Perioperative Medicine
Medical Consultation Interest Group

SGIM 2008

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Gerald W. Smetana, MD, FACP
Agenda

- Introduction (5 min)
  - Dr. Cohn
- Writing Group Update (5 min)
  - Dr. Smetana
- Web-based Curriculum Update (10 min)
  - Dr. Pfeifer
- Preop Evaluation of the Cancer Patient (10 min)
  - Dr. Sahai
- Review - Perioperative Statins (10 min)
  - Dr. Feldman
- ACC Guidelines and POISE (10 min)
  - Dr. Cohn


http://content.onlinejacc.org/cgi/content/full/j.jacc.2007.09.001
ACC Clinical Predictors of Increased Perioperative Risk

- **Active cardiac conditions** ("major"): unstable coronary syndromes (recent MI, class III-IV angina), decompensated CHF, significant arrhythmias, severe valvular disease (AS, MS)

- **Clinical risk factors** ("intermediate"): CAD (prior MI, Class I-II angina), compensated or prior CHF, diabetes (*insulin?*), CRI (Cr>2), CVA

- **(Minor)**: CVA, advanced age, abnormal EKG, non-sinus rhythm, low functional capacity, uncontrolled hypertension
ACC Cardiac Risk Stratification for Noncardiac Surgical Procedures

- **High**: (cardiac risk > 5%)
  - Emergent major operations, aortic and major vascular, peripheral vascular, prolonged procedures with large fluid shifts or blood loss

- **Intermediate**: (cardiac risk < 5%)
  - Carotid endarterectomy, endovasc AAA, (stents/coils), head and neck, intraperitoneal, intrathoracic, orthopedic, prostate

- **Low**: (cardiac risk < 1%)
  - Endoscopic, superficial, cataract, breast
Energy Requirements for Various Activities

- **1 MET**
  - take care of self
  - eat, dress, toilet
  - walk indoors
  - walk 1-2 blocks (level) at 2-3 mph
  - do light work around the house (dust, wash dishes)

- **4 METS**
  - climb 1 flight, go uphill
  - walk on level ground 4 mph
  - do heavy housework (scrub floors, move furniture)
  - do moderate recreational activities
  - participate in strenuous sports

- **≥ 10 METS**
ACC/AHA Cardiac Evaluation & Care Algorithm 2007

Step 1: Need for emergency/urgent noncardiac surgery?
- Yes: To the operating room
- No: Proceed to Step 2

Step 2: Active cardiac conditions?
- Yes: Delay surgery for further evaluation and treatment
- No: Proceed to Step 3

Step 3: Low risk surgery?
- Yes: Proceed with surgery
- No: Proceed to Step 4

Step 4: Good functional capacity (≥4 METS) without symptoms?
- Yes: Proceed with surgery
- No or unknown: Proceed to OR

Step 5: Go to clinical risk factors RCRI (CAD, CHF, DM, CVA, CRI)
- Non-vascular: to OR with BB or NIT?
- Vascular: NIT?
POISE: Perioperative Ischemia Evaluation Trial

- 8351 pts ≥ 45 yrs old; with/at risk for ASHD
- Metoprolol CR (100mg preop; 100 mg 6 hrs postop; 200 mg 12 hrs later and then daily x30 days)
- Dose NOT titrated; held if syst BP<100mmHg
- 1º outcome: MI, cardiac arrest, cardiac death
- 2º outcomes: AF, revasc, CVA, total mortality
- Safety measures: significant bradycardia, hypotension

