Team Challenges in Cardio-Oncology: A Case-Based Approach to Bleeding, Thrombosis and Ischemic Disease

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DISCLOSURE

Past Relevant Financial Relationship(s)
Takeda (ARIAD) Pharmaceuticals, Advisory Board
Bristol-Myers-Squibb, Advisory Board
Amgen, Advisory Board

Current Relevant Financial Relationship(s)
Amgen, Research Funds
Team Challenges in Cardio-Oncology
A Case-based Approach

• Bleeding
• Thrombosis
• Ischemia
Team Challenges in Cardio-Oncology
A Case-based Approach

• Bleeding
  • Thrombosis
  • Ischemia
Bleeding in the Cancer Patient

A query

• Do you hear about this often?

• Do you think it is common?

• Do you think it impacts survival?
Question #1:
Do you hear about bleeding in cancer patients often?

a) Yes, very often
b) Sometimes
c) On rare occasions
d) Never
Bleeding in the Cancer Patient

A query

• Do you hear about this often?

• Do you think it is common?

• Do you think it is impacts survival?
Question #2: Do you think bleeding is common in cancer patients (overall, not only in your practice)?

a) Very common (>10% patients)

b) Common (1-10% of patients)

c) Uncommon (0.1-1%) 

d) Rare (<0.1%)
Bleeding in the Cancer Patient
A Query

• Do you hear about this often?

• Do you think it is common?

• Do you think it impacts survival
Question #3: Do you think bleeding in cancer patients impacts their survival?

a) Yes

b) No

c) Maybe

d) Just tell me
Bleeding in the Cancer Patient

Incidence

- At least 1 bleeding episode in approx. 10% of pts w/advanced and 30% of pts w/hem. malignancies
- Epistaxis
- Hemoptysis
- Hematemesis
- Hematochezia
- Melena
- Hematuria
- Vaginal bleeding
- Ulcerated skin lesions
Circle of Bleeding Risk in Cancer Patients

Co-morbidities (e.g. PUD, liver failure)

Vascular and friable cancers (e.g. urinary, intestinal, lung)

Thrombocytopenia

Surgeries

Medications

- Anti-coagulants
- Anti-platelets
- NSAIDs
- Selective serotonin reuptake inhibitors
- Selective norepinephrine reuptake inhibitors
- Cancer therapeutics
Bleeding in the Cancer Patient

Cancer therapy-induced

Myelodepression
Tumor necrosis
Tissue disruption
Reduced healing

Thrombocytopenia
Platelet dysfunction
Vascular disintegration

Numerous cancer therapeutics!

Cancer therapy

Ibrutinib

VEGF inhibitors
Bleeding in the Cancer Patient

Cancer therapy-induced

Myelodepression

Thrombocytopenia

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Platelet dysfunction

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Vascular disintegration

Numerous cancer therapeutics!

Ibrutinib

VEGF inhibitors
$10.8 B world wide sales in 2014 for angiogenesis inhibitors approved for cancer indications (EvaluatePharma)
Promise of New Vascular-Disrupting Agents Balanced With Cardiac Toxicity: Is It Time for Oncologists to Get to Know Their Cardiologists?

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Shayan Dehdashti and Jose Ortiz, Division of Cardiology, Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH
Jeff Dueck, Department of Radiology and Biomedical Engineering, CASE School of Medicine, Cleveland, OH
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In this issue of the Journal of Clinical Oncology, Bermoep et al report the results of a phase II trial of ZD6126, an interesting agent among the first generation of tubulin binding compounds that function as vascular targeting agents, preciously, vascular disrupting agents (VDA). Representative VDA include ZD6126, combretastatin A4 phosphate (CAP), T715-707, AV-818, and M1-423, all of which bind tubulin heterodimers (p-tubulin/p38), which targets cell adhesion; and 5,6-dimethylxanthenecarboxylic acid (DMXAC), which targets von Willebrand factor and vascular regulatory cascades. Recently, VDAs have made the transition from preclinical in vivo laboratory experiments to early-phase clinical trials in humans. Unlike the more well-known angiogenic agents, such as the humanized monoclonal antibody bevacizumab and the small molecule tyrosine kinase inhibitors sorafenib (BAY 43-9006) and sunitinib (SU11248) that disrupt endothelial cell survival signaling and the recruitment and development of a new tumor blood supply, VDAs are designed to disrupt the established abnormal vasculature that feeds tumors by targeting their intrinsic endothelial cells. Tumor endothelium is primarily reliant on a network of cytoskeletal networks to maintain functional integrity. As more importance with this class of compounds gained in early phase trials, time-resolved cytometry profiles of microvessels, somatosensory, and alveolar capillaries are being used to define the phenotype of vascular active agents, as well as the molecular targets and other therapeutic endpoints in human trials. We will discuss the clinical and antiangiogenic drug development significance of delayed cardiac myosin expression in the utility of biomarkers or pharmacodynamic correlates of drug effects, especially correlating endothelial cells and biomarkers imaging of tumor blood flow and provide caution for enthusiastic commitment to further define the utility of VDAs in contemporary antiangiogenic therapeutic armamentarium.

