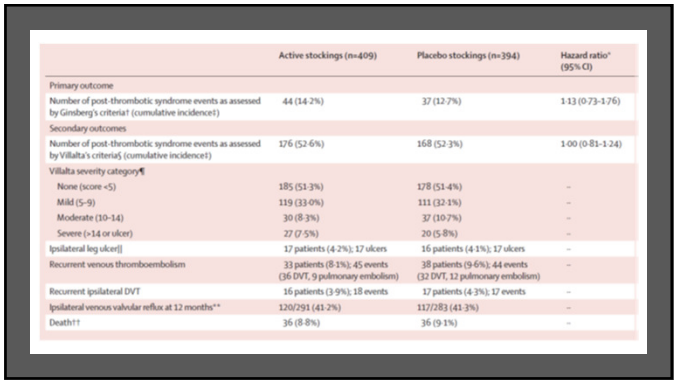

	Active stockings (n=409)	Placebo stockings (n=394)	Hazard ratio* (95% CI)
Primary outcome			
Number of post-thrombotic syndrome events as assessed by Ginsberg's criteria† (cumulative incidence‡)	44 (14·2%)	37 (12·7%)	1·13 (0·73–1·76)
Secondary outcomes			
Number of post-thrombotic syndrome events as assessed by Villalta's criteria§ (cumulative incidence‡)	176 (52·6%)	168 (52·3%)	1·00 (0·81–1·24)
Villalta severity category¶			
None (score <5)	185 (51·3%)	178 (51·4%)	–
Mild (5–9)	119 (33·0%)	111 (32·1%)	–
Moderate (10–14)	30 (8·3%)	37 (10·7%)	–
Severe (>14 or ulcer)	27 (7·5%)	20 (5·8%)	–
Ipsilateral leg ulcer‖	17 patients (4·2%); 17 ulcers	16 patients (4·1%); 17 ulcers	–
Recurrent venous thromboembolism	33 patients (8·1%); 45 events (36 DVT, 9 pulmonary embolism)	38 patients (9·6%); 44 events (32 DVT, 12 pulmonary embolism)	–
Recurrent ipsilateral DVT	16 patients (3·9%); 18 events	17 patients (4·3%); 17 events	–
Ipsilateral venous valvular reflux at 12 months**	120/291 (41·2%)	117/283 (41·3%)	–
Death††	36 (8·8%)	36 (9·1%)	–

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Bottom-line

- Graduated ECS ***did not*** reduce PTS incidence after 1st proximal DVT when compared to placebo stockings.
- Further, ***no difference*** in VLU, recurrent VTE, venous reflux, and QOL
  - Findings similar across subgroups→ age, BMI, and extent of deep vein thrombosis.
  - Even in those with frequent stocking use…→no difference with active ECS.
  - Frequency of use of study stockings very high initially, diminished over time, and similar between the two groups.
    - Similar to the "real world"
- What other experts are saying:
  - Stockings likely don't ***prevent*** post-thrombotic syndrome.
  - In certain pts, do seem to alleviate pain a/w swelling from established post-thrombotic syndrome or an acute deep vein thrombosis.

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CHEST Guidelines…

- An "about face"….

***18. In patients with acute DVT of the leg, we suggest not using compression stockings routinely to prevent PTS** (Grade 2B).

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Case 2

- 45-year-old otherwise healthy male presenting with a moderately swollen, purplish right lower limb. No chest pain, shortness of breath, or pre-syncope.
- Six weeks prior→ foot surgery requiring immobilization.
  - Immobilizer removal week ago, thought pain/swelling related to enhance activity but because of persistence, sought medical attention.
- Vitals WNL. Involved limb moderately swollen; somewhat discolored. Distal foot pulses easily palpated.
- Ultrasound: acute, occlusive thrombus distal femoral, popliteal vein.
- No prescription medications…

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Per 2016 CHEST guidelines, the most favored anticoagulant for this patient is:

- Heparin product → Vitamin K antagonist (Warfarin)
- Direct oral anticoagulant (Rivaroxaban, Apixaban, Dabigatran, Edoxaban)
- Heparin "monotherapy"

