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Managing Anticoagulation and Thrombosis Remotely with COVID-19 Social Distancing: *How to do it in primary care*

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Other: N/A

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Mitigating potential bias

The agenda and faculty for this program was developed by the scientific steering committee from Thrombosis Canada. All faculty have been directed that any recommendations involving clinical medicine are to be based on evidence that is accepted within the profession; and all scientific research referred to, reported, or used in the CME/CPD activity in support or justification of patient care recommendations conforms to the generally accepted standards.

Program learning objectives

After attending this program, participants will be able to:

- Understand key information (what you need to know) about COVID-19 and thrombosis;
- Effectively manage anticoagulant therapy (DOACs, warfarin) remotely;
- Effectively manage suspected or confirmed venous thromboembolism (DVT, PE) remotely.

Agenda

Primary care perspective	COVID-19 and primary care, Thrombosis Canada resources	Alan Bell, MD
COVID-19	Overview and COVID-19 as a hypercoagulable disease	Jim Douketis, MD
Case vignettes	Common thrombosis and anticoagulation problems assessed in primary care	Alan Bell, MD Lana Castellucci, MD Jim Douketis, MD
Outpatient coagulation management		Lana Castellucci, MD
Question period		Alan Bell, MD moderator

Introduction and primary care perspective

Alan Bell, MD, CFPC, FCFP

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The Challenge

- COVID-19 has re-defined provision of primary care

- Diagnosis and management of thrombotic diseases and other conditions requiring anticoagulant management presents specific challenges
  - Suspected VTE requires urgent and decisive action
  - Anticoagulant side effects require immediate management
  - Virtual visits preclude detailed examination
  - Emergency rooms are potential sources of exposure
  - INR monitoring potentially exposes patients to COVID-19 exposure
  - COVID-19 infection is associated with thrombotic and bleeding complications[1]

1. Thachil J et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. ISTH Academy 03/25/20; 290506 https://doi.org/10.1111/jth.14810

Thrombosis Canada has been the voice of thrombosis medicine in Canada since 1991

Our vision

- We believe that providing point-of-care clinical guidance, founded on national and international guidelines, is the most effective and cost-efficient way to improve patient safety and outcomes, within a framework of patient-centred values and preferences.

- We continue with this mandate to assist health care professionals through this pandemic

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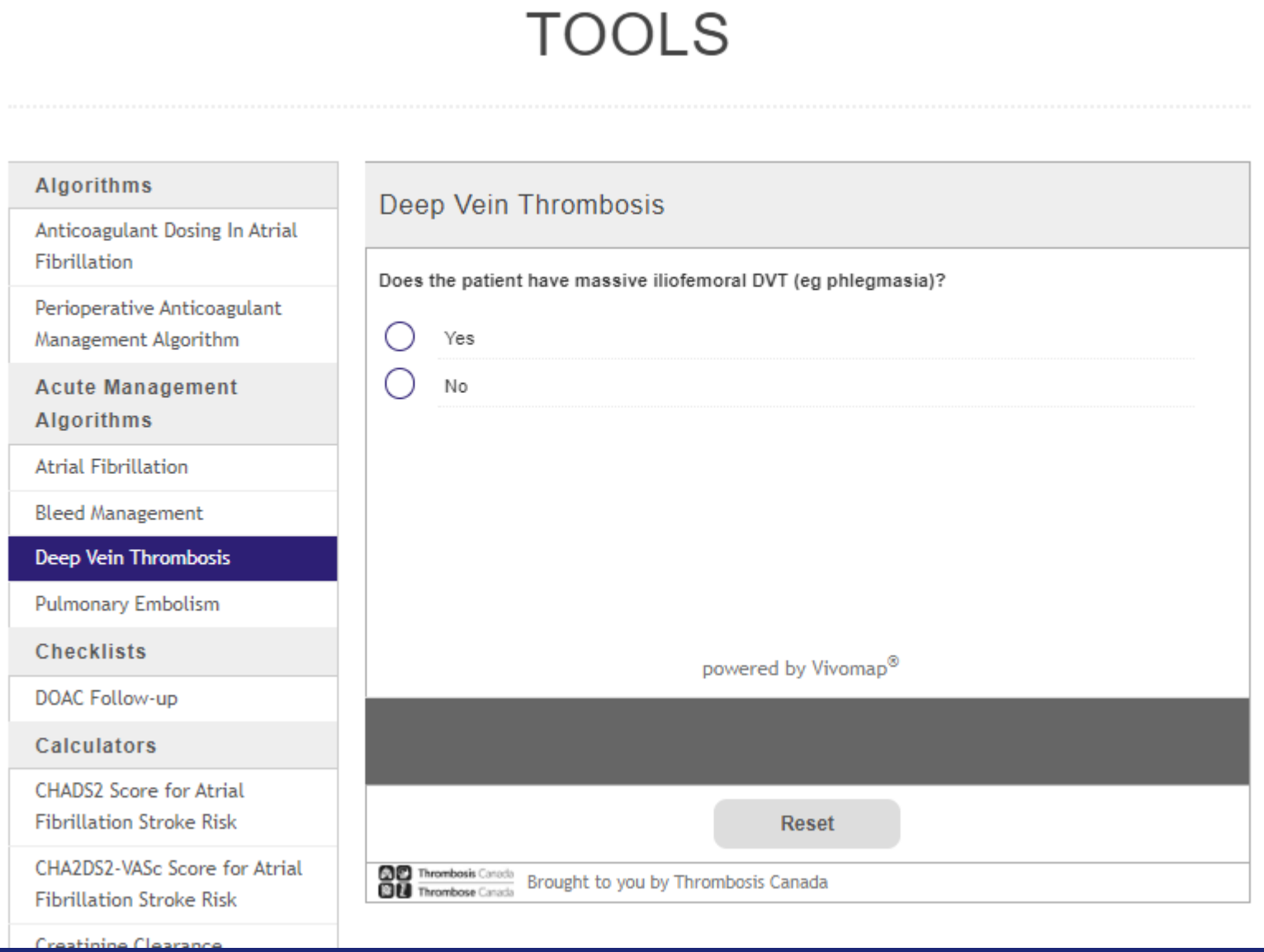
TOOLS
Algorithms
Anticoagulant Dosing In Atrial Fibrillation
Perioperative Anticoagulant Management Algorithm
Acute Management Algorithms
Atrial Fibrillation
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Deep Vein Thrombosis
Pulmonary Embolism
Checklists
DOAC Follow-up
Calculators
CHADS2 Score for Atrial Fibrillation Stroke Risk
CHA2DS2-VASc Score for Atrial Fibrillation Stroke Risk
Deep Vein Thrombosis
Does the patient have massive iliofemoral DVT (eg phlegmasia)?
Yes
No
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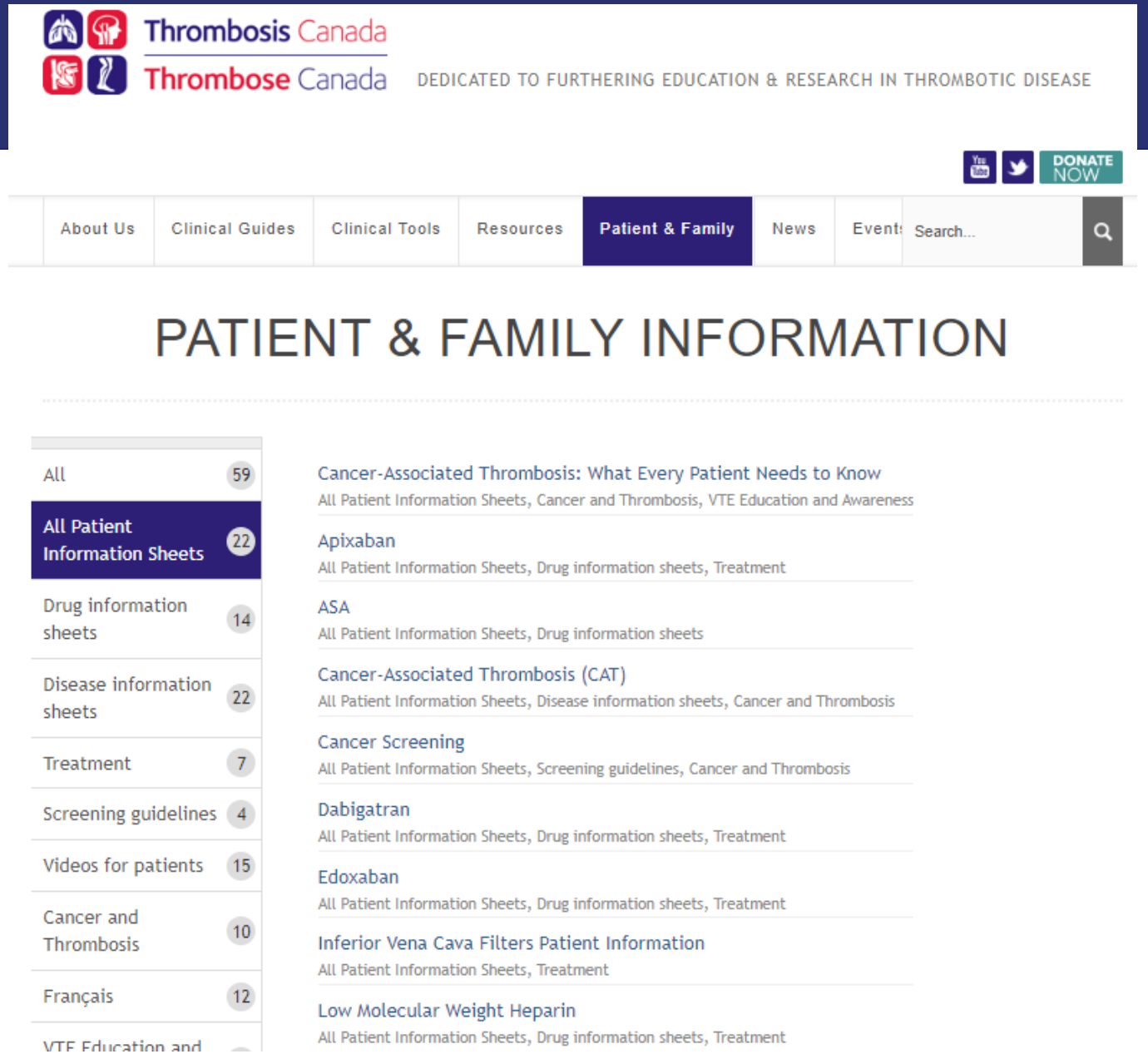
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All Patient Information Sheets, Drug information sheets
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All Patient Information Sheets, Disease information sheets, Cancer and Thrombosis
Cancer Screening
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Edoxaban
All Patient Information Sheets, Drug information sheets, Treatment
Inferior Vena Cava Filters Patient Information
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All Patient Information Sheets, Drug information sheets, Treatment