Intravenous fluid administration, atherogenic syndrome in vascular remodeling and/or pharmacodynamic correlates of drug effects, especially circulating endothelial cells and biomarkers imaging of tumor blood flow and provide caution for enthusiasm in commitment to further define the utility of VDAs in contemporary antangiogenic therapeutic armamentarium.
VEGF Signaling Pathway (VSP) Inhibitors

FDA approved for (advanced)

- renal cell carcinoma
- colorectal cancer
- glioblastoma
- non-small cell lung cancer
- cervical cancer
- ovarian, fallopian tube, or primary peritoneal cancer
- thyroid cancer
- soft tissue sarcoma
- hepatocellular carcinoma
- gastric cancer
- gastrointestinal stromal tumor
- pancreatic neuroendocrine tumors

VSP inhibitors

- Bevacizumab (anti-VEGF)
- Afliberecept (VEGF Trap)
- Ramucirumab (Anti-VEGFR2)

TKI (with anti-VEGF Activity)

- Sunitinib, Sorafenib, Pazopanib
- Axitinib, Cabozantinib, Lenvatinib, Regorafenib, Vandetanib

Effect of Endothelial VEGF Knock-Out

Wild type

VEGF<sup>ECKO</sup>

- Intravascular thrombosis
- Vessel rupture
- Endothelial cell apoptosis and exposure of BM

Apoptosis, thrombosis, and vascular collapse

Autocrine and Paracrine VEGF Signaling
Significance for Endothelial Cells

Paracrine VEGF signaling → Inhibition → Autocrine VEGF signaling

Endothelial Cell Survival

Intravascular thrombosis
Vessel rupture
Endothelial cell apoptosis and exposure of BM

Paracrine VEGF signaling

Autocrine VEGF signaling

Inhibition

In the absence of auto-/intracrine VEGF, paracrine sources are not sufficient to sustain EC survival

Intravascular thrombosis

Vessel rupture

Endothelial cell apoptosis and exposure of BM

Autocrine and Paracrine VEGF Signaling
Significance for Endothelial Cells

In the absence of auto-/intracrine VGEF, paracrine sources are not sufficient to sustain EC survival

Cardiovascular Events – NNH

VEGF Inhibitors

Number Needed to Harm [n]

- HTN: 6
- Severe HTN: 17
- Cardiac ischemia: 85
- ATE: 141
- Cardiac dysfunction: 139
- Clinical HF: 410

Cardiovascular Events – NNH

VEGF Inhibitors

Number Needed to Harm [n]

<table>
<thead>
<tr>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>HTN</td>
<td>6</td>
</tr>
<tr>
<td>Severe HTN</td>
<td>17</td>
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<td>139</td>
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<tr>
<td>Clinical HF</td>
<td>410</td>
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</table>

Fatal CV event: 1259

Bleeding/Thrombosis/Ischemia - NNH

VEGF Inhibitors

Number Needed to Harm [n]

- Bevacizumab
- VEGF TKIs

- Hypertension: Bevacizumab 10, VEGF TKIs 7
- Bleeding: Bevacizumab 18, VEGF TKIs 40
- VTE: Bevacizumab 81
- ATE: Bevacizumab 175, VEGF TKIs 333
- Cardiac ischemia: Bevacizumab 120, VEGF TKIs 200

Calculated based on data from
Totzeck M et al. J Am Heart Assoc. 2017;10,6(8)
Bleeding/Thrombosis/Ischemia – Incidence

VEGF Inhibitors

Incidence [%]

- **Bevacizumab**
- **VEGF TKI**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bevacizumab</th>
<th>VEGF TKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial adverse events</td>
<td>2.06</td>
<td>1.27</td>
</tr>
<tr>
<td>Venous adverse events</td>
<td>5.49</td>
<td>2.54</td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>1.37</td>
<td>1.14</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20.59</td>
<td></td>
</tr>
<tr>
<td>Bleeding</td>
<td>8.6</td>
<td>13.34</td>
</tr>
</tbody>
</table>


Totzeck M et al. J Am Heart Assoc. 2017;10,6(8)
Bleeding/Thrombosis/Ischemia – Relative Risk

VEGF Inhibitors

Calculated based on data from
Totzeck M et al. J Am Heart Assoc. 2017;10,6(8)

Relative Risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Bevacizumab</th>
<th>VEGF TKI</th>
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</thead>
<tbody>
<tr>
<td>Arterial adverse</td>
<td>1.37</td>
<td>1.16</td>
</tr>
<tr>
<td>Venous adverse</td>
<td>1.29</td>
<td>1.02</td>
</tr>
<tr>
<td>Cardiac ischemia</td>
<td>2.47</td>
<td>1.69</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.73</td>
<td>3.78</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2.74</td>
<td>1.19</td>
</tr>
</tbody>
</table>

Calculated based on data from
Totzeck M et al. J Am Heart Assoc. 2017;10,6(8)
### Bleeding Incidence [%]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Bevacizumab</th>
<th>VEGF TKI</th>
<th>VEGF TKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grade</td>
<td>30.4</td>
<td>16.7</td>
<td>9.1</td>
</tr>
<tr>
<td>High grade</td>
<td>3.5</td>
<td>2.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

### Bleeding Relative Risk

<table>
<thead>
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<th>Grade</th>
<th>Bevacizumab</th>
<th>VEGF TKI</th>
<th>VEGF TKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All grade</td>
<td>2.48</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>High grade</td>
<td>1.91</td>
<td>1.16</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Hapani S et al. Oncology 2010;79:27-38
Bleeding – Incidence and Relative Risk
VEGF Inhibitors – Focused Meta-Analysis Results

**Bleeding Incidence [%]**

- Bevacizumab
- VEGF TKI

<table>
<thead>
<tr>
<th>Grade</th>
<th>Bevacizumab</th>
<th>VEGF TKI</th>
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<tr>
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<td>16.7</td>
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</tr>
<tr>
<td>High grade</td>
<td>3.5</td>
<td>2.4</td>
<td>1.3</td>
</tr>
</tbody>
</table>

**Most common bleeding types**
- Epistaxis
- Hemoptysis

**Risk factors**
- High dose bevacizumab (5 mg/kg weekly)
- Sunitinib

**High grade bleeding**
- Renal cell cancer
- Colorectal cancer

Hapani S et al. Oncology 2010;79:27-38
## Fatal Adverse Events (FAEs)  
**Bevacizumab**