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It was a nice run…

- For 1st time Warfarin →"back seat" for VTE anticoagulation
- DOACs now ***preferred over*** VKA
  - Several head to head large, well designed trials demonstrating similar efficacy and safety to VKA
  - Less drug and food interactions
  - Some (but not all…) not requiring heparinization leading to simplified Rx
    - Avoidance of painful (physical and emotional) "shots"
  - Predictable pharmacodynamics and pharmacokinetics
    - Result: no need for blood monitoring, fixed doses, no dose adjustment
  - Acceptably safe generally with less major bleeds; particularly ICH
    - All now with effective antidotes

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TABLE 1 Efficacy and Safety of NOACs for the Treatment of VTE: Results From Clinical Trials

Trial Name (Ref. #)	Design	Treatments	Duration (months)	Patients	TTR (%)	Efficacy Outcome	Safety Outcome
RE-COVER, 2009 (37)	DB	Enoxa/dabigatran (150 mg bid) Enoxa/warfarin	6	2,539 acute VTE	60	Recurrent VTE or VTE-related death: 2.4% enoxa/dabigatran, 2.1% enoxa/warfarin	Major/clinically relevant nonmajor bleeding: 5.6% dabigatran, 8.8% warfarin
RE-COVER II, 2011 (38)	DB	Enoxa/dabigatran (150 mg bid) Enoxa/warfarin	6	2,539 acute VTE	57	Recurrent VTE or fatal PE: 2.3% dabigatran, 2.2% warfarin	Major/clinically relevant nonmajor bleeding: 5.0% dabigatran, 7.9% warfarin
EINSTEIN-DVT, 2010 (39)	Open-label	Rivaroxaban (15 mg bid for 3 weeks, then 20 mg od) Enoxaparin/VKA	3, 6, or 12	3,449 acute DVT	58	Recurrent VTE: 2.1% rivaroxaban, 3.0% enoxa/warfarin	Major/clinically relevant nonmajor bleeding: 8.1% rivaroxaban, 8.1% enoxa/warfarin
EINSTEIN-PE, 2012 (40)	Open-label	Rivaroxaban (15 mg bid for 3 weeks, then 20 mg od) Enoxa/VKA	3, 6, or 12	4832 acute PE	63	Recurrent VTE: 2.1% rivaroxaban, 1.8% enoxa/VKA	Major/clinically relevant nonmajor bleeding: 10.3% rivaroxaban, 11.4% enoxa/VKA
AMPLIFY, 2013 (41)	DB	Apixaban (10 mg bid for 7 days, then 5 mg bid) Enoxa/warfarin	6	5,395 acute VTE	61	Recurrent VTE or VTE-related death: 2.3% apixaban, 2.7% enoxa/VKA	Major bleeding: 0.6% apixaban, 1.8% enoxa/warfarin
Hokusai, 2013 (42)	DB	LMWH/edoxaban (60 mg od or 30 mg od) UFH or LMWH/warfarin	≤12	8,292 acute VTE	63	Recurrent VTE: 3.2% enoxa/edoxaban, 3.5% enoxa/warfarin	Major/clinically relevant nonmajor bleeding: 8.5% enoxa/edoxaban, 10.3% enoxa/warfarin

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Specific Populations

- Elderly: as effective as conventional Rx
  - Caveat: only ~ 5% were > 80 years old in phase III trials
- Renal insufficiency
  - Possibly less efficacy with Rivaroxaban
  - All others, no difference for either efficacy or safety
- Body wt extremes
  - Meta-analysis of phase III trials for acute symptomatic VTE and > 100 kg: no difference when compared to general population.
- Concomitant NSAIDs: no diff in efficacy, always a higher bleeding risk…
- Thrombophilia: All should be safe and equally effective.
  - Only looked at in Dabigatran→ no difference
  - Exception: APLAS particularly, "triple positive"

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DAOC limitations

- Cancer
  - Phase III trials: 2.5-9.4% vs. clinical practice→ 20% malig assoc. VTE
  - Those that were included not accurately reflective of the full spectrum of patient with cancer…
  - In these studies, the comparator was Warfarin and NOT LMWH (standard)
  - Bottomline: results of DOAC studies may NOT be applicable to pt with cancer associated VTE
  - Meta-analysis of DOACs in cancer:
    - Recurrent VTE 3.9% vs. 6% OR 0.63 (CI 0.37-1.10)
    - Major bleeding: 3.2% vs. 4.2% OR 0.77 (CI 0.41-1.44)
  - Recent RCTs: Hokusai VTE and SELECT-D: (open label)
    - Efficacy no worse; increased CRNMB, particularly GIB in GI malignancies
  - Ongoing: ADAM, CARAVAGGIO
    - ADAM→ December 2018