Solutions: COVID-19

https://thrombosiscanada.ca/covid-19/

Overview of COVID-19: primary care and hematologic considerations

Jim Douketis, MD, FRCPC

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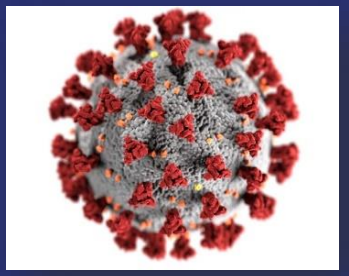
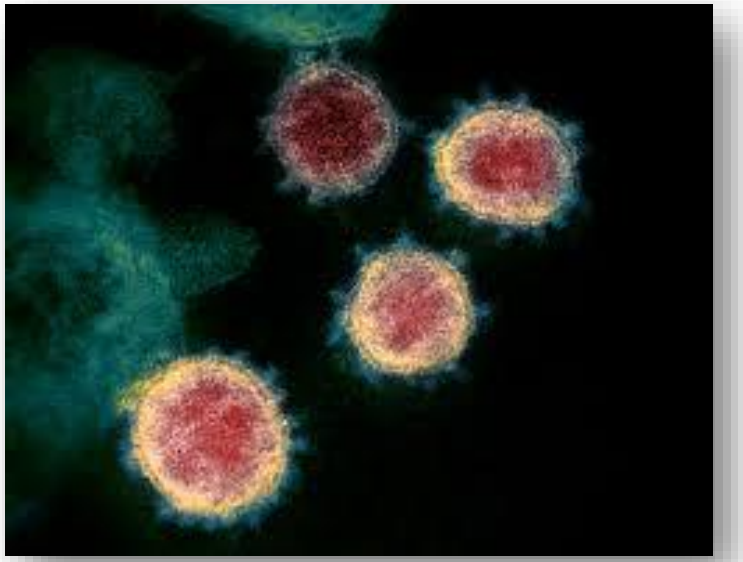
Etiology and epidemiology



Etiology

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), RNA virus that belongs to the *betacoronavirus* (betaCoV) genus
- Genus also includes SARS-CoV (responsible for epidemic in 2002-3)



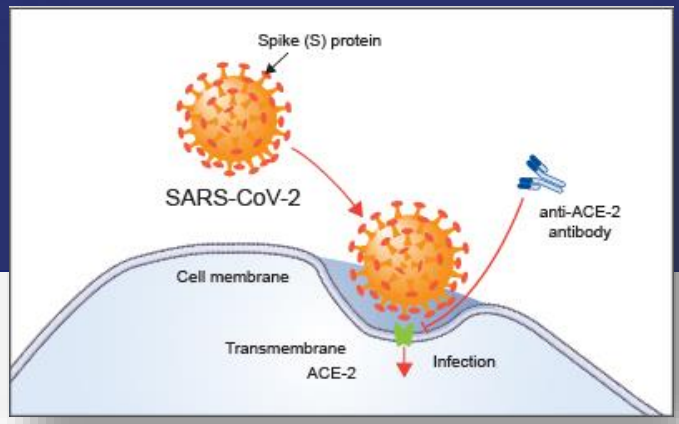
Epidemiology

- Epidemiologic data available at: www.who.int, www.cdc.gov, www.ecdc.europa.eu, https://ipac-canada.org/coronavirus-resources.php
- April 23, 2020:
  - >2,650,000 cases and >184,000 deaths worldwide
  - >42,000 cases and >2,100 deaths in Canada

