ANTICOAG & THROMBOSIS CASES

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Disclosures
I have nothing to disclose

QUESTIONS

• Catheter related thrombosis-pull the line?
• Calf vein thrombosis-do we treat these?
• Thrombophilia work up-do we still do those?

QUESTIONS

• How do we treat this patient with recurrent VTE while ON anticoagulation?
• Does this patient need an IVC filter? Does ANY patient need an IVC filter
• Should this patient with AFIB/VTE/mechanical valve be bridged perioperatively and how?
CASE #1

A 55 year old woman being treated for osteomyelitis of the spine develops right upper extremity swelling. U/S reveals a DVT in the subclavian and axillary vein. She has a PICC line in that arm. She needs 4 more weeks of antibiotics. You start anticoagulation. Do you need to pull the line?

a. Yes
b. No

Take home points
 Treat thru if need line
 AC 1st prior to removal
 3 months duration of tx


Upper Extremity DVT

AC Forum
A similar approach may be considered for cancer patients

SCHOOL OF MEDICINE • UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
**CASE #2**

A 45 year old man presents with moderate calf pain and swelling for 5 days since he was kicked playing soccer. Ultrasound shows DVT in the posterior tibial vein. Does he need anticoagulation?

- a) Yes
- b) No

**NEW CHEST GUIDELINES**

In patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, we suggest serial imaging of the deep veins for 2 weeks over initial anticoagulation (Grade 2C).

Kearon et al CHEST 2012

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**ISOLATED DISTAL DVT**

**TREATMENT**

- **LOW RISK**
  - u/s 1-2 weeks and treat only if extends proximally

- **HIGH RISK**
  - treatment same as proximal DVT

**HIGH RISK**

- + d-dimer
- severe symptoms
- cancer
- VTE history
- no reversible provoking factor
- hospitalized
- near proximal veins
- > 5 cm long, mult veins, > 7 mm

**AC FORUM RECOMMENDS ANTICOAGULATING FOR DISTAL DVT UNLESS HIGH BLEED RISK**

Soleus and gastroc much lower risk than peroneal tibial veins. Consider serial imaging if high bleed risk.
**CASE #2**

A 45 year old man presents with moderate calf pain and swelling for 5 days since he was kicked playing soccer. Ultrasound shows DVT in the posterior tibial vein. Does he need anticoagulation?

a) Yes  
b) No

**Take home points**
- Calf vein thrombosis lower risk of PE
- Risk stratify for progression
- Consider treatment on case by case basis vs treat all

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**CASE #3**

A 68 year old woman falls and fractures her hip. She is in CHF on admission so OR time is delayed. On HD #3 she becomes acutely short of breath and is found to have PE and DVT. How do you manage her anticoagulation perioperatively?

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**IVC Filters**

<table>
<thead>
<tr>
<th>Filter</th>
<th>PE @ 12 days</th>
<th>DVT @ 2 years</th>
<th>PE @ 2 years</th>
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<tr>
<td>Filter</td>
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<td>20%</td>
<td>3.4%</td>
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<tr>
<td>No Filter</td>
<td>5%</td>
<td>11%</td>
<td>6.3%</td>
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</tbody>
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**PREPIC STUDY**

<table>
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<th>DVT @ 2 years</th>
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</tr>
<tr>
<td>No Filter</td>
<td>5%</td>
<td>11%</td>
</tr>
</tbody>
</table>

**PREPIC 8 yr FOLLOW UP**

<table>
<thead>
<tr>
<th>Filter</th>
<th>PE @ 12 years</th>
<th>DVT HR 1.52</th>
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</thead>
<tbody>
<tr>
<td>Filter</td>
<td>3.4%</td>
<td>3.4%</td>
</tr>
<tr>
<td>No Filter</td>
<td>6.3%</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

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**PREPIC 2 2015**

- PE HR 0.32
- DVT HR 1.52

No survival benefit

PREPIC STUDY GROUP: Circulation 2005; Decousus NEJM 1998
IVC Filters

- Most "retrievable" IVC filters are not removed, in real-world practice
- Filter complications are serious: fracture, embolization, thrombosis
- Should not be used in cases of anticoagulation failure
- Should not influence duration of AC
- Indicated if acute thrombosis and contraindication to AC

CASE # 3

A 68 year old woman falls and fractures her hip. She is in CHF on admission so OR time is delayed. On HD #3 she becomes acutely short of breath and is found to have PE and DVT. How do you manage her anticoagulation perioperatively?
**Take Home Points-IVC Filters**

- Retrievable IVC filters are not without complications-risk benefit should be assessed carefully in each case.
- Once placed prophylactic anticoagulation should be started as soon as possible.
- Make retrieval plans for device prior to DC so not inadvertently left in place.

