Common Complex Cases in Thrombosis

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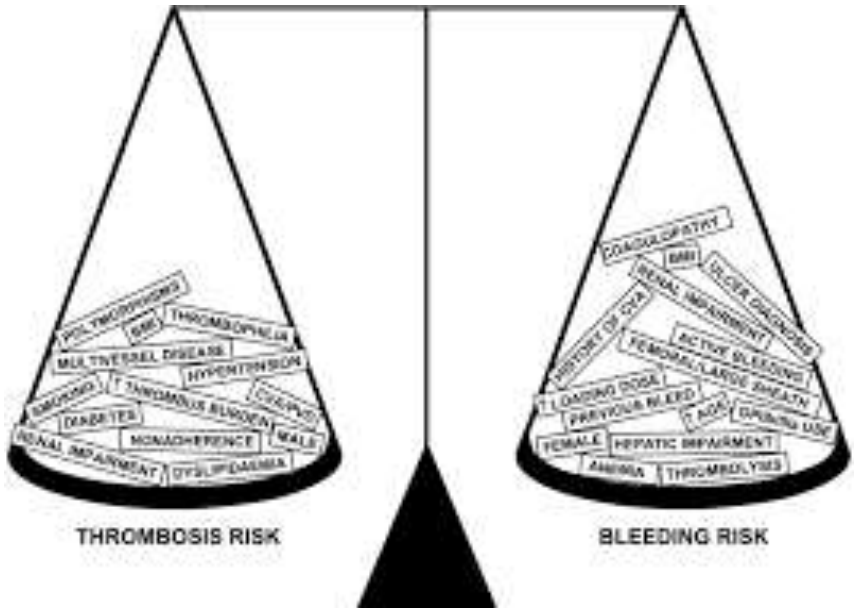
Disclosures

- Speaker has no conflict of interest.

Learning Objectives

1) Manage anticoagulation in a patient with high risk of thrombosis and active bleeding.
2) Management of recurrent/new thrombosis in anticoagulated patient.
3) Counselling a patient who refuses optimal therapy in relation to thrombosis and anticoagulation.



1) Manage anticoagulation in a patient with high risk of thrombosis and active bleeding.

Case 1:

- 81M presents with ALI (R arm)
- Known AF CHADS 2 (HTN, age) not previously anticoagulated due to “frequent falls”
- CTA shows clear cutoff at R brachial artery and left atrial thrombus
- Started on IV Heparin in hospital
- Soon thereafter begins to have bleeding per rectum
- Hb is stable, PTT is supratherapeutic

How do you manage this patient's anticoagulation?

A) Continue heparin and monitor hemoglobin-bridge to oral anticoagulation

B) Stop heparin and restart after 24hours if hemoglobin is stable with bridge to oral anticoagulation

C) Stop heparin and start oral anticoagulation in 1 week if hemoglobin stable with heparin bridge

D) Stop heparin and do not restart anticoagulation

Case 2:

- 87F double mechanical valve + AF
- Chronically anticoagulated on warfarin
- Recent treatment for endocarditis→ INR > 20→vitamin K given + warfarin held
- 3 days later presents with headache
- pre-pontine SAH on CT
- INR = 9
- Neurosurgery consulted→ no role for surgery

How do you manage this patient's anticoagulation?

Acutely:

A) Hold warfarin x 2 days and r/a INR daily

B) Reverse warfarin with PCC and Vitamin K

C) Reverse warfarin with PCC but no Vitamin K

D) Reverse warfarin with PCC and vitamin K and start Heparin as soon as INR normalized

Long term:

A) Stop anticoagulation indefinitely

B) Resume warfarin in 48hours with repeat CT scan

C) Resume warfarin in 7-14days with repeat CT scan

D) Resume warfarin in 30days with repeat CT scan

Case 3:

- 65M diagnosed with large PE 2 weeks ago
- Treated with rivaroxaban
- Presents with melena and dizziness, Hb 90 (130)
- Vital signs are stable
- GI consulted, Pantoloc started

How do you manage this patient's anticoagulation?