<table>
<thead>
<tr>
<th>FAEs</th>
<th>No. of Studies</th>
<th>No. of FAEs/ Total No. of Participants</th>
<th>Incidence of FAEs, % (95% CI)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bevacizumab</td>
<td>Control</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td>Specified</td>
<td>13</td>
<td>67/4219</td>
<td>28/3503</td>
<td>2.1 (1.7-2.7)</td>
</tr>
<tr>
<td>Unspecified</td>
<td>12</td>
<td>95/3878</td>
<td>62/3167</td>
<td>2.6 (1.7-3.8)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>7</td>
<td>23/2403</td>
<td>3/1737</td>
<td>1.3 (0.6-2.9)</td>
</tr>
<tr>
<td>Pulmonary hemorrhage</td>
<td>5</td>
<td>14/1568</td>
<td>0/1145</td>
<td>1.3 (0.4-4.2)</td>
</tr>
<tr>
<td>Gastrointestinal tract perforation</td>
<td>5</td>
<td>7/2318</td>
<td>1/2039</td>
<td>0.3 (0.9-1.7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>12/1154</td>
<td>3/803</td>
<td>1.1 (0.6-1.9)</td>
</tr>
</tbody>
</table>

**Bevacizumab**  
FAE incidence: **2.9%**  
Most common FAE: **Hemorrhage (23.5%)**  

**VEGF-TKI**  
FAE incidence: **1.5%**  
Most common FAE: **Hemorrhage (47.5%)**  
MI (15.%)  

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Ranpura V H. et al. JAMA 2011;305:487-94  
Bleeding in the Cancer Patient
Cancer therapy-induced

Myelodepression
Thrombocytopenia
Tumor necrosis
Tissue disruption
Reduced healing
Platelet dysfunction

Numerous cancer therapeutics!

VEGF inhibitors

Ibrutinib

Cancer therapy
Vascular disintegration
Five years of ibrutinib in CLL

On ibrutinib for 1.5 years and doing great

(Health Unlocked CLL Support Association)
Ibrutinib and Platelet Inhibition

Ibrutinib
Inhibition of Plaque-Induced Platelet Aggregation

Ibrutinib

Bleeding in Cancer Patients

- Overall bleeding incidence: 30-44% in RCTs (12-15% in control group), 50-60% in single arm studies
- High-grade hemorrhage: 1-10% in RCTs (2-6% in control group), 6-7% in single arm studies
- 0.15-0.35% fatal event rate
- Most commonly: subcutaneous and mucosal bleeds (contusions, epistaxis, petechial bleed, hematuria, ecchymosis
- Initially most common: post-procedural bleeds
- Increased risk of bleeding in combination with warfarin and other antiplatelet drugs
## Ibrutinib

### Management of Bleeding Risk

#### Procedures:
- Hold 7 days prior to major (3 days prior to minor) surgery
- Resume 1-3 days after, assuming no procedural complication

#### Antiplatelets:
- Limit aspirin use (stop if primary prevention, only 81 mg if secondary prevention)
- Avoid ibrutinib while on DAPT, consider alternatives
- Start at low dose (280 mg per day) while on antiplatelet therapy and slowly increase (but bleeding events may not be dose-dependent)

#### Anticoagulants
- Avoid, postpone, or consider alternatives to ibrutinib while on anticoagulants
- If no alternatives, consider DOAC (e.g. apixaban)
- In general ibrutinib increases OAC level and effect
Most common Grade 3+ events:
Infection (9%)
Atrial fibrillation (6%)

Overall, 21% developed atrial fibrillation

No grade 3+ bleeding!
Bleeding in the Cancer Patient

Take Away Points

- Common, for various reasons
- Co-morbidities, cancer, and treatment-related risks
- Cancer therapies can increase risk based on effects on
  - bone marrow (myelodepression, thrombocytopenia)
  - vasculature (e.g. VEGF inhibitors)
  - platelets (e.g. ibrutinib)
- Bleeding events can be severe and fatal
Case Presentations
Case #1

66-year-old male, Mr. B.

Referred for a cardio-oncology consultation prior to potential enrollment in a clinical trial

Oncology history

• 3.5 years ago choroidal melanoma, left eye, 9 x 7 x 3 mm, T2a, N0, M0, underwent enucleation
• 2 years ago liver metastases, initiated on pembrolizumab
• 1 month ago, overt progressive disease with a number of enlarging liver metastases; also grade 2 diarrhea
• pembrolizumab discontinued and budesonide initiated
• Now consideration for a clinical trial with nano-particles comprised of Nab-paclitaxel and bevacizumab
Cardiology history

- 3.5 years ago: angina with pos. exercise echo (inf./inferoseptal segments, EF nml)
- 2.5 years ago: PCI of 60% to 70% LAD stenosis for ongoing angina
- Subsequent diagnosis of heart failure with preserved ejection fraction.
- started on a diuretic regimen with significant improvement (now able to lie flat, no PND, no lower extremity edema)
- exercise tolerance: able to walk several blocks, chest discomfort early after two to three blocks, but then able to walk through, able to walk three to four flights of stairs without any significant shortness of breath
Case #1

Additional Past Medical History

• Obesity, class II

• Systemic hypertension

• Hyperlipidemia

• Impaired fasting plasma glucose

• Obstructive sleep apnea, intermittently on CPAP

• GERD
Case #1

Social History
• Works as a loan officer
• Ex-smoker of 20 PKY, stopped 1.5 years ago
• Does not exercise routinely.
• Alcohol on rare occasions; beer <1 per week