**CASE #4**

A 33 year old woman diagnosed with left lower extremity DVT 3 months ago maintained on warfarin present with complaints of pleuritic chest and shortness of breath. A CT angio of the chest reveals new bilateral segmental pulmonary emboli.

**CASE #4**

She reports compliance with her warfarin therapy and has an INR of 2.5 at the time of admission. She is admitted to your service for recurrent VTE.

- How do you manage this?

**Case #5**

A 65 year old man with adeno CA of the lung on chronic dalteparin for cancer associated VTE that occurred 3 months ago develops SOB and chest pain and is found to have recurrent PE. He has not missed a dose of LMWH. What anticoagulation regimen do you recommend now?

- A) rivaroxaban
- B) warfarin with goal inr 3-4
- C) IVC filter
- D) Higher doses of dalteparin
**VTE Recurrence on Oral Anticoagulation**

1. **Is this a true recurrence?**
   - D-dimer
   - Review new + old images

**Treatment Factors**
- Within 1st month of therapy
- Adherence
- VKA sub therapeutic
- AC prescribed incorrectly
- On DOAC and problem med
- AC dose reduced

**Patient Factors**
- Is there cancer
- Is this APLS
- Is this HIT
- Is this antithrombin def
- Myeloproliferative d/o
- PNH
- Dysfibrinogenemia
- Structural

**VTE Recurrence While on LMWH**

**Anticoagulant Therapy**

1. 29. In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dalteparin, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C).

1. 30. In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).

**VTE Despite Anticoagulation**

- Warfarin failure
  - Transition to LMWH for at least a month
  - Do not change to DOAC if reasonable TTR-DOACS non-inferior to warfarin for VTE recurrence- NOT superior
  - AC forum says increase target INR 2.5-3.5 or 3-4 or LMWH
- DOAC failure
  - Transition to LMWH for at least a month
  - AC Forum says consider transition to warfarin
- LMWH failure
  - Increase dosing by 25-35%
  - Change to BID dosing
  - Follow anti-Xa levels

**Management Algorithm of Recurrent VTE in Cancer**

By Lee A Y Y et al. Blood 2013; 122:2310-2317
CASE # 4

A 33 year old woman diagnosed with left lower extremity DVT 3 months ago maintained on warfarin present with complaints of pleuritic chest and shortness of breath. A CT angio of the chest reveals new bilateral segmental pulmonary emboli.

LMWH for at least a month

Case #5

A 65 year old man with adeno CA of the lung on chronic dalteparin for cancer associated VTE that occurred 3 months ago develops SOB and chest pain and is found to have recurrent PE. He has not missed a dose of LMWH. What anticoagulation regimen do you recommend now?

A) rivaroxaban
B) warfarin with goal INR 3-4
C) IVC filter
D) Higher doses of dalteparin

Case #4b

A 55 year old man presents with large unprovoked PE. Do you send a thrombophilia work up?

a) Yes
b) No
c) Are we still doing those?

ASH: Thrombophilia is not associated with Risk of VTE Recurrence

N = 474
HR = 1.3 (95% CI 0.8 - 2.0)

Source: C et al. Blood 2008;112:4432-4436
Christianen et al. JAMA 2005;293(19):2353-2361

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Impact of Acute Thrombosis & Anticoagulation on Thrombophilia Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Acute VTE</th>
<th>Heparin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticardiolipin antibodies</td>
<td>May be elevated</td>
<td>no effect</td>
<td>no effect</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>May be prolonged</td>
<td>prolonged</td>
<td>prolonged</td>
</tr>
<tr>
<td>Protein C, S</td>
<td>decreased</td>
<td>No effect</td>
<td>decreased</td>
</tr>
<tr>
<td>Antithrombin level</td>
<td>decreased</td>
<td>decreased</td>
<td>increased</td>
</tr>
<tr>
<td>Factor VIII level</td>
<td>increased</td>
<td>no effect</td>
<td>no effect</td>
</tr>
</tbody>
</table>