Acutely:

A) Continue rivaroxaban given recent PE and patient hemodynamically stable

B) Hold rivaroxaban and follow Hemoglobin x 24 hour then restart rivaroxaban if stable

C) Hold rivaroxaban and order Doppler to check for DVT to decide on IVC filter

D) Hold rivaroxaban and ask for IVC filter

How do you manage this patient's anticoagulation?

Long term:

A) Resume anticoagulation 48 hours after Hb stabilized and remove IVC filter

B) Resume anticoagulation 1-2 weeks after Hb stablilized and remove IVC filter

C) Do not resume anticoagulation and maintain IVC filter in situ

D) Start prophylactic dose anticoagulation and maintain IVC filter in situ

Management of acute VTE

- Mainstay of treatment is prompt anticoagulation
  - 24 hour window within which to initiate
- *If unable to anticoagulate, then IVC filter*
  - Within 4 weeks of acute VTE event
  - Serial imaging can be of some utility as well
- Massive, hemodynamically unstable PE
  - Mainstay of treatment is thrombolysis (tPA)-contraindicated in case of bleeding
  - Alternatives: thrombectomy, catheter directed lysis, ECMO, other catheter directed techniques without thrombolytics (eg: aspiration, fragmentation)

ACCP Chest Guidelines, 2012 and 2016 editions

Management of ATE

- Acutely: vascular intervention vs thrombolysis
  - Angiography, stent, thrombectomy, surgical bypass (more for atherosclerotic disease)
- Chronically: anticoagulation with warfarin or DOAC with parenteral bridging
  - No role for DOAC in most “high-risk situations” such as mechanical valves, mural thrombus, valvular AF
  - In case of major bleeding must withhold anticoagulation

ACCP Chest Guidelines, 2012 and 2016 editions

ISTH Bleeding definitions

Major bleeding:

1) **Fatal bleeding, and/or**
2) **Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compart- ment syndrome, and/or**
3) **Bleeding causing a fall in hemoglobin level of 20 g L)1 (1.24 mmol L)1) or more, or leading to transfusion of two or more units of whole blood or red cells.**

Minor bleeding:

1) A **clinically relevant non-major bleed** is an acute or subacute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following:
   - A hospital admission for bleeding, or
   - A physician guided medical or surgical treatment for bleeding, or
   - A change in antithrombotic therapy (including interruption or discontinuation of study drug).
2) All other bleeding not described as major bleed or CRNMB

“High risk” of bleeding

- Intracerebral hemorrhage
- Spinal hemorrhage
- Muscular bleed/hematoma
- Retroperitoneal bleed

Any bleeding categorized as “major bleeding”

- Mycotic aneurysm
- Vascular brain metastases (melanoma, thyroid, renal)
- Coagulopathy (DIC, anticoagulation, antiplatelets, hemophilia, thrombocytopenia)
- Surgery (immediate post-op or urgently required)
- Pericardial disease (malignant effusion)
- Epidural catheter

TABLE 2

Thromboembolic risk by anticoagulation indication

Risk stratum	Mechanical heart valve[a]	Atrial fibrillation	Venous thromboembolism
High[b]	Any mitral valve prosthesis Any caged-ball or tilting-disc aortic valve prosthesis Stroke or transient ischemic attack within past 6 months	$CHADS_2$ score of 5 or 6 CHA_2DS_2-VASc score of 6 to 9 (suggesting adjusted stroke rate ≥ 9% per year) Stroke or transient ischemic attack within past 3 months Rheumatic valvular heart disease	Venous thromboembolism within past 2 months Severe thrombophilia (eg, deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Moderate[c]	Bileaflet aortic valve prosthesis and one or more of the following risk factors: atrial fibrillation, prior stroke or transient ischemic attack, hypertension, diabetes, congestive heart failure, age > 75	$CHADS_2$ score of 3 or 4 CHA_2DS_2-VASc score of 5 (suggesting adjusted stroke rate of 5%–9% per year)	Venous thromboembolism within the past 6 months Nonsevere thrombophilia (eg, heterozygous factor V Leiden or prothrombin gene mutation) Recurrent venous thromboembolism Active cancer (treated within 6 months or palliated)
Low	Bileaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	$CHADS_2$ score of 0 to 2 CHA_2DS_2-VASc score of 0 to 4 (suggesting adjusted stroke rate < 5% per year and assuming no prior stroke or transient ischemic attack)	Venous thromboembolism more than 6 months previously and no other risk factors

[a] The valve position affects risk for thromboembolism: the incidence rate for valve thrombosis was 5 times higher in mitral valves than in aortic valves; the incidence rate for embolism was 1.5 times higher in mitral valves than in aortic valves.[11]

[b] High-risk patients may also include those with prior thromboembolism during temporary interruption of vitamin K antagonists (eg, warfarin).