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DOACs and bleeding

- Lack of reversal agent: major issue initially
- Subsequently, multiple trials:
  - Less major bleeding vs Warfarin (particularly ICH)
  - "Real world" trials confirming less bleeding and bleeding assoc mortality with DAOCs
- Pharmacokinetics likely the reason for less bleeding
  - Very little AC left after 2 days off the drug
- Now have true antidotes (not reversal agents) for all DOACS!
  - Remove vs. counterbalance the AC
- Reversal important but not omnipotent!
  - "We don't make a lot of the products you buy. We make a lot of the products you buy better" –BASF
    - Blood thinners don't "make" you bleed. They just make you bleed better!!
  - Source control is still critical.

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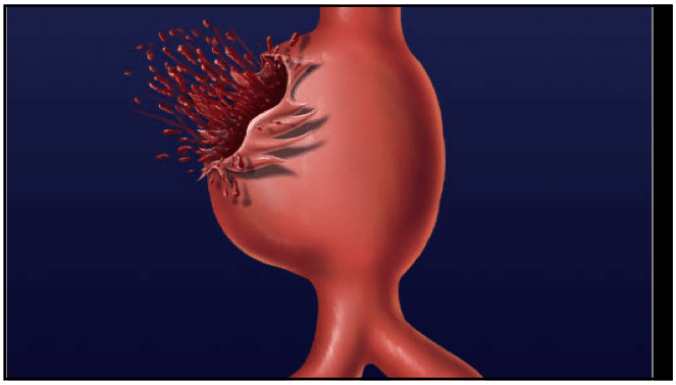

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Antidotes

- Idarucizumab (FDA approval 10/2015)
  - Humanized monoclonal antibody
  - Binds free and thrombin bound dabigatran with high affinity
  - Complete reversal within minutes in healthy volunteers
  - Time to bleeding cessation: 2.5 hr
  - Urgent surgery: 1.6 hours
    - Normal intraoperative hemostasis: 93.4%
  - Thromboembolic events
    - 6.3-7.4%
  - Mortality ~ 19% at 90 d

Related more to underlying thrombotic risk
Rather than an effect of the drug

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Xa inhibitors (Apixaban and Rivaroxaban)

- Andexanet alpha (FDA approval 5/3/2018):
  - genetically modified variant of Factor Xa
  - Acts as a "decoy" to bind factor Xa inhibitors→ neutralizing AC effect
- ANNEXA-A:
  - 66 healthy vlntrs; 5 BID Apix x 3.5 d, then randomized to Andex OR placebo
  - Xa activity decreased by 94% within 2-5 minutes vs 21% with placebo
  - Thrombin generation fully restored within 2-5 min in 100% Andex vs 11% placebo
- ANNEXA-R: similar results
- ANNEXA-4: N 238, acute major bleed (61% brain; 27% GI)
  - Anti-Xa activity reduced by 88-91%
  - 83% with effective hemostasis 12 hrs after administration.
  - 11%→ thrombotic event; 12% mortality at 30 days post administration

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DOAC synopsis

- Effective and safe for non cancer related VTE
  - Pretty much across all subgroups
- Don't mix well with NSAIDs
- "Extended" Treatment safety may be a game changer
  - Chronic recurrent nature of the disease
  - Much easier to take
  - Lower doses effective with same major bleed rate as baby ASA…
- Note the nuances…
  - Cancer; post massive PE; study pop vs real world; d-d interactions; APS
  - Price!!
    - The "Paulson Paradox"
      - Those at most need for financial assistance are the very ones the savings cards don't work for!!
        - No insurance; Medicare without supplemental

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2016 CHEST guidelines take….

***2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy** (all Grade 2B).

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Case 3

- 45-year-old healthy male presenting with….nothing!
- Yesterday, had 6 month recheck CT chest for f/u pulmonary nodule…
- Incidentally, new subsegmental pulmonary emboli right lower lobe.
  - Seen on 2 views with contrast completely surrounding the intraluminal defects
- B LE Ultrasound negative for lower extremity DVT
- D dimer 523 (200-500)
- Vitals WNL. Lungs CTA. Extremity and pulse exam unremarkable.
- Recent podiatric surgery with brace immobilization for 4 weeks; otherwise healthy.
- He is a Jehovah's witness and informs you that he really would prefer to avoid a blood thinner if possible.