Risk Factors for COVID-related Adverse Outcomes

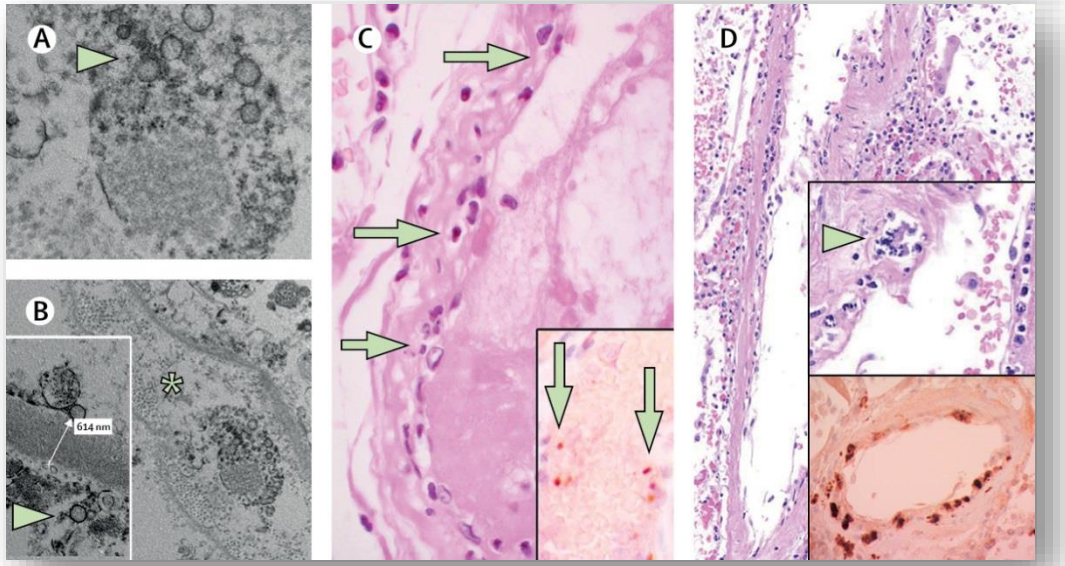
- Advanced age, male sex, obesity, smoking, diabetes, cardiovascular disease

Pathogenesis and communicability



Pathogenesis

- Virus uses lung ACE-2 as receptor, binding to spike glycoprotein on viral envelope
- In response to viral antigens, immune cells release pro-inflammatory cytokines and chemokines, results in uncontrolled systemic inflammatory response
- Endothelial invasion and endothelitis contributes to vascular injury and thrombosis.



Incubation and contagious period

- Incubation period = **2-14 days** (mean = **5 days**)
- Viral shedding highest **~10 days** from time of infection (longer if severe infection)
- Mild infection recovery within **1 week** (up to 2 weeks)
- Severe infection recovery after **3-6 weeks**

Varga Z, et al. *Lancet* April 17, 2020

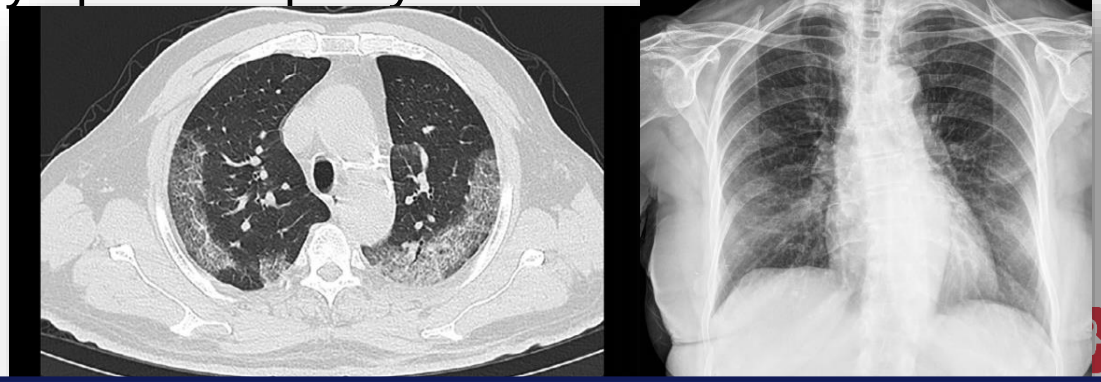
Diagnosis of COVID-19

Diagnosis

- Detect genetic material from virus using PCR (NP swabs)
  Test specificity ~100%, sensitivity 70-80%
- https://www.nejm.org/doi/full/10.1056/NEJMvcm2010260

Clinical and radiological features

- Fever, dry cough, malaise, myalgia, headache, dyspnea (not dehydrated or septic)
- **Unexpected symptoms:** anosmia, dysgeusia, diarrhea, nausea
- **CXR:** bilateral pneumonia features; **CT:** bilateral, peripheral, inferior lobes, ground-glass opacification (week 2), pleural thickening and effusion, lymphadenopathy



Differential Diagnosis

- Influenza, other viral respiratory infections
- Atypical pneumonia
- Pneumocystosis

Treatment of COVID-19

Treatment

- Supportive
- Oxygen therapy, with target of SpO_2 ≥90% (start with 5 L/min, titrate as needed)
- Glucocorticoids contraindicated (except if absolute indication)
- Antibiotics avoided (unless bacterial superinfection suspected, then use ceftriaxone or moxifloxacin)

https://covid19treatmentguidelines.nih.gov/introduction/

https://covidprotocols.org/

Ongoing RCTs investigating:

- Hydroxychloroquine or chloroquine ± azithromycin, colchicine (anti-inflammatory)
- Favipiravir, remdesivir (anti-viral)
- Tocilizumab, sarilumab, siltuximab (interleukin-6 pathway inhibitors)
- Convalescent plasma
- *Therapeutic-dose* heparin (UFH/LMWH) *vs. low-dose* heparin

COVID-19 and thrombosis: key points

1. Severe COVID infection is a **hypercoagulable state** with high VTE incidence in critically ill patients

2. Elevated D-dimers are frequently seen, but it remains unclear if this reflects **hypercoagulability/thrombosis** or merely the **proinflammatory response**

3. All admitted COVID+ patients should receive standard weight-adjusted VTE prophylaxis; there are **insufficient data at this juncture to recommend intensified empiric prophylaxis regimens** (for high D-dimer, ICU patients) outside of clinical trials

Key question for hospitalized patients with COVID-19: *therapeutic anticoagulation in absence of VTE diagnosis*?

