We agree to disagree....
What do the guidelines suggest?

Kambiz Zorriasateyn, MD FACP RPVI

Healthcare for what’s next.
Disclosure:

I do not have any relevant disclosure to this presentation.
67-year-old lady with complicated diverticulitis, who did not respond to medical management, is undergoing open abdominal surgery for partial colectomy. Past medical history is significant for dyslipidemia and COPD. Her family history is significant for recurrent lower extremity deep vein thrombosis in her mother. Her physical exam shows lower abdominal tenderness, +1 bilateral leg swelling and varicose veins. Her BMI is about 35.

Prior medical records showed she was seen in vein clinic few months ago, and underwent venous duplex ultrasound of lower extremities for her varicose veins which reported veno-sclerotic changes of left common femoral vein, and a chronic appearing superficial thrombophlebitis in distal right small saphenous vein.

3 weeks prior, she had been hospitalized 3 days for diverticulitis, and treated IV antibiotic followed by few days oral antibiotic.
Does she need post-operative pharmacological VTE prophylaxis?

Does she need post-operative mechanical VTE prophylaxis?

Does she benefit from both?
61-year-old lady with complicated diverticulitis, who did not respond to medical management, is undergoing open abdominal surgery for partial colectomy. Past medical history is significant for dyslipidemia and COPD. Her family history is significant for recurrent lower extremity deep vein thrombosis in her mother. Her physical exam shows lower abdominal tenderness, +1 bilateral leg swelling and varicose veins. Her BMI is about 35.

Prior medical records showed she was seen in vein clinic few months ago, and underwent venous duplex ultrasound of lower extremities for her varicose veins which reported veno-sclerotic changes of left common femoral vein, and a chronic appearing superficial thrombophlebitis in distal right small saphenous vein.

3 weeks prior, she had been hospitalized 3 days for diverticulitis which was treated with IV antibiotic followed by few days oral antibiotic.

Caprini risk score: High
Probability of venous thromboembolism: ~6% (without prophylaxis)
American College of Chest Physicians
Prevention of VTE in Non-orthopedic Surgical Patients

“For general and abdominal-pelvic surgery patients at high risk for VTE (~6.0%; Caprini score ≥ 5) who are not at high risk for major bleeding complications, we recommend pharmacologic prophylaxis with LMWH (Grade 1B) or LDUH (Grade 1B) over no prophylaxis.

We suggest that mechanical prophylaxis with elastic stockings (ES) or IPC should be added to pharmacologic prophylaxis (Grade 2C).”

International Society of Angiology Guidelines
Nicolaides A. et al. 2013

“LMWH or fondaparinux initiated and dosed according to labelling is recommended (level of evidence: high). In the absence of LMWH or fondaparinux, LDUH 5000 IU commenced preoperatively and continued twice or three times daily can be used (level of evidence: high). Any one of the three may be combined with mechanical methods (GEC and/or IPC), particularly in the presence of multiple risk factors (level of evidence: high).”
**Scenario 1:**

She underwent partial colectomy with primary anastomosis. She is now being discharged home. She was recommended to have at least one more week of antibiotic therapy.

How long does she need to be on pharmacological VTE prophylaxis?

A. During Hospitalization only  
B. 7-10 days following discharge  
C. 4 weeks following discharge  
D. As long as she remains on IV antibiotic
**Scenario 2:**

She underwent partial colectomy with primary anastomosis. She is now being discharged home 4 days following surgery. She was recommended to have one more week of antibiotic therapy.

Her pathology resulted in stage IIa adenocarcinoma along with diverticulitis.

**How long does she need to be on pharmacological VTE prophylaxis?**

A. During Hospitalization only  
B. 7-10 days following discharge  
C. 4 weeks following discharge  
D. As long as she remains on IV antibiotic
Caprini risk score: High (total risk score of 17)

She has high risk with or without cancer !!!
How long does she need to be on pharmacological VTE prophylaxis?

A. During Hospitalization only
B. 7-10 days following discharge
C. 4 weeks following discharge
D. As long as she remains on IV antibiotic
“For high-VTE-risk patients undergoing abdominal or pelvic surgery for cancer who are not otherwise at high risk for major bleeding complications, we recommend extended duration pharmacologic”

“LMWH up to one month after operation (level of evidence: high)”
“Pharmacologic thromboprophylaxis for patients undergoing major surgery for cancer should be continued for at least 7 to 10 days.