Devereaux, AHA 2007
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metoprolol (n=4174), n (%)</th>
<th>Placebo (n=4177), n (%)</th>
<th>Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>243 (5.8)</td>
<td>290 (6.9)</td>
<td>0.83</td>
<td>0.04</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>151 (3.6)</td>
<td>215 (5.1)</td>
<td>0.70</td>
<td>0.0007</td>
</tr>
<tr>
<td>Total mortality</td>
<td>129 (3.1)</td>
<td>97 (2.3)</td>
<td>1.33</td>
<td>0.03</td>
</tr>
<tr>
<td>Stroke</td>
<td>41 (1.0)</td>
<td>19 (0.5)</td>
<td>2.17</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Devereaux, AHA 2007
## POISE: Secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Metoprolol (n=4174), n (%)</th>
<th>Placebo (n=4177), n (%)</th>
<th>Hazard ratio</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revascularization</td>
<td>11 (0.3)</td>
<td>27 (0.6)</td>
<td>0.41</td>
<td>0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>91 (2.2)</td>
<td>120 (2.9)</td>
<td>0.76</td>
<td>0.04</td>
</tr>
<tr>
<td>Significant hypotension</td>
<td>626 (15.0)</td>
<td>404 (9.7)</td>
<td>1.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Significant bradycardia</td>
<td>274 (6.6)</td>
<td>101 (2.4)</td>
<td>2.71</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Devereaux, AHA 2007
Perioperative Evaluation of the Patient with Cancer

Sunil K. Sahai, MD, FAAP.
Assistant Professor
Medical Director, Internal Medicine Perioperative Assessment Center
The University of Texas M.D. Anderson Cancer Center
Learning Objectives

• ONCOLOGIC SURGERY
  • Review the reasons for surgery in cancer patients

• CANCER AND CANCER TREATMENT
  • Describe patient-specific risk factors for perioperative issues in regards to type of cancer.
  • Review common toxicities from chemotherapy which may impact perioperative management.

• PREOPERATIVE EVALUATION AND PERIOPERATIVE MANAGEMENT
  • Review common issues that present in the perioperative period.
Introduction

The perioperative evaluation of a cancer patient is made especially challenging because of the additional physiological burden that cancer and cancer treatments impose on patients.

In some cases, the traditional guidelines fail because a surgery for a cancer is usually not elective. Additionally, time and treatment constraints can prevent medical optimization.

A complete and comprehensive history and physical, along with targeted testing are essential to the perioperative evaluation of the cancer patient.
Cancer Patients are More Complex

- Perioperative Evidence Based Literature
  - First exclusion criteria is usually cancer.
- Comorbid medical conditions.
- Risk factors which predisposed them to develop the malignancy
  - Genetics?
- Risks associated with surgical procedures.
- Non-surgical treatment modalities.
  - Chemo and XRT
In those cancer patients with solid tumors, 75% will have a surgical resection for cure, and 90% will have surgery for either cure or palliation.

Surgery in cancer patients can be divided into five categories. The purpose of which is an important consideration when assessing risks and benefits.

1. Diagnostic
2. Curative
3. Palliative
4. Brachytherapy
5. Surgery unrelated to cancer

In some cases, a surgery may change from one category to another, i.e. a diagnostic open lung biopsy may need to be converted to a lung resection for curative purposes.
Cancer Treatment

The treatment of cancer is not without side effects; which may affect perioperative planning.

- Cardiovascular
- Pulmonary
- GI/Hepatic
- Renal
- Hematologic
Chemotherapy can have cardiovascular side effects, both during treatment and after treatment has been completed.

Side effects of chemotherapeutic agents can be categorized based on class effect, i.e., anthracyclines can cause congestive heart failure.
In those receiving anthracyclines, dexrazoxane is sometimes used. It is an iron chelator, thus preventing the formation of the anthracycline-iron complexes.

Radiation therapy can affect heart tissues.
- Pericardial effusion an early presenting sign
- Fibrous thickening can occur after 18 months
- Radiation therapy can accelerate coronary atherosclerosis.
Cancer & Cancer Treatment: Pulmonary

Some chemotherapeutic agents can cause bronchospasm and/or pulmonary fibrosis/pneumonitis.

Prior radiation therapy to the chest is also a known cause of pulmonary fibrosis. This may lead to decreased vital capacity and reserve, thus potentially increasing the risk of post operative pneumonia.

Those patients with prior lung resections are prone to developing post operative pneumonia.
Cancer of the GI tract is a risk factor for malnutrition. Those receiving radiation therapy frequently have diarrhea, which leads to malabsorption with its associated consequences of weight loss and vitamin deficiency.

Cancer that involves the liver, either as a primary or through metastatic disease may complicate perioperative evaluation through coagulopathies, biliary dysfunction, and malnutrition.