Rapid changes in D-dimer are not diagnostic or specific for VTE

Alternative diagnoses (renal failure, infection) should be ruled out

American Society of Hematology
Consider empiric therapeutic anticoagulation (for suspected VTE) only if: 1. Unexpected clinical deterioration despite overall improvement in inflammatory markers and chest imaging (especially if high D-dimer, fibrinogen) 2. Physical exam findings of VTE (SVT, calf swelling, catheter- or line-related VTE), microvascular ischemia (skin findings)

ACC, ISTH (Bikdeli, JACC 2020)
• Optimal dosing is unknown • Majority of panel members would use prophylactic anticoagulation • Minority considered intermediate or therapeutic dose anticoagulation to be reasonable

ASH 2020; Bikdeli B, et al. *JACC* 2020;doi: https://doi.org/10.1016/j.jacc.2020.04.031.

VTE Prophylaxis for COVID-19: what to do?

- Some institutions have protocols using intermediate or therapeutic dose LMWH if elevated D-dimer – these are empiric and **currently** lack supporting clinical data

- Efficacy of **intermediate or therapeutic dosing based on D-dimer or ventilatory status** is unclear but generally not recommended outside of clinical trial setting

- **All patients admitted to hospital (ward or ICU) with COVID, regardless of D-dimer, should receive standard LMWH prophylaxis**
  - Consider dose adjustment in obese patients (>100-120 kg or BMI > 30)

Managing anticoagulation and thrombosis remotely: case vignettes

Alan Bell MD, FCFP
Lana Castellucci, MD, FRCPC
Jim Douketis MD, FRCPC

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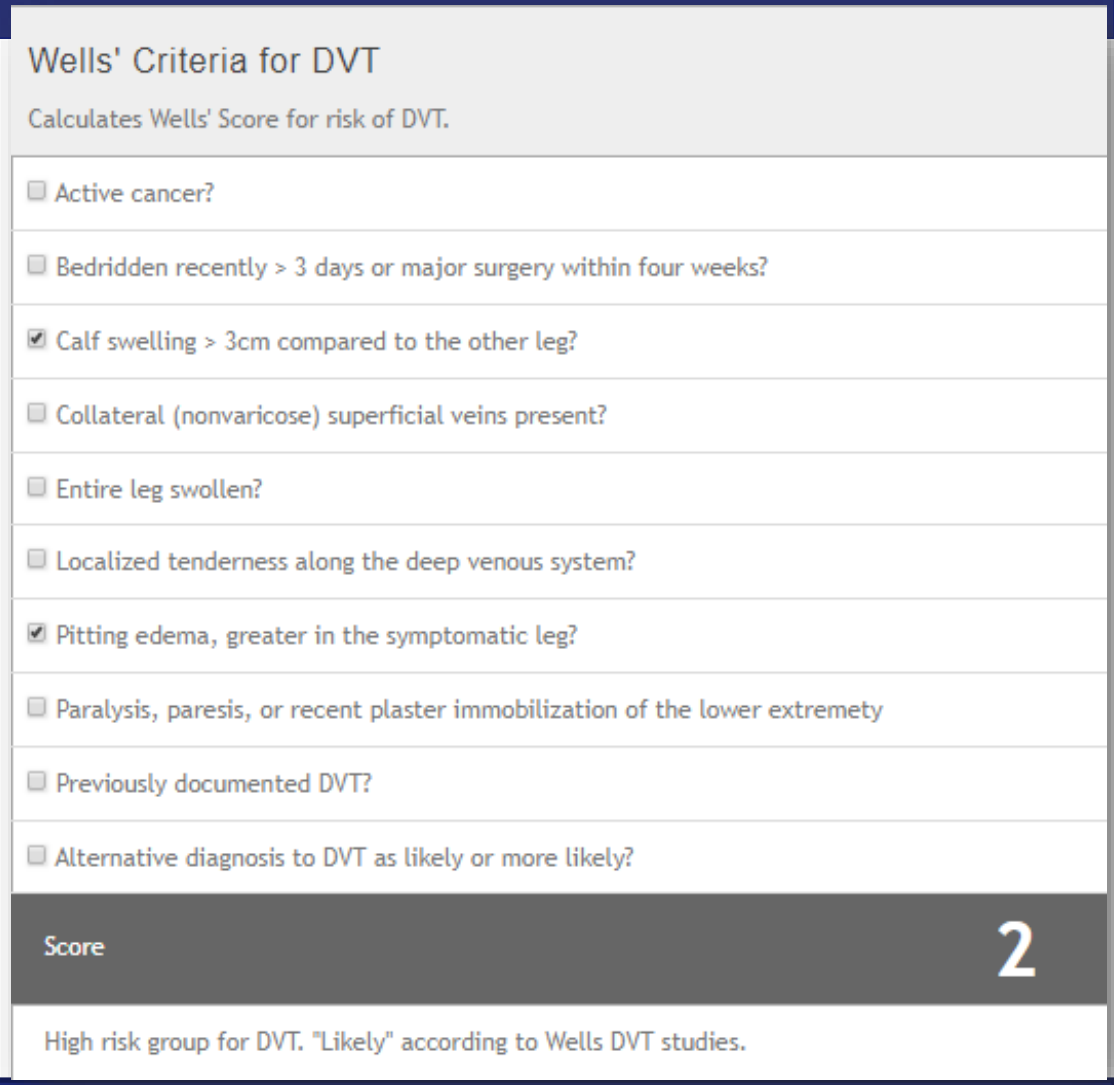
Case vignette #1: suspected or confirmed DVT

- 55-year-old female patient calls about 3-day history of progressive left leg pain. She describes:
  - Unilateral L lower leg pain, redness, swelling from knee to mid-foot “pits” with local pressure
  - No systemic symptoms
  - No chest pain or shortness of breath
  - No clear provoking factors, but has been much less active due to self isolation “spending lots of time in bed”
  - No history of local trauma
- Relevant PMH: obesity, T2DM, mild hypertension, no previous thrombosis
- Last bloodwork (CBC, creatinine) done 9 months ago within normal limits
- Assessed by telehealth…

Q1: *Is it safe to initiate empiric anticoagulant therapy by telehealth*?



Case vignette #1: suspected or confirmed DVT

Actions

- Rx for DOAC is faxed to local pharmacy
  - Apixaban 10 mg bid x 7 days followed by 5 mg bid

  OR
  - Rivaroxaban 15 mg bid x 3 weeks followed by 20 mg OD
- Provided with an imaging requisition for duplex venous compression US
- Provided with a lab requisition for hematology, renal function and biochemistry
- Provided with patient information sheet on DVT, and prescribed DOAC

Patient Information Sheet

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You Have a DVT
Deep Vein Thrombosis

What is a DVT?
A DVT is a blood clot in the deep vein of the leg.

