Use of Anticoagulants in Chronic Liver Disease
The Case:

- 55 year old female with known NASH cirrhosis presents with worsening abdominal pain
- CTP A (6), fully compensated prior to this
- INR 1.3, albumin 3.3
- Last EGD 18 months ago, low risk esophageal varices
Key questions to answer:

• How can we differentiate acute from chronic portal vein thrombosis and should the approach be different?
• Is it safe to use anticoagulants in patients with cirrhosis?
• What is the role of anticoagulants in prevention and treatment of portal vein thrombosis?
Classification of portal vein thrombosis

(A) Type I PVT (n = 41, 82%)
(B) Type II PVT (n = 7, 14%)
(C) Type III PVT (n = 2, 4%)
(D) Type IV PVT (n = 0)

Kim, et al., Clin Transplant 2011:25
Portal vein thrombosis clinical classifications

- **Acute (< 7 days)**
  - Symptomatic
  - Typically involves SMV and PV
  - Can present with bowel ischemia
  - Urgent treatment or surgery

- **Subacute (1-3 mos)**
  - Frequently asymptomatic
  - Typically involves only PV
  - May present as worsening PHTN
  - Therapy individualized

- **Chronic (> 3-6 mos)**
  - Asymptomatic
  - Usually presents on screening
  - Cavernoma-collaterals
  - Anticoagulant therapy of unlikely benefit
Acute PVT

- **Presentation**
  - Acute abdominal pain
  - Bowel ischemia
  - Acute diarrhea/melena
  - Lactic acidosis

- **Consider thrombophilia**
  - Malignancy, fV Leiden, JAK-2

- **Treatment must be rapid and may be life-saving**
  - Thrombolysis
  - Acute anticoagulation
  - Surgical resection
  - Critical care
  - Most need long term anticoagulation

PVT in cirrhosis patients is a different situation
Hemostasis in cirrhosis is “rebalanced”
Hemostasis in cirrhosis is “rebalanced”

- Inflammation, venous stasis, volume depletion
- Thrombosis

- Infection, kidney disease, portal hypertension
- Hemorrhage
Some cirrhosis patients are prothrombotic

Some cirrhosis patients have protein C activity levels similar to those with congenital protein C deficiency.

Incidence and diagnosis of PVT in cirrhosis

- Incidence
  - 1,243 patient screening cohort (ultrasound)
  - 5-year cumulative incidence was 10.7%
  - Many were partial and regression or resolution was common ~70%

Nery et al., Hepatology
Presentation of subacute PVT in cirrhosis

- Frequently marked by acute worsening of portal HTN
  - %62 asymptomatic
  - %38 symptomatic:
    - portal hypertensive bleeding 24%
    - worsening of ascites 14%

High risk population for PVT

- Doppler exam may show high risk population
- Flow rate < 15 cm/s identifies a high risk population

Zocco M. J Hep 51:682-689, 2009
Beware of hepatocellular carcinoma

- HCC spreads by macrovascular involvement
- Typically into the PV
- Enhancing thrombus will not improve with anticoagulation
Which came first: PVT or decompensation?
PVT and decompensation: Cause or symptom?

<table>
<thead>
<tr>
<th>Models</th>
<th>Univariate Models Unadjusted Estimates</th>
<th>Multivariate Models Adjusted for the Baseline Prognostic Variables*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Liver disease progression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Partial PVT</td>
<td>1.58</td>
<td>1.02-2.45</td>
</tr>
<tr>
<td>- Partial or Complete PVT</td>
<td>1.48</td>
<td>0.97-2.26</td>
</tr>
<tr>
<td>Decompensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Partial PVT</td>
<td>1.77</td>
<td>1.07-2.92</td>
</tr>
<tr>
<td>- Partial or Complete PVT</td>
<td>1.61</td>
<td>0.98-2.62</td>
</tr>
</tbody>
</table>

Thus, the present findings suggest that the development of PVT is a marker, but not a direct cause of the progression of liver disease. The activation of coagulation factors in the cirrhotic liver or the portal venous system is the common mechanism for the progression of liver disease, on the one hand, and the development of PVT on the other...
PVT: Significant effect on transplant outcomes

148 occlusive PVT
3147 no or non occlusive PVT

Hazard ratio by Cox multiple regression analysis

Englesbe M. Liv Transplant 2010;16:83-90
Prophylaxis for PVT: Delay decompensation?

