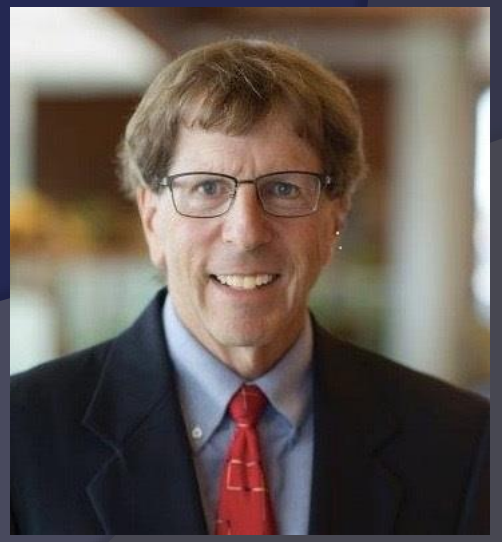
Cases from the Anticoagulation Consult Service

Scott Litin MD MACP

scott.litin@mayo.edu



Nothing to disclose

Objectives

- Superficial Thrombosis Management
- Deep Vein Thrombosis Management
- Using Heparin and Warfarin
- Using DOACs Appropriately
- Calf Vein Thrombosis
- Periprocedural Management of ACs
- Cancer and VTE

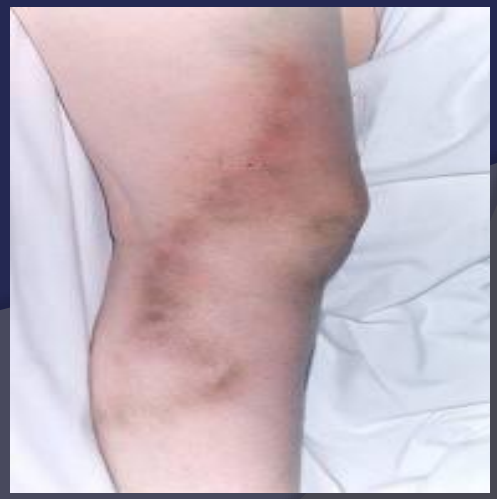
Case 66 yr old woman

- 66 yr old woman presents with 4 day history of right inner thigh and calf tenderness. She denies fever, chills, recent trauma, surgery or travel.

Case 66 yr old woman

PE: BP 138/86, P 78, R 12, BMI 42

- Pt is a 66 year old, obese, white, female
- Right lower extremity warm and tender beginning below the knee to mid thigh along the GS Vein, area red, +1 edema.



Case 66 yr old woman additional testing?

1. d – Dimer
2. MRI abdomen and chest
3. No additional testing; Rx NSAIDs and local care
4. US lower extremity
5. WBC count and CRP

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3. No additional testing; Rx NSAIDs and local care
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ARTICLE | Annals of Internal Medicine

Superficial Venous Thrombosis and Venous Thromboembolism

A Large, Prospective Epidemiologic Study

Hervé Decousus, MD; Isabelle Quéré, MD; Emilie Presles, MD; François Becker, MD; Marie-Thérèse Barrellier, MD; Myriam Chanut, MD; Jean-Luc Gillet, MD; Hervé Guenneguez, MD; Christine Leandri, MD; Patrick Mismetti, MD, PhD; Olivier Pichot, MD; and Alain Leizorovicz, MD, for the POST (Prospective Observational Superficial Thrombophlebitis) Study Group*

Decousus H et al, Ann Intern Med 2010;152:218-224

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- 25% SVT Patients had DVT at time of diagnosis
- 10% SVT Patients had thrombo complications in 3 months following diagnosis
- SVT may not be a benign disease

Decousus H et al, Ann Intern Med 2010;152:218-224

ACCP Guidelines 2012 and 2016

- 8.1.1 Superficial Venous Thrombosis
  - SVT of at least 5 cm **
  - US to rule out DVT
  - Prophylactic SC Doses for 45 days
    - Fondaparinux 2.5 mg, Qday
    - Enoxaparin 40 mg, Qday
    - Dalteparin 5,000 IU, Qday

Kearon C, et al, Chest 2012;141:419S-494S

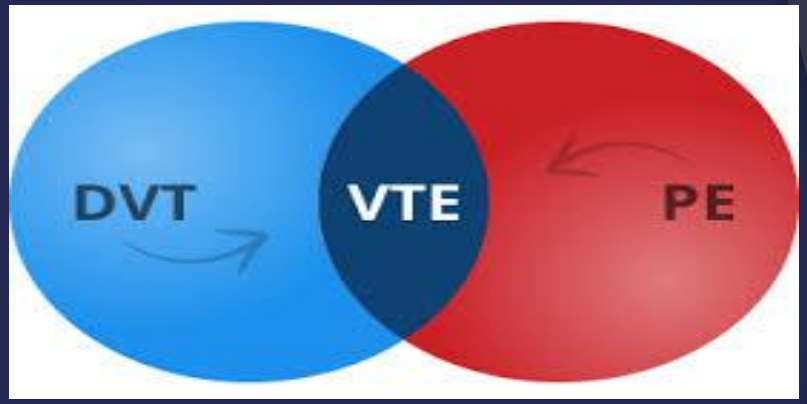
Surprise Trial

- *Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux*

- Rivaroxaban 10 mg daily for 45 days vs fondaparinux 2.5 mg daily for 45 days
- End points 3% vs 2% respectively ; non-inferior

The Lancet Heme; Vol 4, No 3, e105–e113, March 2016 2017

Venous Thromboembolism Cases



Importance

- Deaths due to complications of DVT each year greater than……
- deaths from HIV, breast cancer, and motor vehicle accidents combined

Case of a 61 y/o woman

- 61 yr. old woman was seen in the ED complaining of left calf pain 4 days after flight from Europe to Los Angeles
- Lower extremity US reveals a left distal femoral, popliteal, and posterior tibial thrombosis. The patient has normal CBC, LFTs, and creatinine.
- She is admitted for treatment and discharge planning.