Why are DVTs important?
They can cause short term and long term pain and swelling in the leg. They can move to the lung (pulmonary embolism = PE) and these may cause death.

What can cause a DVT?
Immobility
- Being in bed for a few days or more
- Cast on the leg, not able to stand or walk
- Air travel for 6 or more hours

Injury to blood vessels
- Broken bones, accidents
- Major surgery

"Hypercoagulability" (tendency to clot)
- Medical conditions (such as cancer)
- Hormones (estrogen, pregnancy)
- Genetic risk factors/family history of DVT/PE

Ask your doctor about other risk factors.

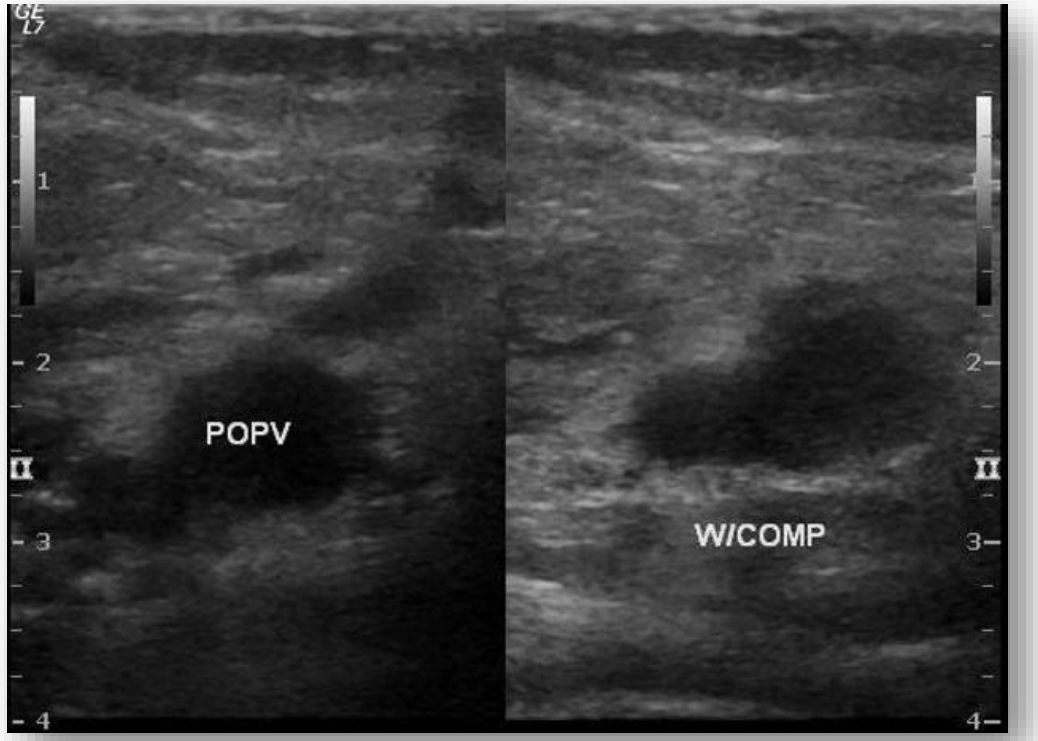
Treatment
- DVT is treated with anticoagulants ("blood thinners")
- Usually pills, but you may start on injections first
- How long you are on treatment will depend on your risk of having another blood clot and your risk of bleeding, but is usually at least 3 months
- Treatment is sometimes long term
- Main side effect is bleeding:
  - Minor (nose/gum bleeds, bruising)
  - Major (coughing blood, blood in vomit, urine or stool, black stool)

What are symptoms of DVT?
- Swelling - usually of one leg
- Pain in the calf, inner thigh or groin
- Redness and warmth of the affected leg
- Rarely (with severe swelling) the leg may:
  - Be cold, have purple/blue discoloration
- Be aware of symptoms of PE:
  - Shortness of breath
  - Chest pain

Take Away Message
- DVT is serious and can lead to life threatening complications
- Anticoagulant treatment should be taken regularly the way your doctor tells you
- Tell your doctor if you have new symptoms of a blood clot or major bleeding

Case vignette #1

- Sent to local vascular laboratory
- Venous US: new DVT in popliteal vein
- A second telehealth visit is arranged…



Q2: ***What do you recommend for treatment and follow-up*****?**

…also, when is it advisable to have an in-person visit**?**

Case vignette #1

What if…

- ***The venous US showed distal (calf) DVT*?**
- ***The venous US showed superficial vein thrombosis*?**

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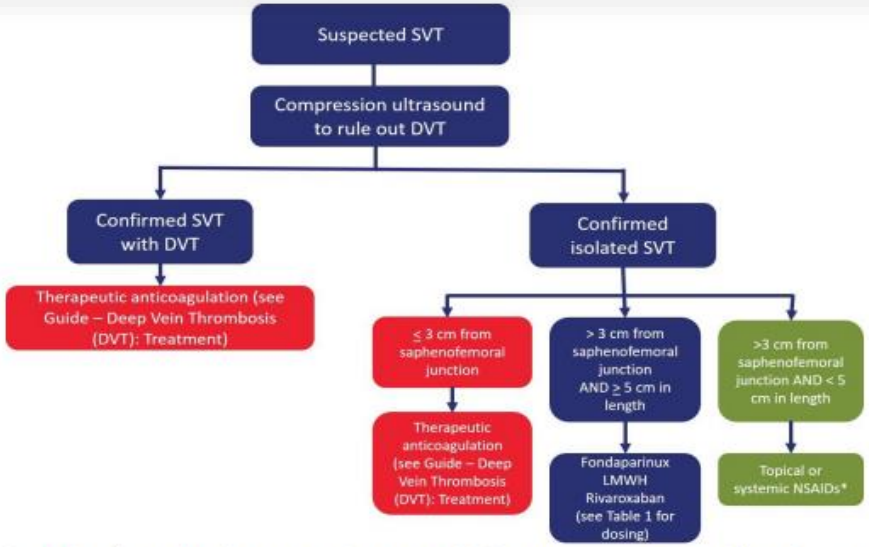


* Prophylactic/intermediate dosing anticoagulation is reasonable for severe symptoms or with risk factors. If not treating or if using topical NSAIDs, monitor for extension with serial U/S

DVT, deep vein thrombosis; **NSAID**, non-steroidal anti-inflammatory; **LMWH**, low molecular weight heparin

Table 1: Treatment Options for SVT >3cm from SFJ and ≥5 cm in Length

Drug Class	Suggested dosing	Duration of treatment
LMWH	Dalteparin 5,000-10,000 units SC daily Enoxaparin 40-80 mg SC daily Nadroparin 2,850-5,700 units SC daily Tinzaparin 4,500-10,000 units SC daily	45 days
Fondaparinux	2.5 mg SC daily	45 days
Rivaroxaban	10 mg PO daily	45 days
Oral NSAIDs	Ibuprofen 400 mg PO TID Naproxen 500 mg PO BID	7-14 days
Topical NSAIDs	Topical diclofenac [Voltaren Emugel®] apply 2 to 4 g to affected area 3 or 4 times daily	7-14 days

Case vignette #2: switching from VKA to DOAC

- Your 79-year-old patient has been receiving long-term treatment with warfarin for atrial fibrillation and you wish to eliminate her need to attend INR testing and transition her to a DOAC.