Chemotherapy in the perioperative period may cause liver dysfunction and lead to a coagulopathy. An albumin less than 3.5 has been shown to increase the risk of postoperative pneumonia.
Chemotherapeutic agents associated with hepatotoxicity
- Methotrexate
- L-Asparaginase
- Cytosine Arabinoside (ARA-C)
- Plicamycin
- 6-Mercaptopurine
Cancer & Cancer Treatment: GU & Renal

Cisplatin based agents and nitrosoureas can cause renal insufficiency. Additionally, tumor location may also impact renal function (i.e., obstructive hydrenephrosis).

Cyclophosphamide can cause hemorrhagic cystitis. Hematuria from bladder cancer may impact perioperative anticoagulation strategies.

Tumor lysis syndrome can cause renal insufficiency.
Cancer & Cancer Treatment: Hematology

- **Cancer is a hypercoagable state**
  - Risk for postoperative DVT due to higher levels of cytokines, clotting factors, and cancer procoagulant A.

- In the immediate postoperative period, Anti-thrombin III may be decreased. Perioperative DVT prophylaxis must be used in all patients.
  - Mucin producing tumors: adenocarcinomas of the pancreas, lung, and GI tract, are particularly at risk. DIC can occur after surgery in these patients.

- Blood counts vary widely; pancytopenia is common, either as a result of treatment, or the disease itself.

- Polycythemia
  - Adrenal, hepatitic, ovarian, renal, and uterine cancers.

- Thrombocytosis
  - Myeloproliferative disease, splenectomy, iron deficiency or inflammation.
Cancer & Cancer Treatment: Neurology

Tumors or metastatic disease of the brain or spinal cord may complicate postoperative DVT prophylaxis.

– Patients on steroids may have elevated blood sugars, leading to steroid induced diabetes.

– Myasthenia gravis occurs in about 50% of those with thymomas. Also, Eaton Lambert syndrome is associated with small cell lung cancer, and Calcium channel blockers need to be avoided in both conditions.
Cancer & Cancer Treatment: Endocrinology

- Cushing’s syndrome from ectopic production of ACTH is seen in small cell lung cancer, pancreatic cancer, carcinoid, and thymic tumors.

- SIADH is seen in a variety of lung cancers, including small cell, large cell, and adenocarcinomas. Pancreatic and duodenal cancers are also associated with SIADH.

- Asymptomatic hyponatremia is not a contraindication to surgery.
Cancer & Cancer Treatment: Endocrinology II

- A variety of conditions can lead to hypercalcemia, including ectopic production of parathyroid hormone, prostaglandins, and metastatic bone disease. Elevated calcium levels need to be investigated for occult hyperparathyroidism.

- Tumors associated with hypercalcemia are breast cancer, non-small cell lung cancer, and multiple myeloma.
Cancer & Cancer Treatment: Endocrinology III

- Hypoglycemia is seen in mesenchymal tumors, adrenocortical tumors, pancreatic non-islet cell tumors, and hepatocellular cancer.

- Hyperglycemia is seen with chemotherapy, and occult diabetes is often revealed during chemotherapy.

- Standard recommendations for diabetes management in the perioperative period also apply to cancer patients.
Cancer & Cancer Treatment: Endocrinology IV

• Adrenal insufficiency is common in those patients who have received steroids in the course of their cancer care.

• Hypothyroidism is common in those patients who receive radiation for head and neck cancers.
Perioperative Evaluation and Management

• Performance status frequently declines during treatment. It is important to assess functional status before and after treatment.

• Nutritional status has far reaching consequences and evaluation by a nutritionist prior to surgery may help optimize the patient. In the severely malnourished, parental therapy in the week before surgery may reduce morbidity. Additionally, nutritional support after surgery is also helpful.

Preoperative Testing

The field of perioperative medicine is moving away from routine preoperative testing; however, we feel that the cancer patient is an exception to this trend.

- Routine lab testing may uncover metabolic or hematologic issues secondary to prior cancer therapy that need to be addressed in the perioperative period.
- CXR and EKG’s may also be indicated for those with history of thoracic cancer or radiotherapy to the chest wall.
- These studies are frequently obtained during the “work-up” of a cancer patient and need not be repeated for the surgical procedure being contemplated if they are relatively recent.
Preoperative Testing: Cardiology

As previously mentioned, complications from cancer and cancer care can include congestive heart failure, ischemic heart disease, hypertension, hypotension, pericarditis and fibrosis.