Enoxaparin Prevents Portal Vein Thrombosis and Liver Decompensation in Patients With Advanced Cirrhosis

ERICA VILLA,* CALOGERO CAMMA,† MARCO MARIETTA,§ MONICA LUONGO,* ROSINA CRITELLI,* STEFANO COLOP,‖ CRISTINA TATA,† RAMONA ZECCHINI,* STEFANO GITTO,* SALVATORE PETTA,* BARBARA LEI,* VERONICA BERNABUCCI,* RANKA VUKOTIC,* NICOLA DE MARIA,* FILIPPO SCHEPIS,* AIMILIA KARAMPATOU,* CRISTIAN CAPORALI,¶ LUISA SIMONI,§ MARIAGRAZIA DEL BUONO,* BEATRICE ZAMBOTTO,* ELENA TURCO,* GIOVANNI FORNACIARI,* SUSANNA SCHIANCHI,* ANNA FERRARI,* and DOMINIQUE VALLA**,*†§"
Enoxaparin Prevents Portal Vein Thrombosis and Liver Decompensation in Patients With Advanced Cirrhosis?

- 70 patients at high risk for PVT were randomized to LMWH 40 IU/day vs. standard of care for 24 months
- %16 PVT in controls vs 0% in treatment group
- Decompensation in placebo 19/36 (52.7%) vs. 4/34 (11.7%) in treatment group
- Bleeding complications: 1 EV bleed in each group, 1 ruptured HCC with hemoperitoneum in enoxaparin group

Gastroenterology. 2012 Nov;143(5):1253-60
Are anticoagulants safe in cirrhosis?
Anticoagulants: Old and New

"Old"
- VKA*
- Unfractionated heparin
- LMWH
  - Enoxaparin
  - Dalteparin
  - Tinzaparin, many more
- Indirect Xa inhibitors
  - Fondaparinux

*Oral agents

"New"
- Direct thrombin inhibitors
  - Argatroban
  - Dabigatran (Pradaxa)*
  - Hirudin-lepirudin
  - Bivalirudin
- Direct Xa inhibitors
  - Rivaroxaban (Xarelto*)
  - Apixaban (Eliquis)*
  - Edoxaban (Savaysa)*
All anticoagulants have bleeding risk

<table>
<thead>
<tr>
<th>Agent</th>
<th>Indication</th>
<th>Incidence of major bleeding, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VTE treatment</td>
<td>2.0 (17/748)</td>
<td>Mismetti et al (2005)²⁰</td>
</tr>
<tr>
<td>LMWH</td>
<td>Enoxaparin</td>
<td>1.7 (63/3621)</td>
<td>Turpie et al (2002)¹⁴</td>
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<tr>
<td></td>
<td>Dalteparin</td>
<td>1.5 (15/983)</td>
<td>Hull et al (2000)²²</td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>3.3 (34/1049)</td>
<td>FRISC II Investigators (1999)²³</td>
</tr>
<tr>
<td></td>
<td>Tinzaparin</td>
<td>2.0 (6/304)</td>
<td>Simonneau et al (1997)²⁴</td>
</tr>
<tr>
<td>Factor Xa inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fondaparinux</td>
<td>2.7 (96/3616)</td>
<td>Turpie et al (2002)¹⁴</td>
</tr>
<tr>
<td></td>
<td>ACS</td>
<td>2.2 (217/10,057)</td>
<td>Yusuf et al (2006)²⁶</td>
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<tr>
<td></td>
<td>Bivalirudin</td>
<td>3.5c (82/2318)</td>
<td>Ebrahimi et al (2005)²⁹</td>
</tr>
</tbody>
</table>

Once PVT is diagnosed

- Perform serial EVBL until no appreciable varices are seen (q 2 week)
- NSBB are controversial
- No need for hospital admission if asymptomatic from PVT
Bleeding complications with anticoagulation

- VKA (warfarin,acenocoumarol)
  - Narrow therapeutic window
  - Liver disease patients are high risk for complications
  - Difficult to follow INR and no defined therapeutic range

- 47 cirrhosis patients with PVT
  - 10 patients with 11 bleeding complications, 5 were deemed related to anticoagulation
  - All were on VKA with target INR 2.5

Low Molecular Weight Heparins: Cirrhosis+ PVT

<table>
<thead>
<tr>
<th>Author</th>
<th>n</th>
<th>Bleeding Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cui (2015)</td>
<td>65</td>
<td>23.5% (1.5 mg/kg daily enoxaparin)</td>
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<tr>
<td></td>
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<td>6.4% (1.0 mg/kg BID)</td>
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<tr>
<td>Senzolo (2012)</td>
<td>35</td>
<td>8.6%</td>
</tr>
<tr>
<td>Amitrano (2010)</td>
<td>28</td>
<td>7.1%</td>
</tr>
<tr>
<td>Francoz (2005)</td>
<td>19</td>
<td>5.2%</td>
</tr>
</tbody>
</table>

Once varices are controlled, bleeding rates appear similar or modestly higher than non-cirrhosis patients.