Q1: ***How do you do this with minimal laboratory involvement?***

Case vignette #2

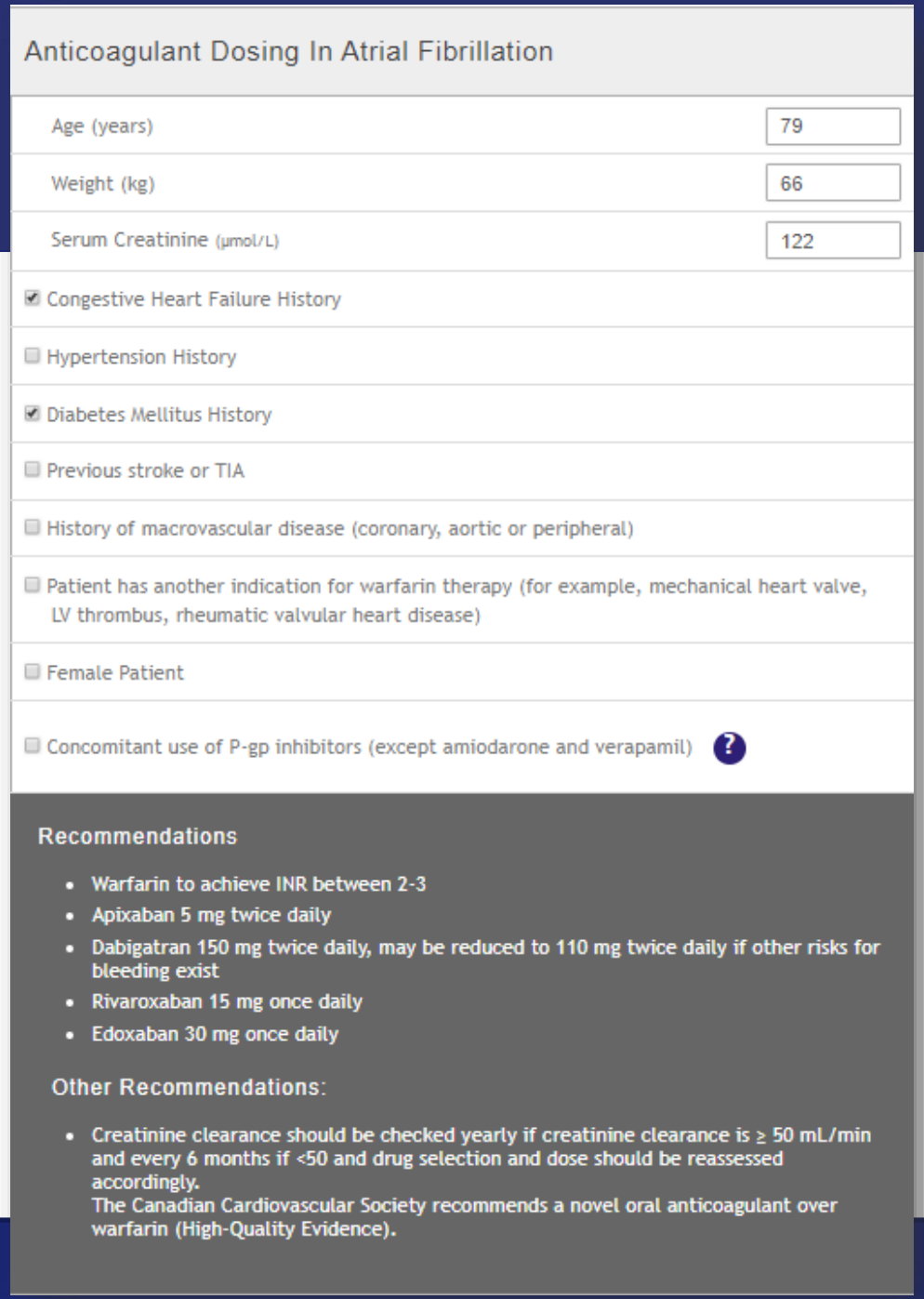
- **Step 1: obtain baseline INR (…after this no further INR tests)**
- **Step 2: advise patient to stop warfarin (…after today's dose)**
- **Step 3: initiate DOAC according to baseline INR**
  - **INR = 2.1-3.5:** *start the DOAC on day +4 (e.g., if last warfarin dose on Monday, start DOAC on Friday)*
  - **INR ≤2.0:** *start DOAC immediately (same day)*
  - **INR 3.5-4.5:** *start DOAC on day +5*
  - **INR >4.5:** *re-check INR on day +5, and start DOAC if INR ≤2.0*

Case vignette #2

DOAC options:

- **Twice-daily**
  - **Apixaban, 2.5-5.0 mg**
  - **Dabigatran, 110-150 mg**
  - **Rivaroxaban, 2.5 mg (PAD or chronic CAD)**

- **Once-daily**
  - **Edoxaban, 30-60 mg**
  - **Rivaroxaban, 15-20 mg (10 mg for VTE)**