Family History
• Mother had breast cancer and leukemia
• Father suffering an MI at age 46
• 1 brother having bypass surgery in his 60s and another brother undergoing PCI in his 50s.
• No DVT/PE history
Medications

- aspirin [BAYER] 81 mg tablet delayed release 1 tablet by mouth one time daily.
- budesonide [ENTOCORT EC] 9-12 mg one time as needed.
- clopidogrel [PLAVIX] 75 mg tablet 1 tablet by mouth one time daily.
- diltiazem 120 mg capsule controlled release 1 capsule by mouth one time daily.
- furosemide [LASIX] 20 mg tablet 1 tablet by mouth one time daily.
- metoprolol tartrate [LOPRESSOR] 25 mg tablet 1 tablet by mouth two times a day.
- pantoprazole 40 mg tablet enteric coated 1 tablet by mouth one time daily.
- simvastatin [ZOCOR] 20 mg tablet 1 tablet by mouth every bedtime.
Case #1

Vital signs

• Height: 178.1 cm. Weight: 116.7 kg. BSA(G): 2.3259 M2. BMI: 36.79 KG/M2.
• Blood Pressure: 104/60 mmHg, single reading, left arm sitting. Pulse Rate: 59/minute

Physical examination

• General: Alert, in no acute distress.
• Skin: No cyanosis, no clubbing.
• Eyes: Anicteric.
• Heart: Regular rate and rhythm. Soft S1, regular S2. No rubs, murmurs, or gallops. No JVP elevation visualized.
• Lungs: Clear to auscultation bilaterally.
• Extremities: Unremarkable.
What are your Cardio-Oncology concerns for Mr. B?

- Hypertension
- Worsening chest pain
- Myocardial infarction
- Stroke
- Atrial fibrillation
- QTc prolongation and Torsades
- Heart failure
- DVT/PE
- Renal failure
- Bleeding
What are the risks?
Cardiovascular Events – NNH

VEGF Inhibitors

Number Needed to Harm [n]

- HTN: 6
- Severe HTN: 17
- Cardiac ischemia: 85
- ATE: 141
- Cardiac dysfunction: 139
- Clinical HF: 410
- Fatal CV event: 1259

What would you do next?

- Ambulatory blood pressure monitoring
- Serial ECGs to assess for ST segment shifts
- Serial ECGs to assess for QTc
- Holter
- Echocardiogram
- Stress test
- Carotid ultrasound
- CCTA
- Overnight oximetry
What did we do?

- Ambulatory blood pressure monitoring
- Serial ECGs to assess for ST segment shifts
- Serial ECGs to assess for QTc
- Holter
- Echocardiogram
- Stress test
- Carotid ultrasound
- CCTA
- Overnight oximetry
Exercise echocardiogram

- Exercise capacity limited (FAC 68%)
- HR limited (72% age-predicted maximal HR)
- Blunted blood pressure response to exercise

- Ejection fraction response from 60% at rest to 70% at peak stress
- Left ventricular end-systolic volume decreased with stress
- No regional wall motion abnormalities with stress (at the achieved workload)

- Stress ECG was negative for ischemia
- No report of chest pain with stress
Now what?
Serial Tests

• Blood pressure
• ECG
• Echocardiogram
• Anything else?
Case #1

66-year-old male

Oncology history, continued

• 1 month after appointment - initiated treatment with nano particles comprised of Nab-paclitaxel and bevacizumab on the clinical protocol
• Serial BP checks OK
• 3 months after the appointment: lost 20 pounds from his baseline due to decreased appetite associated to his chemotherapy
• Started to complain of progressive fatigue, weakness in both lower extremities, and shortness of breath with exertion, worsening over the past weeks
What would you do now?

• Repeat ECG
• Repeat stress test
• Echocardiogram
• Anything else?
EKG

Now

Baseline
What would you do now?

• Repeat ECG
• Repeat stress test
• Echocardiogram
• Anything else?
Echocardiogram

**Hemodynamics**
- **Heart Rate:** 50 BPM
- **Blood Pressure:** 106 / 64 mmHg
- **ECG:** Sinus rhythm

**Media Details**
Server #94

**Final Impressions**
1. Normal left ventricular chamber size with a calculated ejection fraction of 62%. No regional wall motion abnormalities.
2. Findings consistent with normal left ventricular filling pressure.
3. Normal right ventricular size with normal systolic function. Estimated RV systolic pressure 31 mmHg.
4. No significant valvular heart disease. Mild mitral regurgitation.
5. Normal inferior vena cava size with normal inspiratory collapse (>50%).
6. No pericardial effusion.

**Findings**
Intravenous Lumason contrast was administered to enhance endocardial border definition. **LEFT VENTRICLE:** Normal left ventricular chamber size. Normal left ventricular wall thickness. Calculated left ventricular ejection fraction 62%. Left ventricular volumetric assessment not performed because of image quality. No regional wall motion abnormalities. Findings consistent with normal left ventricular filling pressure. Global averaged left ventricular longitudinal peak systolic strain is normal at ~21% (normal = more negative than ~18%). **RIGHT VENTRICLE:** Normal right ventricular size. Normal right ventricular systolic function. Estimated right ventricular systolic pressure 31 mmHg (systolic blood pressure 106 mmHg). **ATRIA:** Normal left atrial size. Left atrial volume index 30 ml/m². Normal right atrial size. **CARDIAC VALVES:** Aortic valve not well visualized. No aortic valve regurgitation. Mildly thickened mitral valve. Mild mitral valve regurgitation. Pulmonary valve not well visualized. Trivial pulmonary valve regurgitation. Normal tricuspid valve. Trivial tricuspid valve regurgitation. **OTHER ECHO FINDINGS:** Normal inferior vena cava size with normal inspiratory collapse (>50%). Normal ascending aorta dimension. Abdominal aorta incompletely visualized. Normal abdominal aorta Doppler flow pattern. Imaging inadequate for detection of atrial level shunt by color flow imaging. No intracardiac mass or thrombus, but the left atrial appendage cannot be visualized adequately with transthoracic echo to exclude thrombus in this location. No pericardial effusion. Prominent epicardial fat layer.
What would you do now?