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Per 2016 CHEST guidelines, the recommended management strategy in this case is:

- Full dose anticoagulant therapy…it is a PE for the love of god!
- Forego anticoagulant therapy but provide education on the s/s of VTE
- Obtain B LE US and if negative, forego anticoagulant Rx but provide education on the s/s of VTE

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"VOMT"

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Uncertainty on Whether to Rx

- Does subsegmental PE mandate Rx?
  - As the abnormalities are small, the diagnosis of PE more likely to be a false positive finding
  - As true subsegmental PE likely from small DVT→ risk of progressive/recurrent VTE anticipated to be lower than in pt with larger PE.
- No randomized trials in patients limited to only subsegmental PE.
- The retrospective data is inconclusive
  - Some identifying no recurrence with AC held; others showing risk similar to larger PE..
- Thus, uncertain whether risk of progressive/recurrent VTE high enough to justify AC.

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RF for recurrent/progressive PE if NOT AC…

- Hospitalization
- Reduced mobility for any reason
- Active cancer (particularly metastatic or active chemotherapy)
- No reversible RF for VTE (recent surgery, long haul travel etc)
- Low Cardio-pulmonary reserve
- Marked symptoms without a better explanation…

Push toward Rx

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Push Toward No Rx…

- High bleed risk
- Pt value system opposing Rx

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If Foregoing AC…

- Education, Education, Education…
  - Return of symptoms develop, or worsen!!
- Consider serial leg US and treat if proximal DVT develops…

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CHEST Guidelines take…

***19. In patients with subsegmental PE (no involvement of more proximal pulmonary arteries) and no proximal DVT in the legs who have a (i) low risk for recurrent VTE (see text), we suggest clinical surveillance over anticoagulation** (Grade 2C), **and (ii) high risk for recurrent VTE (see text), we suggest anticoagulation over clinical surveillance** (Grade 2C).

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Case 4

- 57 y/o male with a h/o CAF ($CHADS_2$=3) on warfarin.
  - Excellent TTR (>80%)
- Advanced OA R knee in need of TKA.
- On lisinopril, Carvedilol, and Metformin
- Vital WNL and exam unremarkable
- Normal kidney function

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Per CHEST guidelines, the recommended periprocedural management strategy is:

- Stop VKA 5 d PTP; restart VKA POD 0; ck INR 3 days, adjust accordingly.
- Stop VKA 5 d PTP, start therapeutic LMWH ~ 3 d PTP, administer last dose LMWH at least 24 hours PTP, restart VKA POD 0, restart intermediate dose LMWH 24 hours after procedure and increase to therapeutic at 72 hours after procedure, ck INR 3 days and adjust accordingly.
- Stop VKA 5 d PTP, admit to hospital ~ 3 d PTP to start wt. based UFH infusion, stop infusion 4 hr PTP, restart infusion 12 hours post op + VKA, cont. wt. based UFH infusion until INR > 2 for 2 consecutive days AND there has been a minimum 5 day overlap.
- Stop VKA 5 days PTP. No pre-procedure LMWH. Restart VKA POD 0, start therapeutic LMWH 12 hours post op. Stop LMWH once INR > 2 for 2 consecutive days AND minimum 5 days overlap.
- Place referral to Swanson, take a deep breath, and move on…

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In 2018, the recommended periprocedural management strategy is:

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Periprocedural AC

- Common!
  - Each year, ~ 250k pts on AC requiring an invasive procedure
  - Afib on Coumadin: ~ 1 in 6 needing AC interruption every year
- Goal: minimize thromboembolism risk; yet avoid periprocedural bleed.
- Past decade, realization that periprocedural bleeding NOT benign.
  - Occurrence of major bleed in periprocedural period: up to 9% case fatality rate
  - Delays resumption of AC, thus increasing the risk of VTE
- Data emerging showing no difference in thromboembolism incidence with "bridging".
- Optimal management often complex and varies depending on reason for AC and procedural bleed risk.
  - High $CHADS_2$, Afib having screening colonoscopy vs. "weak" thrombophilia having neurosurgery

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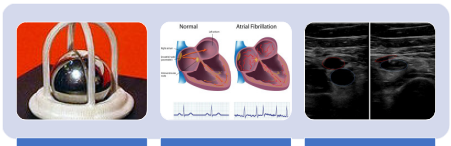
Most Common Indications for Anticoagulation



MHV | Afib | DVT

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1st Is Interruption Even Needed?