Case of a 61 y/o woman

Should you initially start her on one of the direct oral anticoagulants (DOACs)?

1. Yes
2. No (start heparin initially)

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Oral Direct Factor Inhibitors

Advantages:

- Few drug interactions
- No food interactions
- No monitoring
- No continuous dose adjustments
- Safety

SAFETY vs Warfarin:
Major Bleeding

Superior

Apixaban (ARISTOTLE)

5 mg HR 0.69 (0.6 – 0.8)

Edoxaban (ENGAGE AF)

30 mg HR 0.47 (0.41 – 0.55)

60 mg HR 0.80 (0.71 – 0.91)

SAFETY vs Warfarin:
Intracranial bleeding

All DOACs were *Superior*

Dabigatran	0.3%
Rivaroxaban	0.8%
Apixaban	0.3%
Edoxaban	0.4%
Warfarin	0.8% - 1.2%

2016 ACCP Guidelines

- For VTE and no cancer, as long-term anticoagulant therapy, we suggest dabigatran (Grade 2B), rivaroxaban (Grade 2B), apixaban (Grade 2B), or edoxaban (Grade 2B) over vitamin K antagonist (VKA) therapy

CHEST 2016; 149(2):315-352

Direct Oral Anticoagulants

Currently Approved Therapeutic Indications

DRUG	INDICATIONS
Dabigatran	Atrial fibrillation, DVT and PE
Rivaroxaban	Atrial fibrillation, DVT and PE
Apixaban	Atrial fibrillation, DVT and PE
Edoxaban	Atrial fibrillation, DVT and PE

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Apixaban	Atrial fibrillation, DVT and PE
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61 year old woman with DVT

Which anticoagulant strategy is FDA approved for initial treatment?

1. Dabigatran 150 mg twice daily
2. Apixaban 10 mg BID for 7 days followed by 5 mg BID.
3. Enoxaparin 1.5 mg/kg for 7 days then apixaban 5 mg BID
4. Rivaroxaban 15 mg twice daily for 7 days then 20 mg daily
5. Edoxaban 60 mg once daily

61 year old woman with DVT

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Studies of Direct ACs in VTE Therapy

Dose in Normal Renal Function

Drug	Dosage
Dabigatran	Recover Study 150 mg b.i.d *(after 5 – 10 days heparin)*
Rivaroxaban	Einstein Study 15 mg b.i.d for 3 weeks, then 20 mg daily
Apixaban*	Amplify study 10 mg b.i.d for 7 days, then 5 mg b.i.d
Edoxaban*	Hokusai Study 60 mg daily *(after 5 – 10 days heparin)*

* Non-inferiority recurrence rates with possibly decreased bleeding*

Preventing Future DVT

After appropriate treatment for at least 3 months

- Stop A/Cs with observation

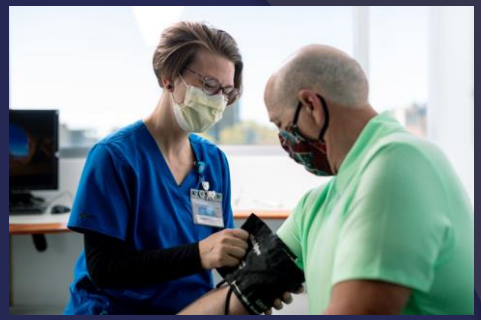
- Continue DOAC at lower dose

  Rivaroxaban 10 mg. daily (Einstein Choice)

  Apixaban 2.5 mg. twice daily (Amplify Extend)

Risk recurrence after unprovoked at 1 year: 7-10% no treatment; 1-2% AC treatment