• Repeat ECG
• Repeat stress test
• Echocardiogram
• Anything else?
What would you do now?

- Repeat ECG
- Repeat stress test
- Echocardiogram
- Anything else?
  - AM Cortisol: 1.3 mcg/dL (ref. 7-25 mcg/dL)
  - ACTH suppressed
Capillary Regression in Endocrine Organs
Case #1

66-year-old male

Oncology history, continued

• Started on prednisone
• Still weakness in both lower extremities and shortness of breath with exertion
Case #1
What would you do now?

- Warfarin
- NOAC
- LMWH
In cancer patients with VTE, we suggest LMWH over VKA therapy (Grade 2C), and dabigatran, rivaroxaban, apixaban, or edoxaban (all Grade 2C)

- Extend treatment regardless of bleeding risk (1B)
- Same anticoagulant used for first 3 months
- Continue until “active” cancer has resolved (1C)
Therapeutic anticoagulation for venous thromboembolism
Acute Management (at diagnosis or during diagnostic evaluation)

- **LMWH (preferred)**
  - Dalteparin (200 units/kg SC daily)
  - Enoxaparin (1 mg/kg SC every 12 hours)
- Fondaparinux (5 mg [<50 kg]; 7.5 mg [50–100 kg]; 10 mg [>100 kg] SC daily)
- Unfractionated heparin IV (80 units/kg load, then 18 units/kg/h, target aPTT of 2–2.5 x control or per hospital standard operating procedures [SOPs])
- Unfractionated heparin SC 333 units/kg load, then 250 units/kg every 12 hours
- For patients who refuse or have compelling reasons to avoid LMWH, the following direct oral anticoagulants (DOACs) are acceptable alternatives for acute management of VTE: apixaban and rivaroxaban
Therapeutic anticoagulation for venous thromboembolism

Chronic Management:

- **LMWH (category 1) is preferred for the first 6 months as monotherapy** in pts with prox. DVT or PE and prevention of recurrent VTE if advanced or metastatic cancer.

- Warfarin (2.5–5 mg every day initially, subsequent dosing for target INR 2–3), initiate warfarin concurrently with the parenteral agent used for acute therapy and continue both therapies for at least 5 days and until the INR ≥2 for 24 hours, during the transition to warfarin monotherapy, the INR should be measured at least twice weekly. Once the patient is on warfarin alone, the INR should be measured initially at least once weekly. Once the patient is on a stable dose of warfarin with an INR between 2 and 3, INR testing can be gradually decreased to once monthly.

- For patients who refuse or have compelling reasons to avoid LMWH, the following DOACs are acceptable alternatives as second-line agents for chronic management of VTE: apixaban, dabigatran, edoxaban, and rivaroxaban.
Therapeutic anticoagulation for venous thromboembolism
Duration of Anticoagulation as Recommended by Guideline:

- **Minimum time of 3 months**
- For non-catheter-associated DVT or PE recommend indefinite anticoagulation while cancer is active, under treatment, or if risk factors for recurrence persist.
- For *catheter-associated thrombosis*, anticoagulate as long as catheter is in place. Recommended total duration of therapy is *at least 3 months*.
- Providers should continue to discuss with patients the risks/benefits of anticoagulation to determine the appropriate duration of therapy.
Case #1

66-year-old male

Follow-up

• Started on enoxaparin 110 mg q12 hours
• After the 1st month, switched to 150 mg q24 hours
• After 3 months, switched to Apixaban 5 mg per day
• Improved SOB
• But progressive metastatic disease, who he succumbed to
Case #2

50 year-old male, Mr. C.

- presented to the ED with fever and chest pain
- the chest pain started this afternoon, 5 hours ago, awakening him from a nap
- the pain has been constant, up to 6/10 in severity, substernal in location, no radiation, but concomitant diaphoresis and nausea

Past Medical History

- poorly-differentiated neuroendocrine tumor of the rectum (5x4x3 cm), dx last month
Case #2

Medications

- cisplatin [PLATINOL]
- dexamethasone [DECADRON]
- etoposide [VEPESID]
- fosaprepitant [EMEND]
- granisetron [KYTRIL]
- cyclobenzaprine 10 mg tablet 1 tablet by mouth every evening
Case #2

Vital signs:
Height: 170.2 cm. Weight: 83.91 kg. BSA(G): 2.01 M2. BMI: 28.973 KG/M2.
Temperature: 37.7 ° C.
Respiratory Rate: 22 breaths/minute.
Blood Pressure: 119/98 mmHg. Pulse Rate: 120/minute.

Physical Exam:
General: pleasant middle aged gentleman in no acute distress; mildly diaphoretic
Heart: regular rate and rhythm; no murmur; 2+ radial and pedal pulses; no LE edema
Pulm: clear to anterior auscultation
Abd: soft, non-tender; normal bowel sounds
Psych: intermittently tearful; alert, oriented; answers questions appropriately
Derm: no rash or ecchymoses
Case #2
Case #2

ANC: 0.33

cTnT: <0.01 ng/mL
What would you do?

A. Echocardiogram
B. Coronary angiogram
C. Chest CT – PE study
D. Chest CT – triple rule out
E. Nitroglycerin, aspirin, clopidogrel, high dose statin
F. Heparin anticoagulation
G. F, then C
H. E+F, then B
I. E+F, then D
Coronary Angiography
Coronary Angiography
Coronary Angiography
Case #2
Now what?