• In high risk patients, consider non invasive testing, which may be predictive of post operative cardiac complications.

• Decisions to delay surgery in high risk patients should be made in consultation with a cardiologist familiar with the patient and the cancer. A resectable cancer may not be so in the future if delayed because of preoperative angiography and stent placement.

Preoperative Testing: Pulmonary

• As mentioned before, chemotherapy can affect the lungs; preoperative spirometry may assist in identifying patients who may need optimization prior to surgery.

• A preoperative therapeutic thoracentesis for a pleural effusion may increase a patient’s pulmonary reserve during surgery.

• Patients with complex head and neck cancers need careful evaluation by anesthesia for any potential airway issues.

• Those patients undergoing head and neck surgery with Obstructive Sleep Apnea need careful evaluation by a pulmonologist as the mask they are using may not be able to fit after surgery and/or jeopardize any skin grafts or reconstructive procedures.
Preoperative Testing: Hematology

Blood counts vary widely in cancer patients

- In general, platelet counts between 50,000 and 2 million are safe for surgery. Those with lower platelet counts may need platelet transfusions, and those with greater counts may need low dose aspirin in the perioperative period.
- Erythropoietin may alleviate anemia, transfuse only when necessary.
- Polycythemia is associated with both bleeding and thrombosis, if needed, phlebotomize until hemoglobin less than 15 g/dl.
Preoperative Testing: Hematology II

- In those patients undergoing subsequent cycles of chemotherapy, neutropenia is fairly common, elective procedures should be timed so that all counts have recovered (usually just prior to the next round of chemotherapy).

- Mucin producing adenocarcinomas can induce DIC in the post operative period.

- Extended DVT prophylaxis is recommended by both the ACCP and NCCN guidelines.
Perioperative Management & Risk Reduction

- Perioperative Beta Blockade
- Diabetes
- Perioperative Anticoagulation
  - “Bridging”
- Corticosteroid Coverage
- Postoperative Pulmonary Complications
- VTE Prophylaxis
Perioperative Risk Reduction

• Perioperative Beta-blockade

• VTE Prophylaxis
  – Prevention of Venous Thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy (June 2006)

• Perioperative Pulmonary Complications
Summary

While the perioperative care of the cancer patient is in many ways unchanged from the usual patient with no cancer history, the unique systemic effects of cancer and cancer therapy pose challenges that need to be taken into account. The role of an internist familiar with cancer and cancer related comorbidities can play an integral part in management of the surgical oncology patient.
### Table 1. Cardiotoxicity Profiles of Chemotherapeutic Agents

<table>
<thead>
<tr>
<th>Drug Class/Name, Generic (Brand)</th>
<th>Cardiac Adverse Events</th>
<th>Relative Frequency of Specific Adverse Effect**</th>
<th>Relative Frequency of Therapeutic Use†</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthracyclines/anthraquinolones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin)</td>
<td>CHF/LV dysfunction</td>
<td>+++</td>
<td>+++</td>
<td>Risk of CHF is cumulative dose and schedule dependent; LV dysfunction is secondary to free radical production; increased risk for young/elderly, after mediastinal XRT, female gender, history of cardiac disease; continuous infusion, liposomal delivery systems, or use of dexrazoxane can reduce toxicity; when appropriately administered, incidence of LV dysfunction is &lt;5%</td>
</tr>
<tr>
<td>Daunorubicin (Cerubidine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epirubicin (Ellence, Pharmorubicin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idarubicin (Idamycin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mitoxantrone (Novantrone)</strong></td>
<td>CHF/LV dysfunction</td>
<td>++</td>
<td>+</td>
<td>Anthraquinone derivative; low propensity for free radical production; myocarditis and arrhythmia can be seen acutely with infusion</td>
</tr>
<tr>
<td><strong>Alkylating agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulfan (Myleran)</td>
<td>Endomyocardial fibrosis</td>
<td>+</td>
<td>+</td>
<td>CHF risk is increased in elderly, after chest XRT, or after prior anthracyclines</td>
</tr>
<tr>
<td></td>
<td>Cardiac tamponade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin (Platinol)</td>
<td>Ischemia</td>
<td>+</td>
<td>++</td>
<td>Rare incidence of hemorrhagic myocarditis, more common with high dose; CHF risk is increased with cumulative dose, in elderly, after chest XRT, or after prior anthracyclines</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>++</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide (Cytoxan)</td>
<td>Pericarditis/ myocarditis</td>
<td></td>
<td>+++</td>
<td>CHF risk is increased with cumulative dose, prior anthracyclines</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td></td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Ifosfamide (Ifex)</td>
<td>CHF</td>
<td>+</td>
<td>++</td>
<td>CHF risk is increased with cumulative dose, prior anthracyclines, chest XRT</td>
</tr>
<tr>
<td>Mitomycin (Mutamycin)</td>
<td>CHF</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
## Cancer & Cancer Treatment: Cardiovascular