[c] Moderate-risk patients may also include those with prior stroke or transient ischemic attack occurring more than 3 months before event.

$CHADS_2$ = 1 point each except as noted: **C**ongestive heart failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes mellitus, and **S**troke or transient ischemic attack (2 points)

CHA_2DS_2-VASc = 1 point each except as noted: **C**ongestive heart failure; **H**ypertension; **A**ge ≥ 75 (2 points); **D**iabetes mellitus; prior **S**troke, transient ischemic attack, or thromboembolism (2 points); **V**ascular disease; **A**ge 65–74; **S**ex category (female)

ADAPTED FROM DOUKETIS JD, SPYROPOULOS AC, SPENCER FA, ET AL; AMERICAN COLLEGE OF CHEST PHYSICIANS. PERIOPERATIVE MANAGEMENT OF ANTITHROMBOTIC THERAPY: ANTITHROMBOTIC THERAPY AND PREVENTION OF THROMBOSIS, 9TH ED: AMERICAN COLLEGE OF CHEST PHYSICIANS EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES. CHEST 2012; 141(SUPPL 2):E326S–E350S. REPRODUCED WITH PERMISSION FROM THE AMERICAN COLLEGE OF CHEST PHYSICIANS.

Colantino et al. Cleveland Clinic Journal of Medicine. 2015

Acute Management

1) **Assess extent of bleed:**
   - Major: Hold/reverse anticoagulation completely
   - CRNMB: Stop oral anticoagulation and consider using shorter acting drug or partially reverse (eg: PCC but no vitamin K)
   - Minor: Continue anticoagulation

     ☆Anticoagulation is a coagulopathy!!

2) **Assess patient's thrombotic risk**
   - This should not alter your management of the bleeding, rather it should guide decision regarding timing of resumption of anticoagulation once bleeding is resolved or at least decreased.
   - IVC filter for VTE patients < 1 month ago (regardless of presence of DVT)

Guiding principles when considering resuming anticoagulation:

1. Need to balance out risk of bleeding with risk of thrombosis to decide optimal timing
2. Need to discuss these risks with patient for informed and collaborative decision making
3. Need to educate patient regarding signs/symptoms of thrombosis and bleeding, especially during this high-risk period
4. Need to follow patient closely until able to ensure that thrombosis and bleeding risk have been optimized

Bleeding considerations

- Consider the clinical impact of the bleed
  - ICH leads to death or disability in 76% of cases vs 3% of cases in GI/GU bleeding
  - Soft tissue bleeds take longer to heal than mucosal bleeds
  - Difficult to clinically follow bleeding in closed compartments vs mucosal bleeding
- Consider the risk of re-bleeding
  - Causes/triggers: trauma, intervention/surgery, INR level
  - Comorbid conditions: coagulopathy, antiplatelet medication, cancer, CKD, CLD, advanced age
  - Definitive intervention: clips for aneurysm, angioembolization, endoscopy, surgery
- General risk of re-bleeding approximately 10% in all cases
  - Risk of recurrent ICH is 2% to 4%/yr and up to 7.5% in some studies

Colantino et al. Cleveland Clinic Journal of Medicine. 2015

Thrombosis considerations

- Consider the overall risk of thrombosis
  - High risk vs low risk as discussed previously
- Consider “rebound effect”
  - Highest risk of thrombosis in 3 months after discontinuation of anticoagulation
- Consider increased risk of thrombosis while patient acutely ill
  - Bleeding increases risk of thrombosis
  - 7% risk of thrombosis during the initial ICH hospitalization and 9% within 3 months