Extended prophylaxis with LMWH for up to 4 weeks postoperatively is recommended for patients undergoing major open or laparoscopic abdominal or pelvic surgery for cancer who have high-risk features, such as restricted mobility, obesity, history of VTE, or with additional risk factors. In lower risk surgical settings, the decision on appropriate duration of thromboprophylaxis should be made on a case-by-case basis (Type: evidence based; Evidence quality: high; Strength of recommendation: moderate to strong)”
“VTE prophylaxis to people undergoing abdominal (gastrointestinal, gynecological, urological) surgery who are at increased risk of VTE. Start mechanical VTE prophylaxis on admission for people undergoing abdominal surgery; Anti-embolism stockings or Intermittent pneumatic compression.

“Continue until the person no longer has significantly reduced mobility relative to their normal or anticipated mobility.”

“Add pharmacological VTE prophylaxis for a minimum of 7 days for people undergoing abdominal surgery whose risk of VTE outweighs their risk of bleeding, taking into account individual patient factors and according to clinical judgement. Choose either: LMWH or fondaparinux sodium.”

“Consider extending pharmacological VTE prophylaxis to 28 days postoperatively for people who have had major cancer surgery in the abdomen”
Extended prophylaxis with Bemiparin for the prevention of venous thromboembolism after abdominal or pelvic surgery for cancer. Prandoni et al.

Prospective, double blind, randomized trail on duration of VTE prophylaxis in cancer patients undergoing abdomen and pelvic surgery.
626 patients were randomized.

- Group A: Bemiparin sodium 3500 IU once daily 8 ± 2 days
- Group B: Beminparin sodium 3500 IU once daily 20 ± 2 days

Follow up with venography on day 20
Patient followed for 3 months

The primary outcome: Composite of DVT, non-fatal PE, and all cause morality at the end of period
The primary safety outcome: Major bleeding
Results:

- 24% RRR of primary efficacy outcome, although no statistically significant
- 40% RRR which statistically significant when other causes of death excluded
- 82% RRR when confined to composite outcome of major VTE only (proximal DVT, symptomatic non fatal PE, and VTE related death)
- No significant increase in bleeding
Table 3 Incidence of events in the modified intention-to-treat population (main efficacy analysis)

<table>
<thead>
<tr>
<th>Outcome, n (%)</th>
<th>Bemiparin (n = 248)</th>
<th>Placebo (n = 249)</th>
<th>RRR (95% CI) (%)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Double-blind period</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Primary efficacy outcome⁷</td>
<td>25 (10.1)</td>
<td>32 (13.3)</td>
<td>24.4 (23.7; 53.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Distal DVT only</td>
<td>19 (7.7)</td>
<td>29 (12.1)</td>
<td>36.6 (10.0; 63.4)</td>
<td>0.10</td>
</tr>
<tr>
<td>Proximal DVT</td>
<td>1 (0.4)</td>
<td>8 (3.3)</td>
<td>87.9 (4.0; 98.5)</td>
<td>0.02</td>
</tr>
<tr>
<td>Distal DVT only</td>
<td>18 (7.3)</td>
<td>21 (8.5)</td>
<td>17.1 (81; 54.7)</td>
<td>0.54</td>
</tr>
<tr>
<td>Non-fatal PE</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Deaths (all-causes)</td>
<td>6 (2.4)</td>
<td>3 (1.5)</td>
<td>-98.6 (-665.1; 51.0)</td>
<td>0.50</td>
</tr>
<tr>
<td>Any DVT, nonfatal PE and VTE-related death</td>
<td>20 (8.1)</td>
<td>32 (13.3)</td>
<td>39.5 (-2.7; 64.4)</td>
<td>0.06</td>
</tr>
<tr>
<td>Major venous thromboembolism⁷</td>
<td>2 (0.8)</td>
<td>11 (4.6)</td>
<td>82.4 (11.5; 96.1)</td>
<td>0.010</td>
</tr>
<tr>
<td><strong>Double-blind plus follow-up periods</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths (all-causes)</td>
<td>8 (3.2)</td>
<td>6 (2.5)</td>
<td>-29.0 (-266.4; 54.6)</td>
<td>0.63</td>
</tr>
<tr>
<td>Any DVT, nonfatal PE and VTE-related death</td>
<td>21 (8.5)</td>
<td>32 (13.3)</td>
<td>36.5 (-6.9; 82.3)</td>
<td>0.08</td>
</tr>
<tr>
<td>Major venous thromboembolism⁷</td>
<td>3 (1.2)</td>
<td>11 (4.6)</td>
<td>73.6 (6.6; 82.5)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Table 4 Incidence of bleeding events in the safety population