<table>
<thead>
<tr>
<th><strong>Antimetabolites</strong></th>
<th><strong>Anticancer Drug</strong></th>
<th><strong>Symptom</strong></th>
<th><strong>Note</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Capecitabine (Xeloda)</td>
<td>Ischemia</td>
<td>+</td>
<td>More common in those with CAD; mechanism is potentially vasospasm or thrombosis.</td>
</tr>
<tr>
<td>Cytarabine, Ara-C (Cytosar)</td>
<td>Pericarditis, CHF</td>
<td>+</td>
<td>Rare cases of cardiomyopathy after experimental high-dose therapy in combination with cyclophosphamide</td>
</tr>
<tr>
<td>Fluorouracil (Adrucil)</td>
<td>Ischemia</td>
<td>+++</td>
<td>Risk increased for CAD, prior chest XRT, concomitant cisplatin therapy; rate and dose dependent; vasospasm is possible mechanism</td>
</tr>
<tr>
<td></td>
<td>Cardiogenic shock</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Antimicrotubules</strong></th>
<th><strong>Anticancer Drug</strong></th>
<th><strong>Symptom</strong></th>
<th><strong>Note</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel (Taxol)</td>
<td>Sinus bradycardia, AV block, ventricular tachycardia</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>+</td>
<td>Often seen with hypersensitivity; CHF possible if given with doxorubicin</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Vinca alkaloids</td>
<td>Ischemia</td>
<td>+++</td>
<td>Increased risk with CAD or prior chest XRT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Biological agents</strong></th>
<th><strong>Anticancer Drug</strong></th>
<th><strong>Symptom</strong></th>
<th><strong>Note</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (Campath)</td>
<td>Hypotension</td>
<td>+++</td>
<td>In setting of infusion reactions</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Hypertension</td>
<td>+++</td>
<td>Severe hypertension (&gt;200/110 mm Hg) seen in 7% of patients in a recent trial</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td>+</td>
<td>CHF occurred in 14% of patients receiving concurrent anthracyclines</td>
</tr>
<tr>
<td></td>
<td>DVT</td>
<td>+</td>
<td>In setting of severe infusion reactions (bronchospasm, stridor, urticaria)</td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>Hypotension</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>R rituximab (Rituxan)</td>
<td>Hypertension</td>
<td>+++</td>
<td>Usually in setting of infusion reactions (hypotension, hypoxia, bronchospasm); severe hypertension and angioedema estimated at 1%</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arrhythmias</td>
<td>+++</td>
<td>Rare fatal cardiac failure; patients with arrhythmias and CAD should be monitored during and after infusion</td>
</tr>
</tbody>
</table>