- Does AC even need to be stopped?
  - 20% procedures "low risk"
  - 2012 Chest Guideline: DO NOT STOP with dental, cataract extraction, or dermatologic procedure
    - Dental: 2 options→ 1. continue VKA but give pro-hemostatic (tranexamic acid) mouthwash OR 2. stop VKA 2-3 days PTP.
      - Option 1: similar rates of M or CRNMB (< 5%) + rare VTE events (<1%) vs. those who stopped AC
  - Although guidelines do not mention DOACs, same recommendations likely apply…
    - given short half life, with minor dental procedures, likely only need to hold one dose PTP

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Key Questions in Determining Optimal Management

- 1st question: Do we need to interrupt?
  - For 20% of procedures, likely not
    - Minor skin, eye, and dermatologic procedures
- 2nd question: If we interrupt, do we need to "bridge"? Often, not!!
- 3rd question: if we should bridge, how?
  - Again, depends on thromboembolic risk and procedure risk
  - Bridging is becoming less popular
    - Does not prevent arterial thromboembolism (at least with lower risk pts) and causes more bleeding
    - Periprocedural bleeding NOT benign

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CHEST Guidelines and Bridging (only those on VKA)

- 2016 update: did NOT address bridging at all
- 2012: dependent on procedural risk of thromboembolism…

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Table 1—*[Introduction] Suggested Risk Stratification for Perioperative Thromboembolism*

Risk Stratum	Indication for VKA Therapy: Mechanical Heart Valve	Atrial Fibrillation	VTE
High	• Any mitral valve prosthesis • Any caged-ball or tilting disc aortic valve prosthesis • Recent (within 6 mo) stroke or transient ischemic attack	• CHADS$_2$ score of 5 or 6 • Recent (within 3 mo) stroke or transient ischemic attack • Rheumatic valvular heart disease	• Recent (within 3 mo) VTE • Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate	• Bileaflet aortic valve prosthesis and one or more of the following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes mellitus, congestive heart failure, age > 75 y	• CHADS$_2$ score of 3 or 4	• VTE within the past 3-12 mo • Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) • Recurrent VTE • Active cancer (treated within 6 mo or palliative)
Low	• Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	• CHADS$_2$ score of 0 to 2 (assuming no prior stroke or transient ischemic attack)	• VTE > 12 mo previous and no other risk factors

CHADS$_2$ = congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, and stroke or transient ischemic attack; VKA = vitamin K antagonist.
*High-risk patients may also include those with a prior stroke or transient ischemic attack occurring > 3 mo before the planned surgery and a CHADS$_2$ score <5; those with prior thromboembolism during temporary interruption of VKAs; or those undergoing certain types of surgery associated with an increased risk for stroke or other thromboembolism (eg, cardiac valve replacement, carotid endarterectomy, major vascular surgery).

BRIDGE
Dealer's Choice
Don't Bridge

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Does Bridging have data to support its use?

- Several recent studies→ not effective and, in fact, may cause harm…
  - Retrospective VTE study[1]; mostly GI procedures at low risk of VTE recurrence;
    - 30 d "clinically relevant" bleeding *higher* in bridge group vs. no bridge
      - 2.7% vs 0.2% HR 17.2 (CI 3.9-75.1)
    - Recurrent VTE: no difference even when analyzing across individual risk categories
      - 21 high risk pts *not* bridged→ zero recurrent VTE
      - 215 mod risk pts not bridged→ 1 recurrent VTE
  - Afib registry[2] with 2803 interruptions → ¾ not bridged; ¼ bridged
    - No difference in risk of stroke or thrombotic events.
    - Higher Bleeding events with bridging:
      - 5% vs 1.3% aOR 3.8 (CI 2.1-7.1) NNTH 27
    - Trend toward *higher* CV event with bridging:
      - 4.6% vs 2.5% aOR 1.6 (CI 0.95-2.8)