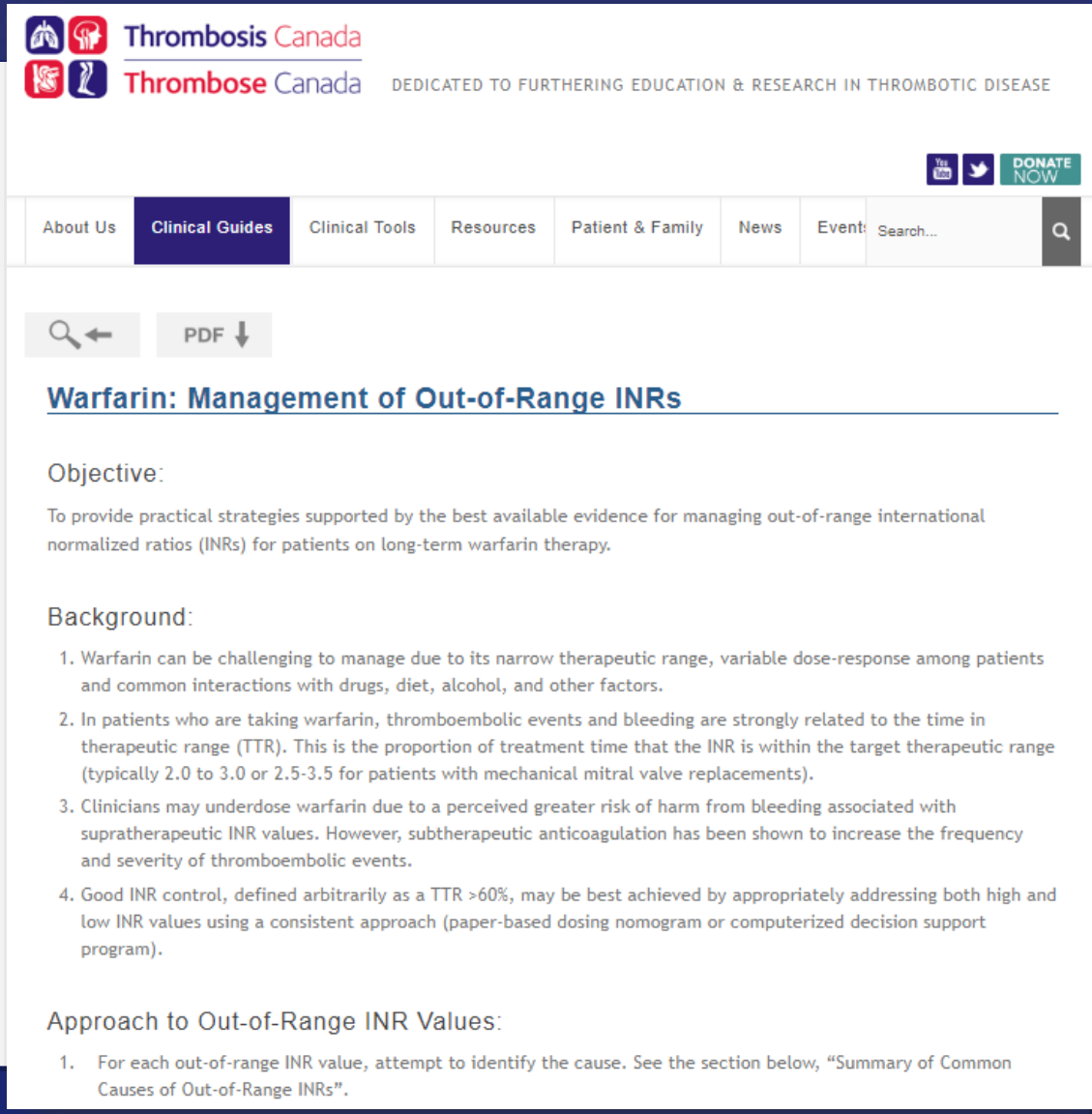


Case vignette #3: anticoagulant-related bleeding

- 60-year-old male on long-term warfarin for a mechanical aortic valve (INR range: 2.5-3.5) calls your office because of “nose bleeds” x 3 weeks. He is worried about going to the ER. He is not taking ASA or NSAIDs.
  - Bleeding intermittently L or R naris
  - Occurring 3-4/week lasting ~ 20 - 60 min and resolves with pressure
  - No other visible bleeding or bruising
- He has lab testing done: Hgb = 115 hypo/micro (N: 125-140); INR = 3.7

Q1: *What do you recommend for warfarin dosing and INR monitoring*?

Q2: *When and how would you give vitamin K*?



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Warfarin: Management of Out-of-Range INRs

Objective:

To provide practical strategies supported by the best available evidence for managing out-of-range international normalized ratios (INRs) for patients on long-term warfarin therapy.

Background:

1. Warfarin can be challenging to manage due to its narrow therapeutic range, variable dose-response among patients and common interactions with drugs, diet, alcohol, and other factors.
2. In patients who are taking warfarin, thromboembolic events and bleeding are strongly related to the time in therapeutic range (TTR). This is the proportion of treatment time that the INR is within the target therapeutic range (typically 2.0 to 3.0 or 2.5-3.5 for patients with mechanical mitral valve replacements).
3. Clinicians may underdose warfarin due to a perceived greater risk of harm from bleeding associated with supratherapeutic INR values. However, subtherapeutic anticoagulation has been shown to increase the frequency and severity of thromboembolic events.
4. Good INR control, defined arbitrarily as a TTR >60%, may be best achieved by appropriately addressing both high and low INR values using a consistent approach (paper-based dosing nomogram or computerized decision support program).

Approach to Out-of-Range INR Values:

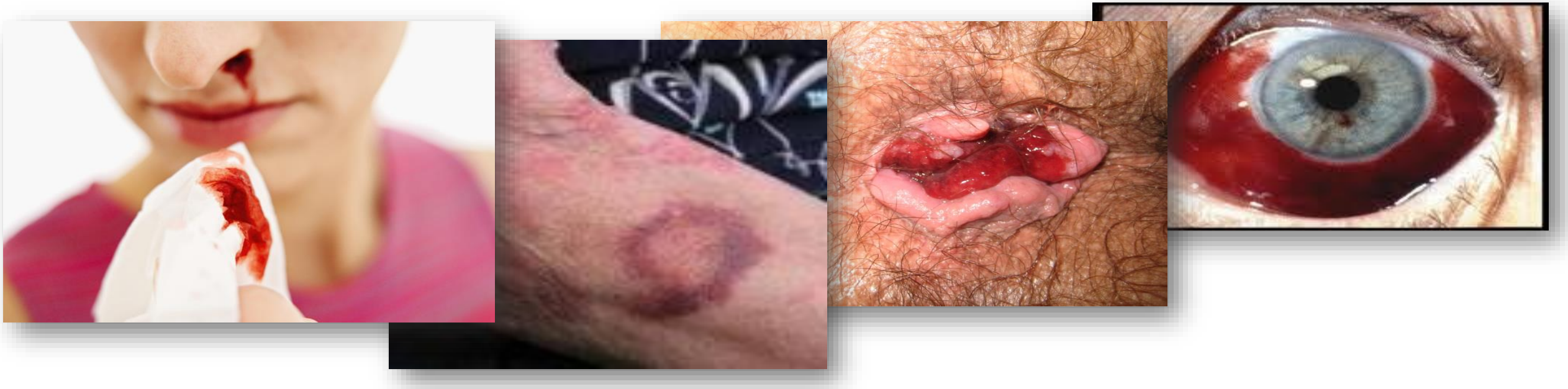
1. For each out-of-range INR value, attempt to identify the cause. See the section below, “Summary of Common Causes of Out-of-Range INRs”.