A. Cardiac MRI
B. Transesophageal echocardiogram
C. Lower extremity Doppler U/S
D. Anticoagulation
E. DAPT
F. Anticoagulation + single anti-platelet
Case #2

Hospital course
• No troponin elevation
• No further events
• Dismissed the next day

New medications
• aspirin 81 mg chewable tablet 1 tablet by mouth one time daily.
• clopidogrel [PLAVIX] 75 mg tablet 1 tablet by mouth one time daily.
• atorvastatin [LIPITOR] 40 mg tablet 1 tablet by mouth every bedtime.
Case #2

• He returns 6 weeks later for a f/u visit
• No recurrent chest pain events
• Interval improvement (reduction) of his malignancy, but still residual disease
• Decision to undergo surgical resection
• Request for cardiovascular PAME evaluation
  – Specific question: continuation of DAPT?
What do you say?

A. Okay to proceed, no change in therapy
B. Stop clopidogrel, resume after surgery, continue aspirin throughout
C. Stop clopidogrel, do not resume after surgery, continue aspirin throughout
D. Stop clopidogrel and aspirin, resume after surgery
E. Stop clopidogrel and aspirin, do not resume after surgery
Case #2

Clinical course
- Seen in general cardiology
- Stopped DAPT
- Underwent surgery
- DAPT was not resumed
- No further events

What if the patient had received a stent?
Antiplatelet Conundrum in Surgery Patients

- Coronary Stent Implant
- Noncardiac Surgery
- Post-operative Bleeding
- Hypercoagulable State
- Stent Thrombosis and Ischemic Complications

Banerjee S et al. J Am Coll Cardiol 2017;69:1861–70
DAPT Duration

SIHD

0 mo
- No Hx PCI or recent CABG
  - Class III: No benefit
- S/P PCI
  - BMS
    - Class I: At least 1 mo (clopidogrel)
  - DES
    - Class I: At least 1 mo (clopidogrel)
- S/P CABG
  - Medical therapy
  - Lytic (STEMI)
  - PCI (BMS or DES)
  - CABG

6 mo
- No high risk of bleeding and no significant bleeding on DAPT
- Class IIb: >1 mo may be reasonable
- Class IIb: >6 mo may be reasonable

12 mo
- No high risk of bleeding and no significant bleeding on DAPT
- Class IIb: >12 mo may be reasonable

Class I: After CABG, resume P2Y12 inhibitor to complete 1 y or DAPT

2016 ACCF/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease
## DAPT Calculator

### Clinical Prediction Score

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>-2</td>
</tr>
<tr>
<td>65-&lt;75</td>
<td>-1</td>
</tr>
<tr>
<td>&lt;65</td>
<td>0</td>
</tr>
<tr>
<td>Cigarette smoking</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>MI at presentation</td>
<td>1</td>
</tr>
<tr>
<td>Prior PCI or prior MI</td>
<td>1</td>
</tr>
<tr>
<td>Paclitaxel-eluting stent</td>
<td>1</td>
</tr>
<tr>
<td>Stent diameter &lt;3 mm</td>
<td>1</td>
</tr>
<tr>
<td>CHF or LVEF &lt;30%</td>
<td>2</td>
</tr>
<tr>
<td>Vein graft stent</td>
<td>2</td>
</tr>
<tr>
<td>Total score range</td>
<td>-2 to 10</td>
</tr>
</tbody>
</table>

### Distribution of Clinical Prediction Score

![Distribution of Clinical Prediction Score](chart.png)

**Yeh RW et al. JAMA. 2016;315:1735-49**
DAPT Calculator

Myocardial infarction or stent thrombosis

- Risk difference (continued thienopyridine – placebo), 12-30 m (%)
  - DAPT score <2
  - DAPT score ≥2

GUSTO moderate or severe bleed

- P=0.02
- 1.55
- 0.37

Net adverse events

- P<0.001
- 0.92

Mortality

- P=0.14
- 0.73
- 0.01

P values are for comparison of risk differences across DAPT score category (interaction)

Yeh RW et al. JAMA. 2016;315:1735-49
Antiplatelet Management

With small-molecule GPIIb/IIIa inhibitors

Low dose aspirin continued throughout

START small molecule GPI
(tirofiban, eptifibatide)

STOP small molecule GPI
(tirofiban, eptifibatide)

RESUME small molecule GPI**
(tirofiban, eptifibatide)

STOP prasugrel

STOP clopidogrel	

-3*

Day -7

-6

-5

-4

-3*

-2

-1

-1

0

+4-6 h

Follow-up until discharge

Surgery

STOP ticagrelor

***With 300-600 mg loading dose, as soon as oral administration possible. Prasugrel or ticagrelor discouraged

*Tirofiban: 0.1 mcg/kg/min; if creatinine clearance <50 mL/min, adjust to 0.05 mcg/kg/min. Eptifibatide: 2.0 mcg/kg/min; if creatinine clearance is <50 mL/min, adjust to 1.0 mcg/kg/min.

**If oral administration not possible

***With 300-600 mg loading dose, as soon as oral administration possible. Prasugrel or ticagrelor discouraged

With Cangrelor

Low dose aspirin continued throughout

START cangrelor*

STOP cangrelor

STOP prasugrel

STOP clopidogrel	

-3*

Day -7

-6

-5

-4

-3*

-2

-1

-6 h

0

+4-6 h

Follow-up until discharge

Surgery

RESUME cangrelor**

RESUME clopidogrel***

*Initiate within 72 hours from P2Y_{12} inhibitor discontinuation at a dose of 0.75 mg/kg/min for a minimum of 48 hours and a maximum of 7 days.