1. Clark et al. *JAMA Intern Med* 2015
2. Steinberg et al. *Circulation* 2015

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

James D. Douketis, M.D., Alex C. Spyropoulos, M.D., Scott Kaatz, D.O., Richard C. Becker, M.D., Joseph A. Caprini, M.D., Andrew S. Dunn, M.D., David A. Garcia, M.D., Alan Jacobson, M.D., Amir K. Jaffer, M.D., M.B.A., David F. Kong, M.D., Sam Schulman, M.D., Ph.D., Alexander G.G. Turpie, M.B., Vic Hasselblad, Ph.D., and Thomas L. Ortel, M.D., Ph.D., for the BRIDGE Investigators*

ABSTRACT

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Bridge Trial

- Randomized, double blind, placebo-controlled trial
  - 8/2015 NEJM
  - Circa 2009-14; 108 sites→ US and Canada
- 1884 afib pts on VKA randomized to "bridging" AC with LMWH (dalteparin 100 IU/kg) or matching placebo given BID starting 3d PTP until 24 hours before; then 5-10 days after procedure.
  - Warfarin stopped 5 days PTP; resumed within 24 hrs after procedure
- f/u continued for 30 days after procedure
- Primary outcomes
  - Arterial thromboembolism→ stroke, system embolism, TIA
  - Major bleeding

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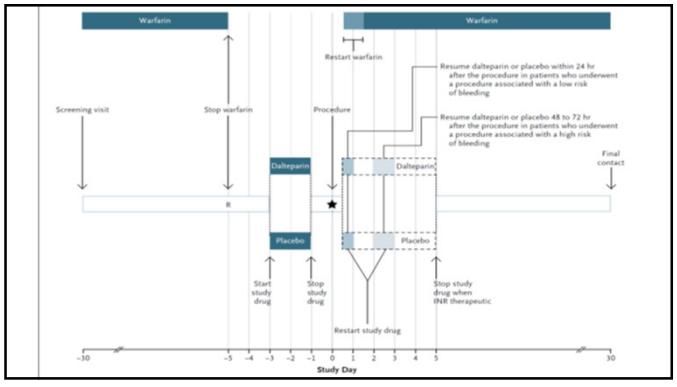

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Bridge Patients

- Eligible…
  - >18 with CAF
    - Confirmed on ECG/pacer
  - Had been on VKA > 3 months
    - Target INR 2-3
  - Having elective operation/procedure where AC interrupted
  - CHADS$_2$: 1 or more…
- Ineligible
  - Mechanical heart valve
  - Stroke, systemic embolism, TIA previous 12 weeks
  - Major bleed previous 6 weeks
  - Cr. Clearance < 30 ml/min
  - Plt count < 100k
  - Planned intracranial, intraspinal, or cardiac surgery

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Result Demographics…

- Mean Age: 71.7
- 73.4% Male
- Mean body wt: 95.8 kg
- Mean $CHADS_2$: 2.3
  - 38.3%: 3 or higher
- 34.7% also on ASA
  - 7.2% yet another antiplt drug
- Most common procedures:
  - 44% GI; 17.2% cardiothoracic; 9.2% ortho
  - ~ 90% minor procedures
- Mean # doses of study drug PTP: 5.0 +/- 1.1; and AP: 16.0+/- 7.9
  - Mean dalteparin dose: 9093+/- 2240 IU SQ BID

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Outcomes

- Incidence arterial thromboembolism→ "Non-inferior"
  - 0.4% (4/918) no bridging group vs. 0.3% (3/895) bridging group
  - Mean $CHADS_2$: 2.6 (range 1-4)
  - 5 of 7 events occurring after minor procedure
  - Mean time after procedure: 19 days (interquartile range: 6-23)
- Major Bleeding→ no bridging "superior"
  - 1.3% (12/918) no bridging vs. 3.2% (29/895) bridging.
    - Relative risk: 0.41 (95% CI 0.2-0.78) P=0.005
  - None fatal
  - Median time to major bleed after procedure: 7.0 days (interquartile range: 4-18)
- No significant difference risk of:
  - AMI, DVT, PE, Death

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Bottomline on Bridging…

- "Bridging"= no difference in art. thromboembolism but triple the risk of major bleed!
- Less minor bleeding without bridging→ 12 vs. 20%
- Supports results of prior nonrandomized trials…
  - Meta-analysis: ~ 13K pt with afib or mechanical heart valves
    - No sig dif in rate of arterial thromboembolism; but higher major bleeding rate
  - RE-LY (1.4K pt) bridge→ higher major bleed rate 6.8% vs 1.6%; no significant effect on arterial thromboembolism (0.5% vs 0.2%)
  - ORBIT-AF (2.2K pt) bridge→ higher major bleed rate for elective procedures.