Colantino et al. Cleveland Clinic Journal of Medicine. 2015

Timing of resumption

Qureshi et al, American Journal of Cardiology, 2014
Colantino et al. Cleveland Clinic Journal of Medicine. 2015
Pennlert et al. Stroke. 2017

Joints, epistaxis

- Same day or within 24 hours

Mucosal bleeding (GI, GU):

- 2-3 days after bleed and up t o1-2 weeks
- Guidance from gastroenterologist and endoscopic findings

Muscular hematoma

- 4-7 days after bleed up to 2-4 weeks

Timing of resumption post ICH

- NO anticoagulation x 24hours
- Safe to use prophylactic dose LMWH (or UFH) as of day 1 post ICH
  - Most guidelines recommend “early” institution of DVT prophylaxis
- Risk of re-bleeding decreases over time while risk of thrombosis increases
- Generally, pts at highest risk of ATE/VTE should resume AC 7-14 days post ICH
- In low thrombotic risk patients, do not resume if spontaneous lobar ICH
- **7-8 weeks** and up to 30 weeks in lower risk patients

Shulman. Blood. 2012
Colantino et al. Cleveland Clinic Journal of Medicine. 2015
Pennlert et al. Stroke. 2017

Take-home points

- Bleeding is most important side effect of anticoagulants
- Extent of bleed rather than risk of thrombosis should guide initial management→ correct coagulopathy!
- Timing of resumption of anticoagulation will depend on location/extent of bleed as well as risk of thrombosis

2)Management of recurrent/new thrombosis in anticoagulated patient.

Case 4:

- 41F presented with neck swelling
- Diagnosed with R IJ thrombosis and bulky LAD
- CT scan to r/o PE demonstrated lung lesions→NSCLC
- Started dalteparin 200U/kg (10000U) once daily=100% dose
- 2 weeks later presents with increased neck swelling
- Increased burden of thrombus in IJ and more PE

How do you manage this patient's anticoagulation?

A) Stop dalteparin and start IV heparin and bridge to warfarin

B) Stop dalteparin and start rivaroxaban

C) Increase dalteparin to 125% dose (250U/kg)

D) Continue dalteparin and monitor anti-Xa levels

Recurrent cancer-associated thrombosis

- 20-30% rate of recurrent thrombosis in anticoagulated cancer patients
- Ensure this is not HITS-check platelets
- **Guidelines recommend dose-escalation of LMWH in these cases**
  - If patient on 75% dose then escalate back to 100% dose
  - If patient on 100% dose then escalate to 120-125% dose
  - Maintain this dose for 4 weeks then r/a
- Very important to counsel and educate cancer patients with thrombosis about signs/symptoms of recurrence and bleeding

Carrier et al, JTH, 2013

Case 5:

- 57M otherwise healthy
- Presents with left sided pleuritic chest pain
- CT PE demonstrates left sided PE
- Treated in hospital with LMWH – symptoms resolved
- Sent home on appropriate dose rivaroxaban
- Returns on day 4 post diagnosis with increasing R-sided chest pain

Differential Diagnosis:

Failure of anticoagulant:

- Inappropriate dosing
- Non-adherence
- Cancer
- Antiphospholipid antibody
- If exposed to heparin --> r/o HIT
- Large clot burden/off label use
- Obese patient/drug interaction
- Acceptable failure rate (efficacy of drug = 98%)

Pulmonary infarct

Natural history of VTE disease

Anti-inflammatory effect of LMWH (theoretical)

Msk pain/cardiac pain/GI pain

Case 6:

- 85M known AF CHADS 3 on apixaban 2.5mg bid
- Normal renal function, weighs 65kg, “looks frail”
- Presents with L MCA CVA
- CTA shows normal carotids
- Pt insists he is adherent

How do you manage this patient's anticoagulation?