Case of a 81 y/o man



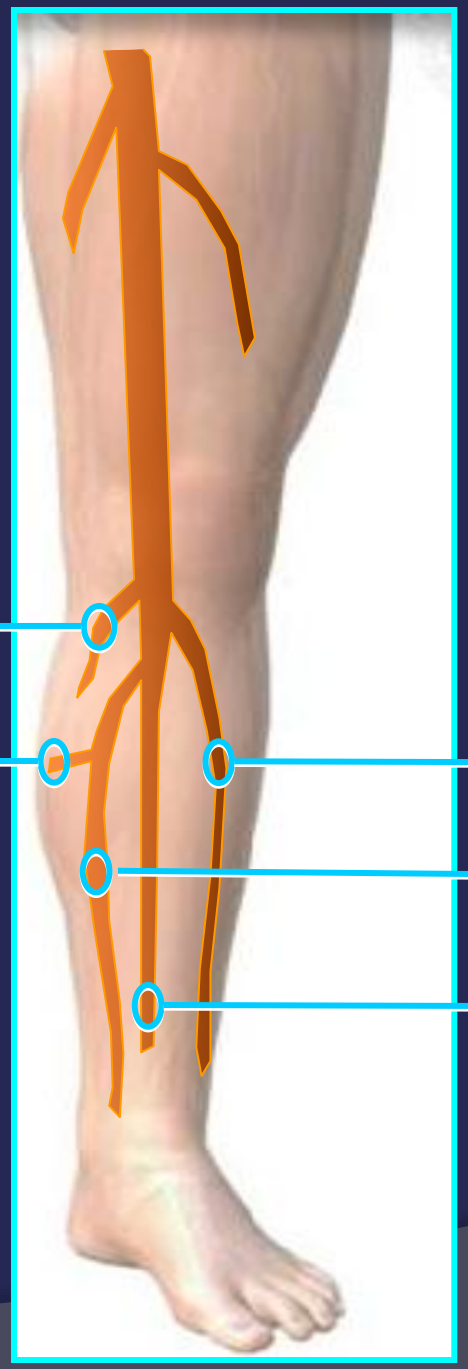
- 81 yr. old man was seen clinic after bumping his left lower leg on a coffee table. There was a small wound and swelling in the calf.
- In urgent care an ultrasound was performed because of the swelling.
- US revealed a short segment 3 cm. acute appearing thrombus in the left posterior tibial vein.

Deep Veins of the Calf

Muscular

Gastrocnemius

Soleal



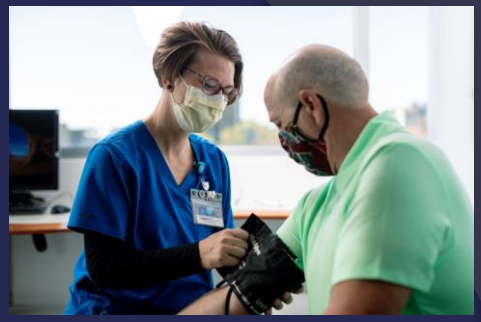
Axial

Anterior Tibial

Posterior Tibial

Peroneal

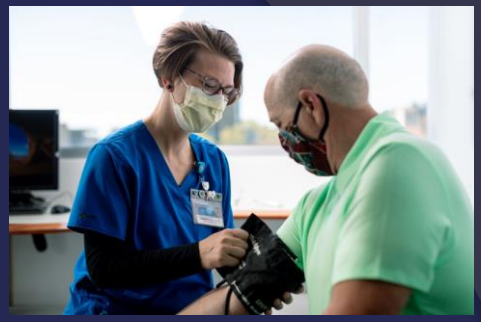
Case of a 81 y/o man



What to do now

1. Anticoagulate for 3 months with a DOAC
2. Anticoagulate for 6 weeks with a DOAC
3. Follow up with serial US exams
4. LMWH for 6 weeks

Case of a 81 y/o man



What to do now

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2. Anticoagulate for 6 weeks with a DOAC
3. Follow up with serial US exams
4. LMWH for 6 weeks

ACCP Guidelines 2016: Acute Calf DVT

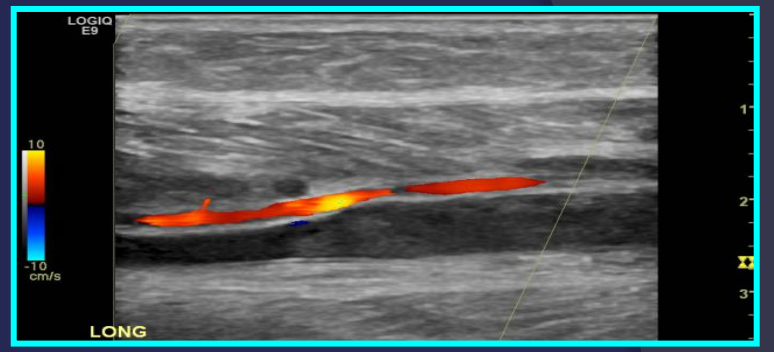
- If symptoms not severe and no risk factors for extension, *suggest serial US imaging* for 2 weeks over anticoagulation (Grade 2C).

- With severe symptoms or risk factors for extension, *suggest anticoagulation* over serial imaging of the deep veins (Grade 2C).

Calf vs. Proximal DVT

Less likely to:

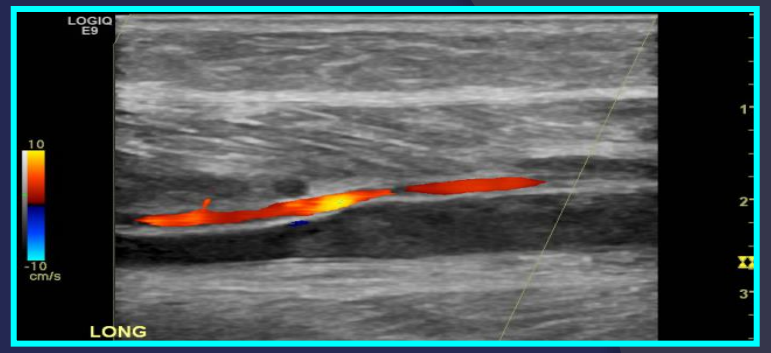
- Propagate
- Cause PE
- Recur
- Post-thrombotic syndrome