Modified after Lindhoff-Last E, ISTH 2013: “Measurement of NOACs and influence on coagulation assays”

When to CONSIDER Work up for Laboratory Thrombophilia
- Women of childbearing years
- Patients with suspicion for APLS
- Strong family history of VTE
- Patients with recurrent VTE
- Thrombosis in “weird places”
- Results will influence therapy
- IF done prefer to do when out of acute phase (after 3 months/except when high suspicion for APLS)

More importantly Conditions Associated with VTE
- CANCER
- IBD
- Behcets
- HIT
- DIC
- ITP
- Myeloproliferative d/o
- Nephrotic syndrome
- PNH
- OSA
- Wegeners
- SLE
- Burgeers
- RA
- Autoimmune disease
- Hyperthyroidism
- Hyperhomocysenemia
- Celiac
- Sickle cell/sickle trait
**Case #4b**

A 55 year old man presents with large unprovoked PE. Do you send a thrombophilia work up?

a) Yes  
b) No  
c) Are we still doing those?

---

**Which of these patients should receive bridge therapy postoperatively**

1. 75 yo man AFIB CHADS-vasc=5 on warfarin s/p L hip fx repair.
2. 50 year old man on warfarin for recurrent VTE, last event June 2012 s/p bowel resection
3. 65 year old man on warfarin with mechanical mitral valve s/p bowel resection
4. All of the above

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**Perioperative Anticoagulation**

- Does anticoagulation need to be stopped?
- How many days prior does anticoagulation need to be stopped?
  - Which agent
  - What is renal function
- Should this patient be bridged? When should anticoagulation be started postoperatively

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**American College of Chest Physicians 2012 Guidelines**

- CHADS2: validated to estimate **YEARLY** incidence of thromboembolism with temporary anticoagulant interruption
- Clinical translation:
  - Low (CHADS0-2: <5%) ➞ no bridging
  - Moderate (CHADS2 3-4: 5-10%) ➞ sometimes bridged
  - High (CHADS2 5-6 ≥10%) ➞ usually bridged
"The suggested thromboembolic risk stratification shown in Table 1 is based largely on indirect evidence from studies outside of the perioperative setting involving patients with a mechanical heart valve, chronic atrial fibrillation, or VTE who either were not receiving anticoagulation (ie, placebo instead of a VKA in patients with chronic atrial fibrillation) or were receiving less-effective treatment (eg, ASA instead of VKA in patients with a mechanical heart valve.”
BRIDGE Trial

<table>
<thead>
<tr>
<th></th>
<th>No Bridge (N=918)</th>
<th>LMWH Bridge (N=895)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial thromboembolism</td>
<td>4 (0.4%)</td>
<td>3 (0.3%)</td>
<td>P=0.01 for noninferiority</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>12 (1.3%)</td>
<td>29 (3.2%)</td>
<td>P=0.005 for superiority</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>110 (12%)</td>
<td>187 (20.9%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- No bridging noninferior to bridging anticoagulation for thromboembolism risk
- No bridging superior to bridging for bleeding risk

Randomized Controlled Trial

- Lower than expected even rate for ATE
- <3% patients CHADS2 5-6
- Many high risk surgical procedures not represented
- GI procedures: 40%

33 observational studies and one RCT

<table>
<thead>
<tr>
<th></th>
<th>Bridged (N=7118)</th>
<th>Nonbridged (N=5160)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE</td>
<td>0.9%</td>
<td>0.6%</td>
<td>0.8 (0.4-1.5)</td>
</tr>
<tr>
<td>Overall Bleeding</td>
<td>13.1%</td>
<td>3.4%</td>
<td>5.4 (3.0-9.7)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>4.2%</td>
<td>0.9%</td>
<td>3.6 (1.5-8.5)</td>
</tr>
</tbody>
</table>

Sub-analysis of RE_LY (RCT warfarin vs dabigatran)
- Detailed prospective analysis
- Anticoagulation interrupted for
  - 1424 warfarin patients (27.5% bridged)
  - 2709 dabigatran patients (15.4% bridged)
- TE not reduced by bridging (overall event rate low)
- Bridged patients had higher rate of TE
- Bridging associated with more major bleeding
  - Warfarin: OR 4.62, p<0.0001
  - Dabigatran: OR 3.68, p<0.0001
• Prospective registry study: AF
• 2803 interruptions, bridging used in 24%