**If oral administration not possible

***With 300-600 mg loading dose, as soon as oral administration possible. Prasugrel or ticagrelor discouraged

Banerjee S et al. J Am Coll Cardiol 2017;69:1861–70
Case #3

83-Year-Old Male, Mr. F.

• Awoke with retrosternal chest pressure, 10/10 in intensity, at 4 a.m.
• Associated with diaphoresis and dyspnea
• 3 SL nitroglycerine tablets resulted in partial relief of symptoms
• Presents to the ED for further evaluation
Case #3

Past Medical History

- CAD, s/p CABG 9 years ago
- Hyperlipidemia
- Hypertension
- Obesity
- COPD
- Esophageal adenocarcinoma (T3, N0, M0)
Case #3

Medications

• Aspirin 81 mg per day
• Atenolol 100 mg per day
• Losartan 100 mg per day
• Furosemide 80 mg per day
• Simvastatin 80 mg per day
• Symbicort 160 – 2 inhalations bid
• Modified FOLFOX: Fluorouracil IV via ambulatory pump for 46 hours (no bolus), started yesterday after oxaliplatin
Case #3

Physical Examination

• BP: 141/82 mm Hg, HR 124 BPM, RR 17 per minute
• General: Alert, no acute distress
• Heart: RRR, reg. S1 + S2, no gallops, murmur, rubs
• Lungs: Reduced breath sounds, prolonged expiration
• Vessels: No JVD, reduced distal LE pulses bilaterally
Case #3

ECG during chest pain

ECG 8 days prior
Case #3

ECG during chest pain

ECG 15’ later, CP resolved with NTG

Herrmann J et al. Circulation 2016; 133:1272-89
Case #3

cTnT: 0.05 => 0.11 => 0.09 ng/mL

Started on Clopidogrel, unfractionated heparin, Metoprolol, and Nitroglycerin, and transferred for coronary angiography
Case #3
Case #3
Case #3
Case #3
Case #3
Case #3
Case #3

How would you manage this patient?

A. Continue Aspirin and Metoprolol, cardiac MRI

B. Continue Aspirin, Clopidogrel, and Metoprolol, non-invasive cardiac stress testing

C. Continue Aspirin, Clopidogrel, Metoprolol, start Imdur, no further testing

D. Continue Aspirin and Nitroglycerin drip, stop 5-FU, no further testing
5-FU Cardiotoxicity

**DIRECT CELLULAR DAMAGE**
- Metabolism of 5-FU into toxic fluoracetate
- Altered DPD enzyme activity
- Free radical damage
- Induced apoptosis
- Mitochondrial uncoupling and reduced aerobic efficiency
- Direct myocardial cell damage
- Myocarditis

**ISCHEMIA**
- Coronary vasospasm
- Primary smooth muscle dysfunction
- Impaired synthesis of NO
- Direct endothelial cell damage
- Endothelial dysfunction
- Increased levels of vWF
- Altered RBC morphology and impaired oxygen carrying capacity
- Takotsubo cardiomyopathy
- Platelet aggregation and thrombotic occlusion

Sara JD et al. Ther Adv Med Oncol 2018, 10: 1-18
5-FU Cardiotoxicity

Rechallenge
- Controversial
  - Recurrence up to 90%; death up to 13%.
  - Avoid if possible
- Individualized decision weighing risks and benefits
- Patients with significant CAD who undergo revascularization: can retreat if close observation and if benefits > risks
- Patients with nonsignificant CAD: avoid 5-FU if possible
  - If not possible and risk/benefit ratio acceptable attempt cautious challenge with BOLUS regimen
  - pretreat with 48 h of aspirin, CCB and long-acting nitrate
  - careful observation and continuous ECG monitoring
  - discontinue 5-FU if any symptoms/signs of cardiac event

Use of alternative FU drugs
- UFT
  - Contains tebufur which is a FU prodrug, and uracil which competitively inhibits the degradation of FU
  - < 1% incidence of cardiotoxicity
  - Not available in the USA (available in Japan and other Asian and South American countries)
- S-1
  - Contains tebufur, gimedaril which inhibits the enzyme DPD that breaks down FU and oteracil which inhibits phosphorylation of FU
  - No reported cardiotoxicity to date
  - Not available in the USA (available in several Asian and European countries)

Antidote therapy?
- Toxicity is thought to be related to metabolite FUTP
  - Uridine is a naturally occurring nucleoside: competes with FUTP for incorporation into RNA
  - Can reduce FU toxicity to normal tissues
  - Has not been studied in FU-related cardiotoxicity
  - Can cause phlebitis and requires central access for administration
  - Uridine triacetate is an oral active prodrug of uridine
    - Higher bioavailability
    - Approved by FDA in 2015 (for FU or capecitabine overdose in patients with severe/life-threatening toxicity of cardiovascular or central nervous system)
    - Could be used in severe toxicity

Sara JD et al. Ther Adv Med Oncol 2018, 10: 1-18
Case #4

65-Year-Old Female, Ms. P.