1) Add ASA
2) Continue current dose of apixaban
3) Increase apixaban dose
4) Change to another DOAC
5) Change to warfarin

Case 6a:

- 85M known AF CHADS 3 on apixaban 5mg bid
- Normal renal function, weighs 65kg
- Presents with L MCA CVA
- CTA shows normal carotids
- Pt insists he is adherent

How do you manage this patient's long term anticoagulation?

a) Continue apixaban at current dose
b) Add ASA
c) Change to another DOAC
d) Change to Warfarin

Summary of Phase 3 DOAC RCTs

	RELY 150 vs 110		ROCKET	ARISTOTLE	ENGAGE 60 vs 30	
ATE	↑	↔	↔*	↵↑	↑	↔
All Bleeding	↔	↓	↔	↓	↓	↓
ICH	↓	↓	↓	↓	↓	↓
GI Bleed	↑	↔	↑	↔	↑	↓

	RECOVER	EINSTEIN	AMPLIFY	Hokusai
VTE	↔	↔	↔	↔
Bleeding	↔	↔	↓	↔

DOAC “failure”

- None of the studies demonstrate 100% efficacy
- ARISTOTLE (apixaban):
  - Primary event rate of **1.17%/yr** reported
  - Less than 5% of patients on 2.5mg BID dose
- RELY (dabigatran):
  - Dabigatran 150mg BID dose had **1.11%/yr** event rate
- Special populations excluded/limited

Exclusions/Limited data

Indication for anticoagulation:

- Acute stroke
- Valvular atrial fibrillation
- Mechanical heart valves
- LV thrombus
- Unusual site thrombosis (PVT,CVT)
- Most thrombophilia (APS)
- Cancer associated thrombosis

Patient characteristics:

- Impaired renal function/dialysis
- Impaired liver function
- Pregnant/breastfeeding/pediatric
- Concomitant use of azoles, CCB, ART, rifampin
- Extremes of weight
- Extremes of age

☞ Caution in these situations→ default to warfarin

Dosing

A-fib:

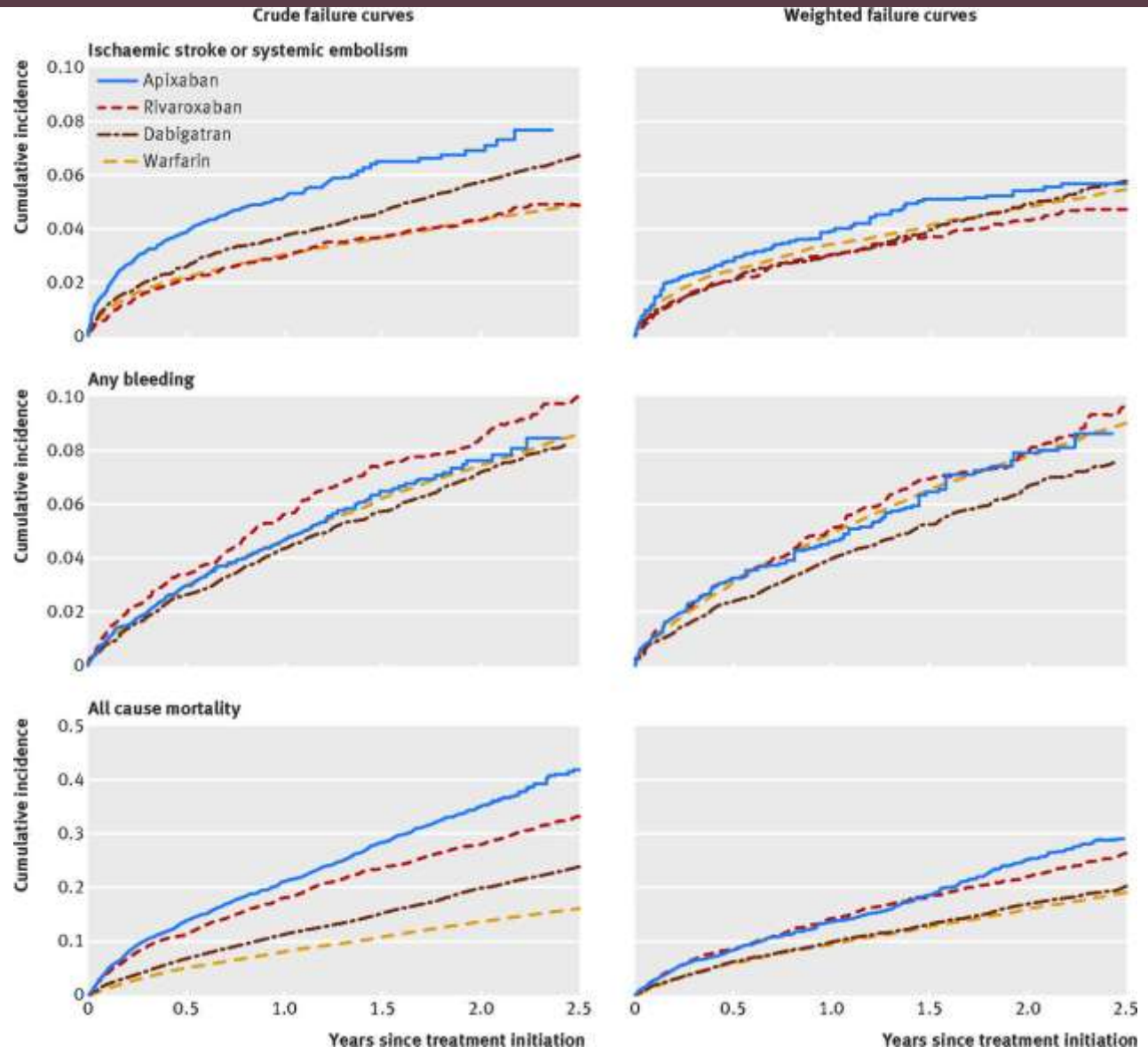
- Rivaroxaban:
  - 20mg PO DIE for CrCl > 50ml/min
  - 15mg PO DIE for CrCl 30-50 ml/min
- Apixaban:
  - 5mg PO BID for CrCl > 25ml/min
  - 2.5mg PO BID if 2/3: age > 80, wt < 60kg, Creat > 133
- Dabigatran:
  - 150mg PO BID
  - 110mg PO BID