<table>
<thead>
<tr>
<th></th>
<th>Bridged</th>
<th>Nonbridged</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleed</td>
<td>5.0%</td>
<td>1.3%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>TE (stroke or systemic embolism)</td>
<td>0.6%</td>
<td>0.3%</td>
<td>P=0.5</td>
</tr>
<tr>
<td>Composite endpoint (MI, stroke, systemic embolism, major bleeding, hospitalization)</td>
<td>13%</td>
<td>6.3%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

• Kaiser Permanente VTE study
• Observational study
• 1178 warfarin treated patients
  • 96% patients: VTE >1 year before study entry
  • 31% received bridging

<table>
<thead>
<tr>
<th></th>
<th>Bridged</th>
<th>Nonbridged</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE</td>
<td>0</td>
<td>3</td>
<td>P=0.56</td>
</tr>
<tr>
<td>Clinically relevant bleeding</td>
<td>15</td>
<td>2</td>
<td>P=0.01</td>
</tr>
</tbody>
</table>

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**Summary of recent literature**

- Majority of patients with AF experience net harm from bridging
- Should only be offered after careful consideration and for highly selected patients
- No published data on bridging vs nonbridging for mechanical valves
- Patients should be informed that the practice of bridging in non-evidence-based: expert opinion
  - Ideally, goal is to prevent a thromboembolic event
  - Recent studies demonstrate:
    - Greatly increased risk of bleeding: 2.5-5 fold
    - No study demonstrated a reduction in thromboembolism from bridging
  - RE-LY analysis strongly suggests that bridging is not needed with DOAC therapy
Patients Who May Benefit From Bridge Therapy

- Patients with any thromboembolism during past interruptions of anticoagulation, or while on therapeutic anticoagulation
- Patients with VTE CVA or TIA within past 3 months
- Patients with recent (within 1 month) evidence of mural thrombus or left atrial appendage clot
- Patients with a mitral mechanical valve
- Patients with VTE and a properly diagnosed severe hypercoaguable state (antiphospholipid syndrome, protein C/S deficiency, antithrombin deficiency)

High risk for thromboembolism

- Bridge therapy seems to be unnecessary for patients on DOACs
- List accounts for <10% of patients receiving warfarin
- Bridge after careful consideration, full justification, and discussion with patient/providers
- Patients remaining on this high-risk list do not have evidence of net benefit from bridging; they are the groups for which the published literature have not already shown a lack of such benefit
- Under-representation in the published studies
- Consider delaying elective procedure for first three months after VTE

- Highest risk period

NOTES

These are general recommendations and not intended to replace clinician judgment.

Individual patient risk profiles, procedure risk, and provider/patient preference may influence recommendations.

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Case #1

Which of these patients should receive bridge therapy perioperatively?

- 75 yo man CHADS2=4 on warfarin s/p left hip fracture repair.
- 50 year old man on warfarin for recurrent VTE, last event June 2012 s/p bowel resection
- 65 year old man with mechanical mitral valve on warfarin s/p bowel resection

Case 1a

- 65 year old man on mechanical mitral valve on warfarin s/p bowel resection. You restart full dose bridge therapy
  1. on POD#0 with IV heparin, no bolus
  2. on POD#1 with IV heparin, no bolus
  3. no sooner than POD#2 with IV heparin, no bolus
  4. Why did this issue have to come up on my shift?

ACCP Guidelines

- 4.4. In patients who are receiving bridging anticoagulation with therapeutic-dose SC LMWH and are undergoing high-bleeding-risk surgery
  - We suggest resuming therapeutic-dose LMWH 48 to 72h after surgery instead of resuming LMWH within 24 h after surgery (Grade 2C)
Risk of Bleeding with Bridging after Major Surgery

Table: Major Bleeding

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Minor Surgery</th>
<th>Major Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive Procedure</td>
<td>0% (0.02-3.7%)</td>
<td>20% (9.1-35.7%)</td>
</tr>
</tbody>
</table>

Case 1a

65 year old man on with mechanical mitral on warfarin s/p bowel resection. You restart full dose bridge therapy