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Caveats…

- Do these results "hold" for the higher risk afib pts?
  - Very few with $CHADS_2$ 5-6
- Major procedures a/w high clotting and bleeding *not* represented…
  - CEA, Major cancer sx, cardiac surgery, neurosurgery
- Cannot apply to those with mechanical heart valves
  - Excluded
- Warfarin…. What is Warfarin!?
  - Despite the rise of DOAC, many remain on Warfarin…
    - Altru Anticoagulation Clinic ~ 750 pts

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What is not known

- Pre-procedure only vs post-procedure only bridging
  - No studies that I am aware of…
- Optimal timing post procedure for restarting
  - Bridge trial:
    - low bleed risk procedure→ resumed therapeutic dose LMWH within 24 hrs
    - High bleed risk procedure→ resumed therapeutic dose LMWH 48-72 hrs after
- Modified (lower) LMWH dose post procedure and how long?

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DOAC ≠ Bridging

- Think of DAOC as "oral" LMWH
  - Very similar onset and offset of action
    - Onset: 2-4 hrs
    - T1/2: ~ 12 hrs
  - If on DOAC, you are in essence, "bridging"
  - Simplifies perioperative management
    - No need for subcutaneous injections and multiple AC (LMWH and VKA concomitantly)
  - Perioperative recommendations hinges on three factors:
    - 1. ATE risk (pt)
    - 2. Bleed risk (procedure)
    - 3. Kidney function

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High Thrombotic Risk Management **before** procedure

Dabigatran	Rivaroxaban Edoxaban	Apixaban
	Bleed risk high Last dose before procedure	
4 days	3 days	2 days
	Bleed risk not high Last dose before procedure	
3 days	2 days	1 day

CrCl 30-40 ml/min—prolong discontinuation by 24-48 hours

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Non-high Thrombotic Risk Management **before** procedure

Dabigatran	Rivaroxaban Edoxaban	Apixaban
	Bleed risk high Last dose before procedure	
5 days	4 days	3 days
	Bleed risk not high Last dose before procedure	
4 days	3 days	2 days

CrCl 30-40 ml/min—prolong discontinuation by 24-48 hours

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High Thrombotic Risk Management **after** procedure[1,2]

Dabigatran	Rivaroxaban Edoxaban	Apixaban
	Bleeding Risk – High 48-72 hrs after procedure	
Consider lowering initial dose to 75 mg BID	Consider lowering initial dose to 10 mg daily	Consider lowering initial dose to 2.5 mg BID
	Bleeding Risk—Not High ≥ 24 hrs after procedure	

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1. Assuming adequate hemostasis
2. After craniotomy and spine neurosurgery, hold for at least 3 days and until neurosurgery team decides it is safe to restart

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Non-high Thrombotic Risk Management **after** procedure[1,2]

Dabigatran	Rivaroxaban Edoxaban	Apixaban
	Bleeding Risk – High ≥ 72 hrs after procedure	
Consider lowering initial dose to 75 mg BID	Consider lowering initial dose to 10 mg daily	Consider lowering initial dose to 2.5 mg BID
	Bleeding Risk—Not High 48 hrs after procedure	

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1. Assuming adequate hemostasis
2. After craniotomy and spine neurosurgery, hold for at least 3 days and until neurosurgery team decides it is safe to restart

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Periprocedural Pearls…

- May not even need to interrupt…
  - Minor skin, eye, dental procedures
- Bridging standing on increasingly "shaky" ground
  - Only with very high thrombotic risk
  - Consider waiting an extra day OR initiating post procedure LMWH at a lower dose
    - Most complications occur in restarting AC to soon after high bleed risk procedure…
- DOACs do not require bridging….ever.
  - T1/2 roughly the same as LMWH
  - Time to peak AC also similar to LMWH
- Shortcut: look at the package insert and add another day…

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Summary

- DAOCs have supplanted VKA for the majority of VTE
  - Minus cancer-associated VTE
- We still don't know much about post-thrombotic syndrome
  - ECS do not prevent
- Small subsegmental PE, in the right circumstance, may not require AC
  - Scan the legs if foregoing Rx
- Bridging has fallen further out of favor
  - In low ATE risk patients, does not work but does cause more bleeding…
  - DOAC use will further limit bridging

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Many Thanks…

Questions??

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