• Presents for outpatient chemotherapy
• Towards the end of paclitaxel infusion she developed “central heartburn” radiating to the left arm
• Not responsive to Tums but improved with sublingual nitroglycerin and morphine
• Requests completion of chemotx w/carboplatin
• Progressive chest discomfort and shortness of breath prompting hospital admission
Case #4

Past Medical History

• Raynaud’s
• Rheumatoid arthritis
• GERD
• Bilateral pleural effusions, s/p talc pleurodesis of left loculated effusion 1 month ago
• Metastatic ovarian cancer, s/p total abdominal hysterectomy w/extensive debulking 1 month ago
Case #4

Medications

- Acetaminophen ES 500-1000 mg PO QID
- Calcium 600 with PO qhs
- Fexofenadine 45 mg PO qd
- Metoprolol tartrate 100 mg PO BID
- Multivitamin 1 tablet PO qd
- Omeprazole 20 mg PO qd
Case #4

Physical Examination

• Temp 36.6° C, BP 139/83 mmHg, HR 119 BPM, RR 17/min, O2sat 97% on 3 lpm, BMI 24 kg/m2

• General: Alert, no acute distress

• Heart: Tachycardic, regular. Normal S1, S2. No m/r///g.

• Lungs: Bibasilar crackles, reduced BS over the right base.


• Extremities: +1 to +2 pitting edema bilaterally up to the knees. +2 pulses throughout.
Case #4

Acute ECG

ECG 1 month prior
Case #4

Acute ECG

ECG 4 hours later
What is your diagnosis?
What would be your medication recommendation?

A. Continue Metoprolol at 100 mg BID
B. D/c Metoprolol, start Carvedilol 25 mg BID
C. Start Lisinopril 5 mg qd
D. A and C
E. B and C
More chemotherapy -
What would you advise?

A. Further chemotherapy is prohibitive
B. Continue with carboplatin only
C. Change paclitaxel to docitaxel
D. Continue with current chemotherapy with vasodilator treatment and close monitoring
Follow-up

- Carvedilol 37.5 mg BID in lieu of metoprolol
- 5 mg of isosorbide dinitrate before chemotherapy
- Chest pain after 80% of paclitaxel infusion (130 mg)
- Resolution with 1 SL NTG without recurrence during completion with carboplatin (440 mg)
- No further symptoms during subsequent therapies
Case #4

1 month follow-up
Case #4

April 2014

May 2016
Case #5

61-Year-Old Female, Ms. N.

- Awoke from sleep with shortness of breath
- Experienced band-like squeezing pain around her chest
- Diaphoresis, light-headedness, and nausea
- No palpitations, no syncope
- Took 2 baby aspirin and drove herself to the ED
Case #5

Past Medical History

• Hypertension
• Migraine headaches
• Depression
• Left chest wall sporadic desmoid tumor, s/p wide local excision, neg. margins 4 years ago
• Chronic circumferential pericardial effusion without hemodynamic compromise 7 years ago
• Chronic myelogenous leukemia, dx 7 years ago
Case #5

Medications

- Citalopram 20 mg PO daily
- Metoprolol succinate 50 mg PO daily
- Rizatriptan 5 mg PO PRN
- Tasigna 300 mg PO BID
Case #5

Physical Examination

• BP: 131/62 mmHg, HR 75/minute, RR 18/minute, O2 sat 97% on RA, BMI 33.09 KG/M2
• General: Alert and oriented. No acute distress.
• Heart: Regular rate and rhythm. No murmurs. No rubs.
• Lungs: Clear to auscultation bilaterally.
• Abdomen: Soft, nontender, nondistended. No hepatojugular reflux.
• Extremities: Warm, well perfused. No edema.
Case #5

Acute ECG

ECG 3 months ago
cTnT:  <0.01 => 0.04 => 0.05 ng/mL

Started on Diltiazem, Lovenox, Aspirin
What would you do next?

A. Chest CT – PE protocol
B. Echocardiogram
C. Non-invasive stress test
D. Coronary angiography
Negative for PE and pulmonary parenchymal disease
Case #5

Normal LV and RV size and function, no RWMAs, no valve disease, RVSP 27 mmHg, no pericardial effusion
Case #5
Case #5
Case #5

Promus Premier 3.0x28 mm
Case #5
Case #5

Acute ECG

ECG Post-PCI
What would you recommend upon discharge?

A. DAPT
B. Statin therapy
C. Anticoagulation
D. Sotalol
E. A and B
F. A, B, and C
G. A, B, C, and D

Any other information that would influence your recommendation?
Case #5

Medications

• Citalopram 20 mg PO daily
• Metoprolol succinate 50 mg PO daily
• Rizatriptan 5 mg PO PRN
• Tasigna 300 mg PO BID
Case #5

Medications

• Citalopram 20 mg PO daily
• Metoprolol succinate 50 mg PO daily
• Rizatriptan 5 mg PO PRN
• Tasigna 300 mg PO BID
WARNING: QT PROLONGATION AND SUDDEN DEATHS

See full prescribing information for complete boxed warning.

- **Tasigna** prolongs the QT interval. Prior to Tasigna administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies (5.2). Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments (5.2, 5.3, 5.7, 5.15).
- **Sudden deaths** have been reported in patients receiving nilotinib (5.3). Do not administer Tasigna to patients with hypokalemia, hypomagnesemia, or long QT syndrome (4, 5.2).
- Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors (5.8).
- Avoid food 2 hours before and 1 hour after taking the dose (5.9).
Nilotinib and QTc

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- Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors (5.8).

- Avoid food 2 hours before and 1 hour after taking the dose (5.9).
Nilotinib and QTc

ECG baseline, 7 days after dose change

QTc >480 msec?

- Withhold Nilotinib*
- Check K, Mg and correct
- Review concomitant medication discontinue QTc prolonging drugs

Reassess in 2 weeks

QTc <450 msec (within 20 msec of baseline)
Resume Nilotinib at same dose

QTc 450-480 msec
Resume Nilotinib at reduced 400 mg dose

* Permanently if recurrent after dose reduction
Case #5

Follow-up

- Changed to dasatinib 50 mg once a day
- Mild periorbital edema and diarrhea
- Bcr-Abl p210 mRNA negative
- Molecularly undetectable CML
- No further cardiac events over 3 years