ACCP Guidelines 2016

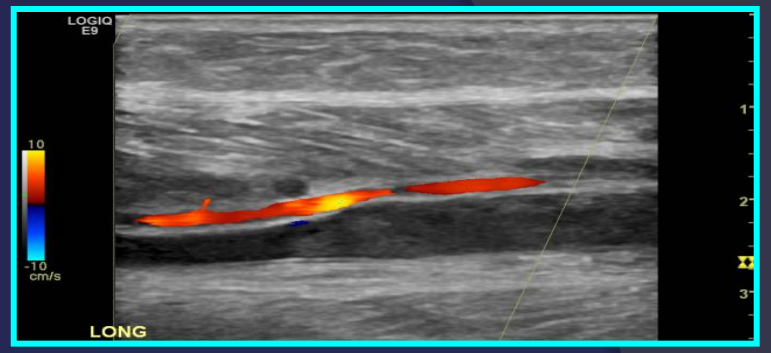
Calf DVT: Summary

- Individualize
- Severe symptoms, treat (2C).
- Risk factors, treat (2C).
- Thrombus propagation, treat (1B).
- Treatment duration = 3 months (1B).



ACCP Guidelines 2016

Calf DVT: Summary



- If mild symptoms and
  no risk factors for extension,
  repeat US weekly x 2 (2C).
- If no extension, then no treatment (1B)
- High risk for bleeding favors ultrasound surveillance over anticoagulation.

ACCP Guidelines 2016

Case of a 76-year-old woman

A 76-year-old woman undergoes ablation for symptomatic PAF. Six months later asymptomatic from AF. Past history hypertension and moderate mitral regurgitation.

She is currently treated with metoprolol and apixaban. She notes easy bruising but no major bleeding.

She inquires if she can stop anticoagulation.

What do you recommend regarding anticoagulation?

1. Transition apixaban to warfarin.
2. Discontinue apixaban and transition to aspirin.
3. Continue apixaban.
4. Obtain a 30-day rhythm monitor. If no atrial fibrillation then discontinue apixaban and start aspirin.

What do you recommend regarding anticoagulation?

1. Transition apixaban to warfarin.
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Valvular Atrial Fibrillation

Defined

- Mechanical valve – in any location
- Rheumatic mitral valve stenosis

DOACs Should Not Be Used!

2014 AHA/ ACC Guideline for AF. JACC. Vol. 64, No. 21, 2014; 2019 ACC / AHA update

What is NOT Valvular Atrial Fibrillation

- Mitral regurgitation
- Aortic stenosis and regurgitation
- Tricuspid regurgitation

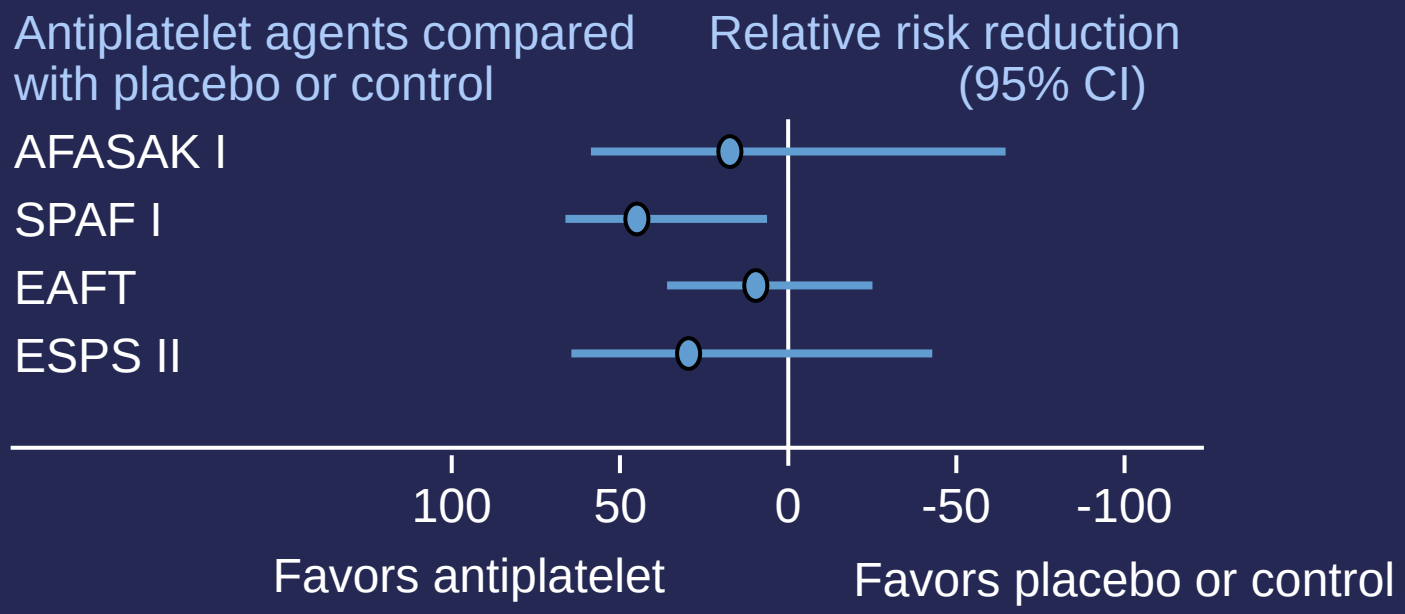
* TAVI: No data on DOAC use

Rhythm Control and Anticoagulation?