  (both for CrCl > 30 ml/min)
- *RAMQ Code CV 155 for all of the above*
- Edoxaban:
  - 60mg PO DIE for CrCl > 50ml/min
  - 30mg PO DIE for Crcl 30-50ml/min

VTE:

- **Rivaroxaban**:
  - 15mg PO BID x 21 days then 20mg PO DIE
  - Can now consider 10mg PO DIE after 6 months but not covered
  - Codes: CV 157 for DVT x 6 months or CV 165 for PE x long term
- **Apixaban**:
  - 10mg PO BID x 7 days then 5mg PO BID (not covered > 6 months)
  - Can decrease to 2.5mg PO BID after 6 months
  - Codes: CV 169 for full dose x 6 months then CV 170 for reduced dose
- Dabigatran:
  - 1 week of LMWH thenby 150mg PO BID
- Edoxaban:
  - 1 week of LMWH then 60mg PO DIE

Effectiveness study looking at reduced doses of NOACs showed higher rates of stroke with Apix 2.5 dose (Nielsen et al. *BMJ* Feb 2017)



Take-home points

- Thrombosis on anticoagulation is not implausible and has a differential diagnosis → think about cancer, HIT, APLAS
- Anticoagulation is not 100% efficacious – just like OCP!
- Must pay careful attention to prescribe appropriate dose of DOAC in appropriate context → not a “one size fits all” approach

3) Counselling a patient who refuses optimal therapy in relation to thrombosis and anticoagulation.

Case 7:

- 57M recurrent VTE
- VTE #1 2002 provoked PE post MVA/trauma→IVC filter and 3 months of anticoagulation
- VTE #2 2015 unprovoked DVT → 6 months of anticoagulation and requested to stop
- VTE #3 2018 SVT flush to SFJ unprovoked → 3 months of anticoagulation and requested to stop
- Prefers herbal treatments with naturopath including natural anticoagulants such as garlic

Case 8:

- 87F recurrent LE unprovoked DVT's
- Chronically anticoagulated
  - Most recent anticoagulant apixaban
- Spontaneous ICH Nov 2015
- AC held, patient followed in hospital, no focal neuro deficits→d/c home
- 1 month later, acute proximal DVT