1. on POD#0 with IV heparin, no bolus
2. on POD#1 with IV heparin, no bolus
3. no sooner than POD#2 with IV heparin, no bolus

Case #2a

An 80 yo woman is s/p fall and ORIF og the hip. She was on apixaban preoperatively for NVAF. When would you resume her full intensity anticoagulation therapy post operatively for stroke prevention?

a. Evening of surgery
b. Post op day #1
c. No sooner than post op day #2 or 3

Resumption of DOACs post operatively

- DOACs have rapid onset of anticoagulant effect (~1-4 hours)
  - Analogous to using LMWH
  - Caution with resuming too soon
- Timing of resumption dependent on type of procedure
  - Low bleed risk: resume 24 hours post-op
  - High bleed risk: resume NO SOONER THAN 48-72 hours post-op
- May consider “step-up” approach
  - Lower or prophylactic dose of DOAC for initial 24-48+ hours; if/when tolerated, increase to treatment dose DOAC

Resumption of DOACs

Anticoagulation FULLY therapeutic within 1-2 hours
Only dabigatran has a reversal agent

Case #2a
When would you resume her full intensity anticoagulation therapy for stroke prevention?
- Evening of surgery
- Post op day #1
- No sooner than post op day #2 or 3**

** remember if you restarted warfarin without a bridge post op patient would not be fully anticoagulated until POD# 5-10. risks of full dose anticoagulation on POD#2-3 may outweigh benefits. May opt to wait longer to restart DOAC.

Take Home Points BRIDGING
- Periprocedural bridge therapy is associated with marked increased risk of bleeding
- Consider on a case by case basis for highest risk patients
- Early resumption of full dose anticoagulation after major surgery associated with higher bleed rates
- Periop DOAC management dictated by renal function and procedure bleeding risk

Take Home Points
- Catheter-associated VTE does not mandate catheter removal and requires 3 months of anticoagulation once catheter is removed
- Risk stratify each patient to determine IF calf vein thrombosis needs treatment
**Take Home Points**

- Recurrent VTE while on anticoagulation requires detailed review to assure it is anticoagulation failure and exploration for APLS cancer and consider structural defect
- Thrombophilia testing not routinely recommended. If sent result more reliable after acute phase.

**Key Literature**

- Kearon et al. Antithrombotic Therapy for VTE Disease. CHEST 2012;141(2)(Suppl):e419s-e494s
- Aujesky et al. outpatient versus inpatient treatment of acute pulmonary embolism: a international open labeled randomized non inferiority trial Lancet 2011; 378:41-48
- Delfabbro et al Use of aspirin and or low molecular weight heparin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomized, controlled trialLancet 2013; 381: 1107-15

**TSOAC and Thrombophilia Testing**

<table>
<thead>
<tr>
<th>Anticoagulant</th>
<th>Direct Thrombin Inhibitor</th>
<th>Indirect Thrombin Inhibitor</th>
</tr>
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<tbody>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
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<tr>
<td>Rivaroxaban</td>
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<tr>
<td>Edoxaban</td>
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<tr>
<td>Apixaban</td>
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<td></td>
</tr>
<tr>
<td>Chromeplast</td>
<td></td>
<td></td>
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<tr>
<td>Inhibit Activity</td>
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<tr>
<td>DOAT</td>
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*1 Randomized in only one study*
Primary efficacy outcome: incidence of arterial thromboembolism (ATE) at 30 days (stroke, systemic embolism, transient ischemic attack)
- one-sided ‘non-inferiority’ test within a margin of 1% of placebo to dalteparin comparing ATE rates

Primary safety outcome: major bleeding at 30 days
- two-sided ‘superiority’ test was performed to compare major haemorrhage rates
- The study had 90% power for the two primary end points.

Bridge therapy associated with 3 fold increased risk of bleeding
No ↓ in TE with heparin bridge regardless of dose of LMWH u Low-int dose of LMWH associated with lower risk of bleed.
The BRIDGE Trial

Use of bridge therapy was associated with a hazard ratio of 17.2 for clinically-relevant bleeding (95% CI 3.9-75.1).

No difference in recurrent VTE even with high-risk patients.

BRIDGING IN VTE

- Use of bridge therapy was associated with a hazard ratio of 17.2 for clinically-relevant bleeding (95% CI 3.9-75.1).
- No difference in recurrent VTE even with high-risk patients.