Continue CHA_2DS_2-VASc based stroke prophylaxis

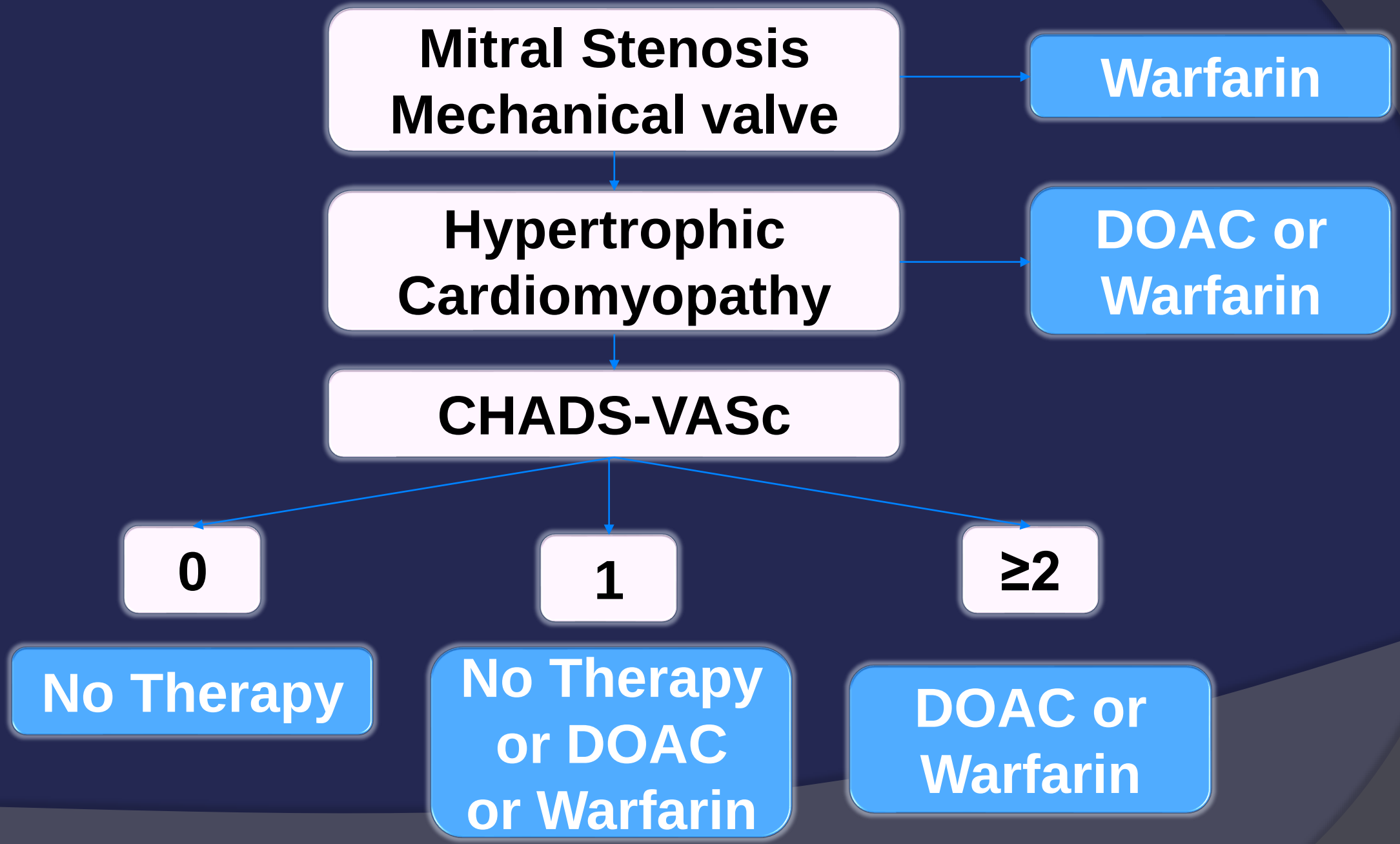
Regardless of antiarrhythmic drug or ablation

Aspirin for Stroke Prevention?



ACC/AHA, ESC, and Chest guidelines <u>DO NOT</u> Recommend ASA for Stroke Prevention

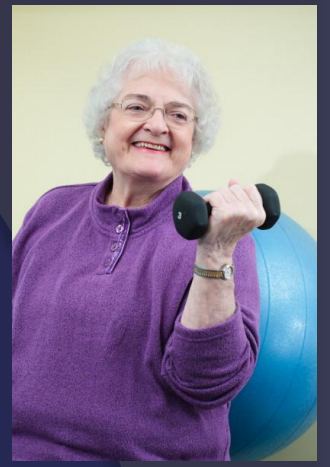
Hart et al: Ann Intern Med 146:857, 2007


Mitral Stenosis
Mechanical valve
Warfarin
Hypertrophic
Cardiomyopathy
DOAC or
Warfarin
CHADS-VASc
0
1
≥2
No Therapy
No Therapy
or DOAC
or Warfarin
DOAC or
Warfarin

Clinical Pearls

- A rhythm control strategy does not impact stroke prophylaxis recommendations.
- Warfarin is the preferred oral anticoagulant for valvular atrial fibrillation.