Adapted from Intagliata, et al, *Clinical Liver Disease; 2016 June 28*
# Direct-acting oral anticoagulants (DOAC)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dosing</th>
<th>Liver Disease</th>
<th>Renal Disease Dose Adjustment</th>
<th>Reversal Agent</th>
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</thead>
<tbody>
<tr>
<td>Apixaban (Eliquis)</td>
<td>Twice daily</td>
<td>Child A&amp;B</td>
<td>Yes</td>
<td>In approval process*</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>Twice daily</td>
<td>Child A&amp;B</td>
<td>Yes</td>
<td>Yes, Praxbind</td>
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<tr>
<td>Edoxaban (Savaysa)</td>
<td>Once daily</td>
<td>Child A only</td>
<td>Yes, ineffective if CrCl&gt;95</td>
<td>In approval process*</td>
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<tr>
<td>Rivaroxaban (Xarelto)</td>
<td>Once daily</td>
<td>Child A only</td>
<td>Yes, contraindicated with CrCl&lt;30</td>
<td>In approval process*</td>
</tr>
</tbody>
</table>

Andexanet * alfa
## DOACs in cirrhosis patients

39 patients with cirrhosis, 20 on DOAC and 19 on traditional anticoagulation (not all for PVT)

<table>
<thead>
<tr>
<th></th>
<th>Any</th>
<th>Major</th>
<th>Moderate</th>
<th>Mild</th>
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<tbody>
<tr>
<td>Traditional group (LMWH and/or warfarin)</td>
<td>3/19 (16%)</td>
<td>Fatal</td>
<td>GI bleed (1)</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ICH (1)</td>
<td></td>
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<tr>
<td>DOAC group (factor Xa inhibitors)</td>
<td>4/20 (20%)</td>
<td>Non-fatal</td>
<td>GI bleed (1)</td>
<td>Vaginal bleeding (1)</td>
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<td></td>
<td></td>
<td>ICH (1)</td>
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Results of Anticoagulation

Figure 2 | Outcome of anticoagulation for the treatment of portal vein thrombosis in patients with cirrhosis.

Clinical trials in cirrhosis and anticoagulation

- Anticoagulation for Non-occlusive Portal Vein Thrombosis in Patients With Liver Cirrhosis (LMWH) – China
- The Effect of Anticoagulation in Cirrhotic Patients With Portal Vein Thrombosis: A Multicenter RCT (LMWH/VKA) – China
- Multicenter Prospective Randomized Trial of the Effect of Rivaroxaban on Survival and Development of Complications of Portal Hypertension in Patients With Cirrhosis (CIRROXABAN) – Spain
- Prevention of PVT and decompensation, with enoxaparin (CHILDBENOX) – France
Back to the case:

- 55 year old female with known NASH cirrhosis presents with worsening abdominal pain
- Placed on apixaban 2.5 mg BID
- Three months later near complete resorption of PVT
- She continues on the liver transplant list
Summary

○ How can we differentiate acute from chronic PV thrombosis and should the approach be different?
  • Acute: symptoms of bowel ischemia or acute congestion, should be treated emergently or semi-urgently
  • Chronic: asymptomatic or worsening of portal hypertension, treated on a case-by-case basis less urgently
Summary

- Is it safe to use anticoagulants in patients with cirrhosis?
  - There are many different types of anticoagulants in cirrhosis
  - Vitamin K antagonists have very narrow safety window
  - Low molecular weight heparins are well tested in patients with cirrhosis
  - Direct acting oral anticoagulants are being used more often in patients with cirrhosis and have encouraging results
  - Bleeding risk from esophageal varices is not effected by anticoagulants
  - Bleeding events related to anticoagulation are probably not significantly different from the general population
Summary

- What is the role of anticoagulants in prevention and treatment of portal vein thrombosis?
  - Acute symptomatic PVT: urgent anticoagulation
  - Chronic asymptomatic PVT: individualized but benefit is most likely in the pre-transplant population
  - Prophylaxis for PVT: benefit unproven but there are intriguing clinical trial data on delaying decompensation and prolonging survival