<table>
<thead>
<tr>
<th>Bleeding event, n (%)</th>
<th>Bemiparin (n = 215)</th>
<th>Placebo (n = 310)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During the double-blind period</strong></td>
<td></td>
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</tr>
<tr>
<td>Major bleeding*</td>
<td>2 (0.6)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td><strong>During the double-blind plus follow-up periods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
</tr>
</tbody>
</table>

*Major bleeding during the double-blind period was the primary safety outcome.
Duration of prophylaxis against venous thromboembolism with Enoxaparin after surgery for cancer
ENOXACAN II investigators

Prospective open label but double blind on curative open abdominal and pelvic cancer surgery
Small size: 332 patients
Enoxaparin 40 mg for 6-10 days vs + 21 days

Follow up with venogram day 25-31

Primary end point: DVT

Results:

By end of treatment:
- 12% DVT in placebo group vs 4.8% DVT in Enoxaparin group
  60% risk reduction

By end of 3 months:
- 13.8 % in placebo group vs 5.5% in Enoxaparin group

- Primary safety end point: No significant difference in bleeding

Figure 2. Effect of extended-duration (27-31 days) thromboprophylaxis with enoxaparin on combined rates of symptomatic and asymptomatic venous thromboembolism (VTE) events in patients undergoing cancer surgery at (A) the end of the double-blind treatment period and (B) 3 months.10 *P = 0.02;
^P = 0.01. DVT = deep-vein thrombosis; PE = pulmonary embolism.

A Randomized study on 1-Week Versus 4-Week Prophylaxis for Venous Thromboembolism After Laparoscopic Surgery for Colorectal Cancer

Giancarlo Angelli et al.

275 patients from 2010 to 2012 were randomized to either 1 or 4 week of LMWH.
Venous duplex was done in 8 ± 2 and 28±2 for VTE.
CTPE or V/Q scan was done for suspicion for clinical pulmonary embolism.

- VTE 9.7% of short term prophylaxis vs 0% in extended prophylaxis by end of day #28
- No differences in major bleeding.
American College of Chest Physicians

VTE estimation is Orthopedic patients

- Symptomatic VTE rate 1.5%
- 50% observed in the immediate postoperative period
- Estimated untreated symptomatic VTE 4.3% for first 90 days

“For patients undergoing major orthopedic surgery, we suggest extending thromboprophylaxis in the outpatient period for up to 35 days from the day of surgery rather than for only 10 to 14 days”
A paradigm from colectomy surgery  


3464 patient from 15 hospitals in Michigan included urgent, non-urgent, open and laparoscopic

The over all 30-days symptomatic VTE rate was 2.2% (4% with cancer) despite documentation for following American College of Chest Physicians Guidelines in 92% of patients (3185) with more than 75% received pharmacologic plus mechanical prophylaxis.

2.2% we are talking about remaining at moderate Caprini risk range up to 30 days!

Is our patient fit in about pool?
Longitudinal follow up cohort of 3741 patient with VTE history and 15.5% (580) underwent surgery (808 procedure).

<table>
<thead>
<tr>
<th></th>
<th>Cumulative risk of recurrent VTE</th>
<th>95% CI, 1.2%-3.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 months</td>
<td>2.1%</td>
<td></td>
</tr>
<tr>
<td>3 months</td>
<td>3.1%</td>
<td>2.1%-5.1%</td>
</tr>
<tr>
<td>6 months</td>
<td>4.6%</td>
<td>3.1%-6.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HR of recurrence at one month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-orthopedic</td>
<td>8.2</td>
</tr>
<tr>
<td>Orthopedic</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Cumulative incidence of recurrent VTE in patient unexposed to surgery at 3 months: 0.8% (95% CI, 0.6%-1.1%)