Case of a 78 y/o woman

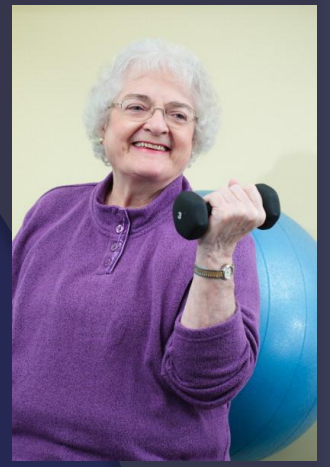


- 78 year old woman taking warfarin due to atrial fibrillation.
  She has treated high BP, but no hx of stroke, or CHF. ***$CHADS_2$-is 3***
  $CHADS_2VASC$- is 5
  She has a renal mass and is scheduled for a partial left nephrectomy.

  Would you bridge this patient
  with heparin therapy?

1. Yes
2. No

Case of a 78 y/o woman



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The $CHADS_2$ Score: Risk of Stroke in Atrial Fibrillation Without Anticoagulation

- *One point each*
  - CHF
  - HTN
  - Age > 75
  - DM
- *Two points*
  - Stroke

Score	*N*	*Adjusted Stroke Rate* (per 100 patient-years)
0	120	1.9
1	463	2.8
2	523	4.0
3	337	5.9
4	220	8.5
5	65	12.5
6	5	18.2

Gage et al, JAMA. 2001;285:2864-2870

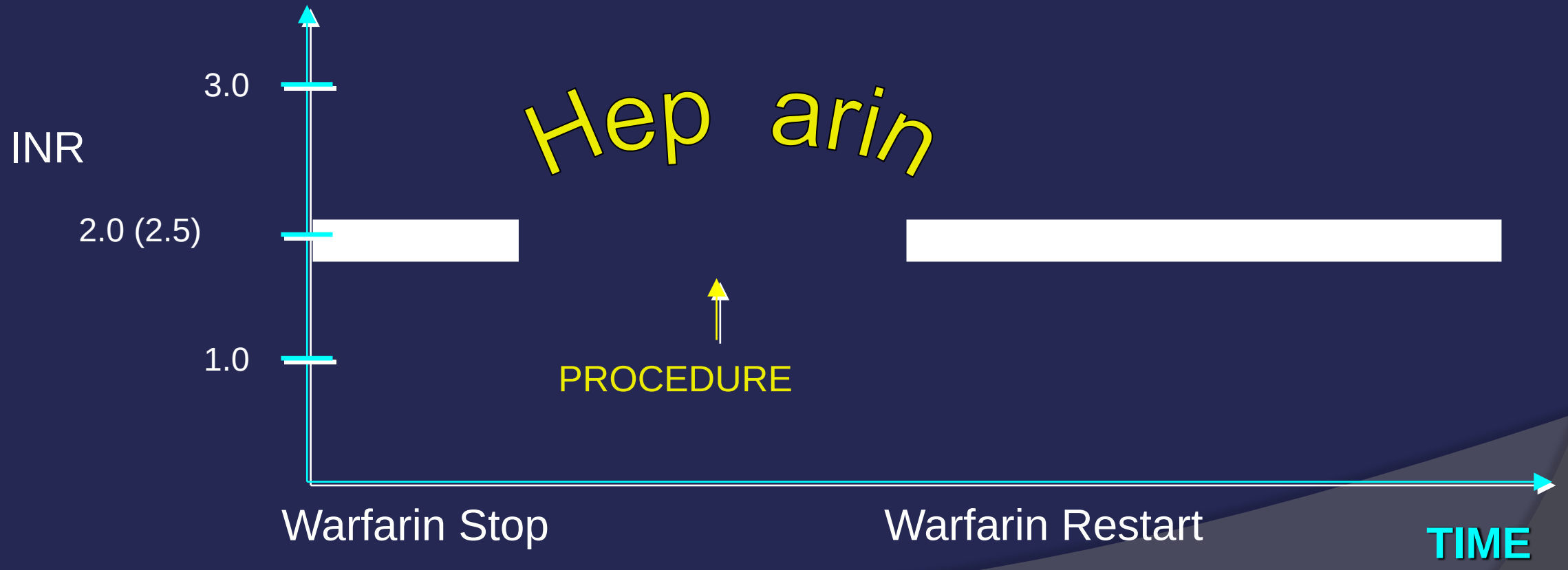
Risk factors		
C	Congestive Heart Failure	+1 point
H	Hypertension	+1 point
A_2	Age ≥75	+2 point
D	Diabetes	+1 point
S_2	Stroke/TIA History	+2 point
V	Vascular Disease	+1 point
A	Age 65-74	+1 point
S	Sex (Female)	+1 point

Stroke risk per year	
SCORE	% RATE PER YEAR
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

Reference: European Heart Rhythm Association. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J.* 2010;31(19):2369-2429.

Bridging Therapy

Heparin substitution during warfarin interruption



Goals of Bridging Therapy

- Minimize ***thromboembolism*** during warfarin interruption.
- Minimize ***bleeding***.
- Minimize ***inconvenience***.
- Minimize ***economic*** burden.

Approach to Bridging Therapy: Three Key Questions

1. Need to stop anticoagulation?
2. Need bridging therapy?
3. How and when to restart anticoagulation after a procedure?

Need to Stop Warfarin?