Long term treatment

- Recurrent unprovoked VTE
- Known severe thrombophilia (eg: antiphospholipid antibody)
- HERDOO2, Vienna, DASH = prediction models
- Serial D-dimers
- Active cancer/cancer treatment (6 months or until cancer free)
- AF > CHADS 1, non-valvular AF, mechanical valve, severe PAD, *cryptogenic stroke*

Discussion points

- Understand why patient reluctant to pursue recommended therapy
- Patient preference is important to consider and respect
- It is your responsibility to ensure that patient is making informed decision
  - Can provide estimates of risks over time
- Not anticoagulating does not mean “do nothing”:

➢ **Counsel about signs/symptoms of recurrence and remind patient to seek emergent medical attention**

➢ **Educational pamphlets or websites can be useful (eg: Thrombosis Canada)**

Risk of Thrombosis (VTE)

Risk factor	1st year	Next 5 years
BK DVT	3-6%	<10%
Provoked	3%	10%
Weakly provoked	5%	15%
Unprovoked	10%	30%
Recurrent	>10%	>30%

Kearon, Blood 2005

Non-valvular Atrial Fibrillation

Table 2. Risk of Stroke in National Registry of Atrial Fibrillation (NRAF) Participants, Stratified by $CHADS_2$ Score*

$CHADS_2$ Score	No. of Patients (n = 1733)	No. of Strokes (n = 94)	NRAF Crude Stroke Rate per 100 Patient-Years	NRAF Adjusted Stroke Rate, (95% CI)†
0	120	2	1.2	1.9 (1.2-3.0)
1	463	17	2.8	2.8 (2.0-3.8)
2	523	23	3.6	4.0 (3.1-5.1)
3	337	25	6.4	5.9 (4.6-7.3)
4	220	19	8.0	8.5 (6.3-11.1)
5	65	6	7.7	12.5 (8.2-17.5)
6	5	2	44.0	18.2 (10.5-27.4)

*$CHADS_2$ score is calculated by adding 1 point for each of the following conditions: recent congestive heart failure, hypertension, age at least 75 years, or diabetes mellitus and adding 2 points for having had a prior stroke or transient ischemic attack. CI indicates confidence interval.

†The adjusted stroke rate is the expected stroke rate per 100 patient-years from the exponential survival model, assuming that aspirin was not taken.

**60% relative risk reduction with anticoagulation

Bleeding risk factors

- Advanced age
- Cancer
- Kidney or liver failure
- Comorbidity and reduced functional capacity
- Antiplatelet therapy
- Thrombocytopenia
- Previous bleeding
- Diabetes
- Frequent falls
- Poor anticoagulant control
- Recent surgery
- Previous stroke
- Anemia
- Alcohol abuse

ACCP 2016

Risk of bleeding

Risk of bleed	No RF	1 RF	> 2 RF
Baseline	0.3%	0.6%	>2.5%
With AC	0.5%	1%	>4%
Total	0.8%	1.6%	>6.5%

*Note that though the risk of bleed seems far less significant than the risk of thrombosis, you must consider the case-fatality of bleed vs thrombosis as well.

ACCP 2016

Risk/Benefit

- VTE: 30% risk of recurrence over 5 years in unprovoked VTE
- AFib: CHADS2 score and/or CHADSVASC score
  - CHADS3 = 6% per year risk of stroke for example
- Mechanical valve:
  - 25% risk of thrombosis in 1st year
  - 15% risk of thrombosis as of 2nd year with gradual decrease over time thereafter
- Annual risk of bleeding = 2% in moderate risk patients

BUT:

Case-fatality of recurrent VTE=3.6% << Case-fatality of major bleeding =11%

Case-fatality of stroke=15-50%>>Case-fatality of major bleeding

Take-home points

- Patient preference in matters of chronic anticoagulation is important to consider
- Must counsel patient with regard to overall annual risk of thrombosis and risk of bleeding
- Generally risk of thrombosis > risk of bleeding, BUT must consider case-fatality→most significant with stroke


HAVE YOU FORGOTTEN HOW TO HAVE A CONVERSATION WITHOUT POWERPOINT?
I'LL TAKE QUESTIONS AT THE END.
TOM FISH BURNE
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Questions