Risk and Risk Factors Associated With Recurrent Venous Thromboembolism Following Surgery in Patients With History of Venous Thromboembolism.
Banné Nemeth et al. JAMA 2019
Table 1. Characteristics of Patients Included in the Multiple Environment and Genetic Assessment (MEGA) Follow-Up Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) (N = 3741)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>48.4 (12.8)</td>
</tr>
<tr>
<td>Women</td>
<td>2020 (54.0)</td>
</tr>
<tr>
<td>BMI, mean (SD)*</td>
<td>26.8 (4.4)</td>
</tr>
<tr>
<td>Comorbidity*</td>
<td></td>
</tr>
<tr>
<td>No major illness</td>
<td>2748 (73.9)</td>
</tr>
<tr>
<td>Any major illness</td>
<td>1569 (41.1)</td>
</tr>
<tr>
<td>COPD</td>
<td>204 (5.4)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>18 (0.5)</td>
</tr>
<tr>
<td>Kidney disease</td>
<td>35 (0.9)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>111 (3.0)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>16 (0.4)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>46 (1.2)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>23 (0.6)</td>
</tr>
<tr>
<td>Arterial thrombosis</td>
<td>197 (5.3)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>94 (2.5)</td>
</tr>
<tr>
<td>Angina</td>
<td>47 (1.2)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>9 (0.3)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>38 (1.0)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>41 (1.1)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease.
* Calculated as weight in kilograms divided by height in meters squared. Data missing for 326 patients.
* Number total and any major illnesses missing for 424 patients.
Retrospective VTE risk scoring method validation for 8216 patients
Of those, 67% were general surgery.
She only received inpatient VTE prophylaxis and nothing happened!
2 year later....

She presented with sepsis as result of community acquired MRSA pneumonia which, following recent viral respiratory tract infection. She required intubation and mechanical ventilation for 48 hours, and stayed in ICU for total of 3 days until she was weaned off vasopressors. Her central line catheter was removed at time of discharge from ICU. Her hospital course complicated with clostridium difficile diarrhea and colitis. Her hospital stay extended to 10 days.

She is now being discharged....
How long does he need to be on pharmacological VTE prophylaxis?

A. During entire hospitalization
B. During hospitalization and 7-10 days following discharge
C. During hospitalization and 4 weeks following discharge
D. During hospitalization and extend prophylaxis beyond discharge until he discharged from skilled nursing facility
“For acutely ill hospitalized medical patients at increased risk of thrombosis, we recommend anticoagulant thromboprophylaxis with low molecular-weight heparin [LMWH], low-dose unfractionated heparin (LDUH) bid, LDUH tid, or fondaparinux”

“In acutely ill hospitalized medical patients who receive an initial course of thromboprophylaxis, we suggest against extending the duration of thromboprophylaxis beyond the period of patient immobilization or acute hospital stay”
In acutely ill medical patients, the American Society of Hematology (ASH) guideline panel suggests using UFH, LMWH, or fondaparinux rather than no parenteral anticoagulant (conditional recommendation, low certainty in the evidence of effects).

In acutely ill medical patients, the ASH guideline panel recommends inpatient over inpatient plus extended-duration outpatient VTE prophylaxis (strong recommendation, moderate certainty in the evidence of effects).
“For acutely ill medical patients prophylaxis with LDUH 5000 IU b.d. or t.d.s. (Level of evidence: high) or LMWH (enoxaparin 40 mg o.d. or dalteparin 5000 U o.d.) (Level of evidence: high) for 6-14 days are recommended. Single daily doses of 2.5 mg of fondaparinux is an alternative (level of evidence: high)"

“Extended duration of thromboprophylaxis may be considered in female patients, patients older than 75 years or severe immobility, but should be determined on an individual basis.”
Venous Thromboembolism in the Outpatient Setting

1897 patients from 1999 to 2003 with confirmed diagnosis of VTE (DVT or PE)

- 73% outpatient VTE
- 23.1% with recent surgery
- 36.8% with recent hospitalization

- More VTEs were diagnosed in the 3 months following hospitalization than during hospitalization

<table>
<thead>
<tr>
<th>Table 1. Demographic and Clinical Characteristics of Patients According to Setting of VTE (Outpatient vs Inpatient)</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Age, mean, y</td>
</tr>
<tr>
<td>Age:</td>
</tr>
<tr>
<td>&lt;50</td>
</tr>
<tr>
<td>55-64</td>
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<tr>
<td>65-74</td>
</tr>
<tr>
<td>&gt;75</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>BMI:</td>
</tr>
<tr>
<td>&lt;25.0</td>
</tr>
<tr>
<td>25-29.9</td>
</tr>
<tr>
<td>≥30.0</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Meta-data: Data are given as percentage of patients, unless otherwise indicated. Because of rounding, percentages for demographic factors may not total 100. In addition, some patients had more than 1 risk factor in their medical history.