- Some procedures can be done without stopping or with INR at low end of target range
  - Examples:
    - EMG, Cataract surgery, Dental surgery
- Avoid unnecessary stoppage

Dunn, AS. Arch Intern Med. 2003;163:901-908

Bridging LMWH *increases bleeding* but does *not reduce clotting*

- Meta-analysis
  - 7118 patients (AF, Valves, DVT/PE)

	Bridged	Not Bridged
Thromboembolism	0.9%	0.6%
Major bleeding	4.2%	0.9%

OR 3.6 (95%CI 1.52 – 8.50)

Circulation 2012;126:1630

Bridge Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

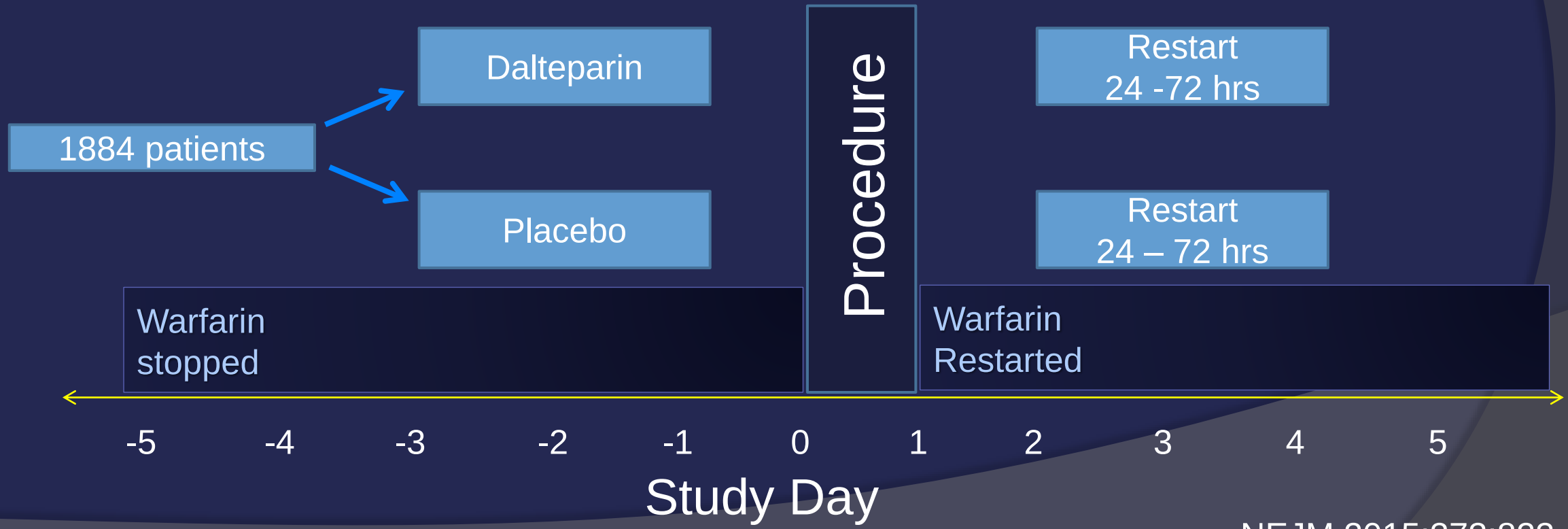
Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

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*

Published on line NEJM.org June 22, 2015 NEJM 373;9 August 27, 2015

Perioperative Bridging Anticoagulation in Atrial Fibrillation: Bridge Trial

- Inclusion: NVAF ≥ 1 risk factors on warfarin undergoing an invasive procedure



NEJM 2015;373:823

Perioperative Bridging Anticoagulation in Atrial Fibrillation: Bridge Trial

Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†

NEJM 2015;373:823
EJM 2015;373:823

BRIDGE TRIAL in NVAF:
Bottom Line

- Periprocedural ***thrombotic rates low*** (<1%).
- Bridging LMWH ***does not reduce*** this rate in ***low risk*** patients.
- Bridging LMWH ***increases major bleeding*** by 2%.

Bridge Trial Caveats

- $CHADS_2$ Score
  - Mean 2.3 ± 1.0
  - Only 3% had scores > 4
- Procedural Bleeding Risk
  - Relatively high

NEJM 2015;373:823

2017 ACC NVAF Bridging Guidance

Thromboembolic Risk

Low ($CHA_2DS_2Vasc \leq 4$, ***no prior stroke/TIA***)

- No Bridging

Moderate (CHA_2DS_2Vasc 5 or 6 or ***remote*** stroke/TIA*)

- If low bleeding risk — Bridge with heparin
- If high bleeding risk — No Bridging

High ($CHA_2DS_2Vasc \geq 7$ or ***recent*** stroke/TIA*)

- Bridge with heparin

*Stroke/TIA acuity divider: 3 months

J Am Coll Cardiol 2017;69:871

Seems complicated!

Can this be simplified?

Bridging Therapy for NVAF: Our take!

Low Risk

- ***No prior*** stroke/TIA, embolism or intracardiac thrombus
- No Bridging

High Risk

- ***Prior*** stroke/TIA, embolism or intracardiac thrombus
- Bridging

Neither ***CHA_2DS_2Vasc*** nor ***stroke acuity*** have been validated for periprocedural management.

If Bridging LMWH is indicated, ***how*** do you do this?

Non-valvular Atrial Fibrillation

1. 5 days prior, stop warfarin, check INR, CBC, and creatinine*
2. Begin LMWH pre-op when INR < 2.0
   - Typically @ 3 days prior
   - Enoxaparin 1 mg/kg every 12 hr
   - Last dose 24 h prior to surgery
3. Check INR on morning of procedure
4. Restart warfarin immediately post op
5. ***Do not restart therapeutic heparin for at least 48 hr*** and until hemostasis is achieved.