Anticoagulation and minor bleeding

- What easy things can you do to reduce patients' bleeding risk while on warfarin or a DOAC?
  - Need for ASA? (…what about NSAIDs?)
  - Switch from warfarin to a DOAC?
  - When can a low-dose DOAC be used?
    - Apixaban, 2.5 mg twice-daily
    - Edoxaban, 30 mg daily
    - Rivaroxaban, 10-15 mg daily

Case vignette #3

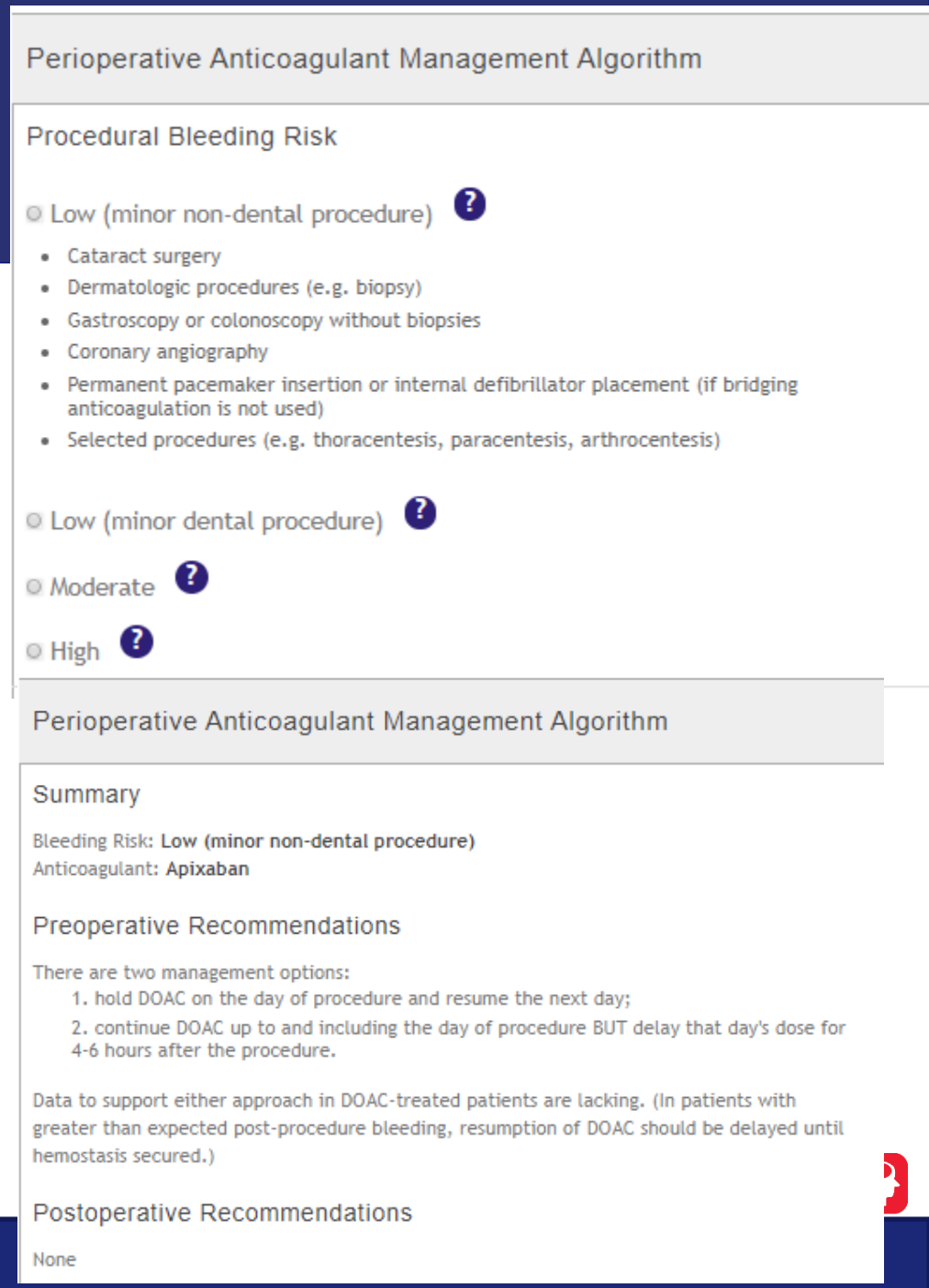
What types of bleeds should NOT concern you?



Case vignette #4: peri-op anticoagulant management

- Your 74-year-old patient with AF CHAD2 score 4 on DOAC has a flare of inflammatory osteoarthritis involving his L knee x 2 weeks.
- He is having difficulty with ADL
- You are avoiding NSAID and acetaminophen is not helping
- He has benefited from intra-articular steroid in past and is asking if you can inject his knee again
- You agree to an in office visit for IA steroid

How should his anticoagulant be managed?



Case vignette #5: frequency of INR monitoring

- 57-year-old female with mechanical mitral valve implanted 6 months ago taking warfarin (INR range: 2.5-3.5) and baby ASA has INR testing done every 2-3 weeks and good INR control (TTR >70%).

***Can the frequency of INR testing be safely reduced*?**

Managing anticoagulants, especially VKAs, remotely: hematologist perspective

Lana Castellucci, MD, FRCPC
Slides courtesy of Sudeep Shivakumar, MD, FRCPC

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Managing anticoagulants, especially VKAs, remotely

- Warfarin management requires frequent bloodwork for INR monitoring
- Many patients worried about risk of getting bloodwork
  - Requires trip outside the house
  - Concerns about waiting for tests in areas with large amounts of people
- Has to be balanced against risk of being on warfarin without monitoring
  - Bleeding and thrombosis risks
  - However, risk of thrombosis when off anticoagulation for days in atrial fibrillation is low according to perioperative studies

Ways to mitigate frequent bloodwork

- Less frequent INR draws
  - For patients that are on stable doses of warfarin with therapeutic INR, can extend INR frequency to every 8-12 weeks (instead of monthly or more frequent)
  - May be appropriate for patients with lower thrombotic risk
    - DVT/PE over 1-3 months old
    - Atrial fibrillation with low CHADS score
    - Low risk mechanical aortic valves

Ways to mitigate frequent bloodwork

- Less frequent INR draws
  - Some labs across Canada are using time-tickets to minimize patient exposures
    - Patients wait in car until time for their test
    - Quebec has CLSCs (community health centres) to expedite process

Ways to mitigate frequent bloodwork

- Use of alternate ways of monitoring INR
  - Some pharmacies have point of care machines
    - Provinces may have programs where a pharmacist can check INR and adjust dose
  - Point of care machines can be purchased by patients
    - Machines may be a few hundred dollars, but test strips can be $$$
    - Not covered so may only be appropriate for select patients

Ways to mitigate frequent bloodwork

- Switching to direct oral anticoagulant (DOAC)
  - DOACs are approved for the management of DVT/PE and stroke prevention in atrial fibrillation
  - No routine lab monitoring needed
  - Rivaroxaban and apixaban do not require LMWH run-in for acute DVT/PE
  - Provincial pharmacare programs may make exceptions for coverage during this time
    - Nova Scotia, British Columbia and Alberta are approving DOACs if COVID-19 is used as justification

Managing warfarin and DOACs remotely

- Risk of bleeding is <2% per year
- Can check in on patients by phone
  - Ask about bleeding complications, compliance, side effects
  - Be aware of drug-drug interactions, especially with new meds
- High INRs on warfarin can often be managed by holding warfarin alone if INR<10 and no bleeding

Questions

Alan Bell, moderator

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