All, 39% of the patients (33.7%) were missing data for BMI.

Recent indicates active or occurring within 3 months of diagnosis of VTE.
Randomized, Placebo-Controlled Trial of Dalteparin for the Prevention of Venous Thromboembolism in Acutely Ill Medical Patients; PREVENT
Goldhaber et al. Circulation 2004

3706 patients randomized to Dalteparin 5000 IU daily or placebo for 14 days and followed for 90 days.

Study for low risk patient

**Primary end point:** Combination of symptomatic DVT, symptomatic PE, asymptomatic DVT and sudden death by day 21

Incident of VTE was reduced from 4.96% to 2.77% (absolute RR = 2.19%)
45% incident reduction \((P=0.0015)\)

Low incidence of major bleeding in Dalteparin and placebo (0.49% vs 0.16%)
Extended-duration venous thromboembolism prophylaxis in acutely ill medical patients with recently reduced mobility.


A randomized placebo-controlled trial from 20 countries

Medical patients age > 40 or older with recent reduced mobility for 3 days or without and with bathroom privilege (Age > 75 (initially age > 40), history of VTE, active or previous cancer)

Total of 7500 enrolment

2975 patients Lovebox 40 mg

2988 patients Placebo

28 ± 4 vs 14 ± 4 days of Lovenox 40 mg

Primary standpoint: Incidence of VTE up to day 28 ± 4

Result:
- Extended prophylaxis reduced VTE by 4% vs 2.5% in placebo group (0.0011).
- Major hemorrhage was more frequent in extended prophylaxis group 0.8% vs 0.3%
- Extended therapy reduced VTE in medically ill patients with reduced mobility without bathroom privilege more than increase bleeding. Benefits restricted to subgroup of women, age > 75 and severe immobility.
Rivaroxaban for Thromboprophylaxis in Acutely Ill Medical Patients (MAGELLAN)
Cohen A. et al. for the MAGELLAN investigators
NEJM 2013

Randomized trial of total of 1801 patient who randomized to receive 10±4 days of Enoxaparin 40 mg or placebo for 35±4 days, or to receive placebo for 10±4 and Rivaroxaban 10 mg for 35±4 days.

Primary efficacy outcome: VTE up to 10 days and 35 days accordingly for inferiority and superiority.

2.7% VTE in both 10 days of Enoxaparin and Rivaroxaban groups.
4.4 VTE in 35 days Rivaroxaban group and 5.7% in 35 days of Rivaroxaban group.

Bleeding 2.8% and 4.1% of Rivaroxaban and 1.2% and 1.7% of Enoxaparin group respectively.

Rivaroxaban was noninferior to Enoxaparin during 10 days treatment course but overall associated with significantly higher risk of bleeding.
Apixaban versus Enoxaparin for Thromboprophylaxis in Medically Ill Patients (ADOPT)

Goldhaber S. et al. NEJM 2011

6528 patients
Double blind placebo controlled for medical patients with CHF and respiratory failure with at least one risk factor for VTE

Apixaban 2.5 mg twice daily for 30 days
Enoxaparin 40 mg once daily for 6-14 days

Extended prophylaxis with Apixaban was nonsuperior to Enoxaparin

Major bleeding 0.47% of Apixaban group vs 0.19% of Enoxaparin group

Extended Thromboprophylaxis with Betrixaban in Acutely Ill Medical Patients (APEX)
Cohen A. et al. APEX Investigators NEJM 2016

Randomized controlled trial for patient with medical illnesses.

7513 patients

Enoxaparin 40 mg once daily for 10±4 days and placebo for 35 to 42 days
Betrixaban 80 mg once daily for 35-42 days and placebo for 10±4

There was no significant difference in composite of proximal DVT and symptomatic VTE
No significant difference in bleeding
There was some benefit in using Betrixaban in subgroup of patient with higher risk
Conclusion:

• All guidelines are advocating for risk assessment and prevention of VTE during hospitalization
• More controversies on VTE prevention strategy are seen outside of acute and hospital course.
• Generalization of currently available limited data may lead to missed opportunities for VTE prevention particularly in high-risk patients

In absence of validated and evidence based data for each clinical setting, individualized and patient centered clinical decision should remain the guideline for VTE prevention, a guideline which should be revised as given patient clinical course changes.