What about other AC Indications?

Mechanical Heart Valves Our take

Low risk

- Bileaflet aortic prosthesis
- Sinus rhythm
- No history of stroke/TIA or embolism
- No Bridging indicated

High risk

- Everything else; Bridging therapy indicated

Bottom Line

Patients with Mechanical Heart Valves should never receive DOACs

What about other AC Indications?

Venous Thromboembolism Our take

Low risk

- Remote thrombus ***more than*** 3 months ago

High risk

- Recent thrombus ***less than*** 3 months
- Cancer
- Severe thrombophilia

Peri-procedural management of novel oral anticoagulants

Not discussed in Chest Antithrombotic Guidelines

For DOAC therapy, very simple!

Dabigatran
(Pradaxa)

Rivaroxaban
(Xarelto)

Apixaban
(Eliquis)

Edoxaban
(Savaysa)

PAUSE TRIAL

The Perioperative Anticoagulation Use for Surgery Evaluation

JAMA Internal Med: Published online August 5, 2019.

PAUSE TRIAL

PARTICIPANTS

3007 long-term users of apixaban, dabigatran, or rivaroxaban; were scheduled for an elective surgery

or procedure; and could adhere to the DOAC therapy interruption protocol enrolled

JAMA Internal Med: Published online August 5, 2019.

PAUSE TRIAL

INTERVENTION

The DOAC stopped 1 day before a low–bleeding-risk procedure and 2 days before a high–bleeding-risk procedure.

The DOAC regimens were resumed 1 day after a low–bleeding-risk procedure and 2 to 3 days after a high–bleeding-risk procedure.

Follow-up of patients occurred for 30 days after the operation.

JAMA Internal Med: Published online August 5, 2019.

PAUSE TRIAL

OUTCOMES

Major bleeding and arterial thromboembolism (ischemic stroke, systemic embolism, and transient ischemic attack)

JAMA Internal Med: Published online August 5, 2019.

PAUSE TRIAL

RESULTS

Major bleeding 0.9% - 1.8%

Systemic emboli 0.16% – 0.60%

JAMA Internal Med: Published online August 5, 2019.

PAUSE TRIAL

CONCLUSIONS

In this study, patients with AF who had DOAC therapy interruption, a perioperative management strategy without heparin bridging or coag testing was associated with low rates of major bleeding and arterial thromboembolism.

JAMA Internal Med: Published online August 5, 2019.

Case of a 79-year-old man

Patient with non small cell cancer of the lung is diagnosed with a left femoral DVT during chemotherapy.

What would you suggest for the first 6-months of anticoagulation for this cancer pt

1. Enoxaparin 1 mg/kg twice daily for 6 months
2. LMWH Dalteparin 200 units/kg daily for 1 month and then 150 units/kg daily for remaining months
3. Treatment dose LMWH for 5 days overlapped with warfarin for the remaining months
4. Prophylactic dose DOAC for 6 months
5. Treatment dose DOAC for 6 months

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VTE in the patient cancer patient

- Cancer patients have a 4 to 7-fold increased risk of VTE
- Rx challenging; cancer patients have higher risk of recurrent VTE and major bleeding
- SQ LMWH has been the suggested therapy in guidelines but < 50% adhere to long term Rx
- DOACs preferred for VTE in non cancer pts, but in cancer pts guidelines still suggest LMWH

NEJM 378;7 nejm.org February 15, 2018; *Thrombosis Research 173 (2019) 158–163*

CANCER ASSOCIATED VTE: Summary

- One-fifth of all incident VTE is attributed to cancer
- One-fifth of all cancer develop VTE
- Cancer site, stage, duration and treatment are all associated with risk of incident and recurrent VTE
- VTE recurrence rates are high in cancer patients
- VTE adversely impacts overall survival

Four Important Trials

• HOKUSAI VTE Cancer	Edoxaban
• SELECT-D	Rivaroxaban
• ADAM VTE	Apixaban
• CARAVAGGIO	Apixaban

Summary: Compared to LMWH (Dalteparin)

Less recurrence DVT, NS difference bleeding or mortality

DOAC Therapy for Acute VTE

Guideline	Recommendation
ASCO	**YES** Initial treatment with LMWH followed by edoxaban, rivaroxaban
NCCN	**YES** Initial treatment with LMWH followed by edoxaban, rivaroxaban
ITAC	**YES** Initial treatment with LMWH, DOAC, unfractionated heparin or fondaparinux followed by LMWH or DOACs

DOACs vs LMWH for treatment of cancer associated thrombosis:

A systematic review and meta-analysis

Conclusions:

- DOACs better than LMWHs to prevent recurrent VTE but with a sl increased risk of major bleeding

- Subgroup analyses suggest DOACs may be at the highest risk for bleeding in pts with GI cancer

Thrombosis Research 173 (2019) 158–163

In Summary

- Superficial Thrombosis Management
- Deep Vein Thrombosis Management
- Using Heparin and Warfarin
- Using DOACs Appropriately
- Calf Vein Thrombosis
- Periprocedural Management of ACs
- Cancer and VTE

Cases from the Anticoagulation Consult Service

Scott Litin MD MACP

scott.litin@mayo.edu