(continues)
## Cancer & Cancer Treatment: Cardiovascular

### TABLE 1. (Continued)

<table>
<thead>
<tr>
<th>Drug Class/Name,Generic (Brand)</th>
<th>Cardiac Adverse Events</th>
<th>Relative Frequency of Specific Adverse Effect*</th>
<th>Relative Frequency of Therapeutic Use†</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>CHF/LV dysfunction</td>
<td>++</td>
<td>+</td>
<td>LV dysfunction is uncommon when given as a single agent, but there is an increased incidence when given with cyclophosphamide, anthracyclines, and/or paclitaxel</td>
</tr>
<tr>
<td>Interleukins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-2</td>
<td>Hypotension</td>
<td>+++</td>
<td>+</td>
<td>Usually seen at higher doses, associated with capillary leak syndrome (hypotension, hypoperfusion, edema, and effusions); severe hypotension 3%; transient LV dysfunction seen during infusion</td>
</tr>
<tr>
<td></td>
<td>Arrhythmias</td>
<td>+</td>
<td></td>
<td>In the setting of a vascular leak syndrome (hypotension, edema, hypoalbuminemia)</td>
</tr>
<tr>
<td>Denileukin diftitox (Ontak)</td>
<td>Hypotension</td>
<td>+++</td>
<td>+</td>
<td>Increased risk with preexisting cardiac dysfunction or prior cardiotoxic therapy</td>
</tr>
<tr>
<td>Interferon-α</td>
<td>Hypotension</td>
<td>+</td>
<td>+</td>
<td>Rare cases of LV dysfunction/arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Ischemia</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LV dysfunction</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinoic acid (Tretinoin)</td>
<td>CHF Hypotension</td>
<td>+</td>
<td>+</td>
<td>May occur in the setting of retinoic acid syndrome (respiratory distress, fever, pulmonary infiltrates)</td>
</tr>
<tr>
<td></td>
<td>Pericardial effusion</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arsenic trioxide (Trisenox)</td>
<td>QT prolongation</td>
<td>+++</td>
<td>+</td>
<td>Important to maintain normal electrolytes and to discontinue QT-prolonging drugs; fatal torsades de pointes has been reported</td>
</tr>
<tr>
<td>Imatinib (Gleevec)</td>
<td>Pericardial effusion,</td>
<td>+</td>
<td>++</td>
<td>Severe fluid retention can rarely be fatal</td>
</tr>
<tr>
<td></td>
<td>CHF</td>
<td></td>
<td></td>
<td>Dose related, occurring in 50–70% of patients receiving &gt;300 mg/d</td>
</tr>
<tr>
<td></td>
<td>Edema</td>
<td></td>
<td></td>
<td>Rare fatal cardiac toxicity reported after high-dose cyclophosphamide before bone marrow transplantation</td>
</tr>
<tr>
<td>Pentostatin (Nipent)</td>
<td>CHF</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Thalidomide (Thalomid)</td>
<td>CHF</td>
<td>+</td>
<td>+</td>
<td>Known severe congenital defects in fetuses; prescribers should be registered in STEPS program; patients with multiple myeloma are routinely given low-dose warfarin for DVT prophylaxis</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>+</td>
<td>+</td>
<td>Usually seen with rapid infusion</td>
</tr>
<tr>
<td>Etoposide (Vepesid)</td>
<td>Hypotension</td>
<td>+</td>
<td>++</td>
<td></td>
</tr>
</tbody>
</table>

XRT indicates external beam radiation therapy; DVT, deep vein thrombosis; and STEPS, System for Thalidomide Education and Prescribing Safety.

*Relative frequency of specific adverse effect: + indicates rare (<1%); ++, uncommon (1–5%); ++++, common (6–10%); and +++++, frequent (>10%).
†Relative frequency of therapeutic use: + indicates infrequent; ++, common; and ++++, very frequent.
The Role of Statins in Perioperative Medicine

An Update for SGIM
April 2008
Lenny Feldman LF@jhmi.edu
Check out JHCME.com
Objectives

- Evaluate evidence for the pleiotropic effects of statins
- Synthesize the data from "acute" statin treatment in nonsurgical settings
- Examine the current perioperative statin literature
- Investigate the possible harms of perioperative statins
Questions to Answer

- Do we need to start statins urgently for surgery if a patient should be on one chronically?
- If a patient does not necessarily need statins chronically, is major noncardiac surgery a reason to start one?
  - Which statin, what dose, and for how long?
- Is there an increased risk of harm in the perioperative period?
Acute Pleiotropic Effects of Statins

- Blunt neutrophil-induced injury
- Increase nitric oxide release
- Antithrombotic effects
- Antiproliferative effects
- Anti-inflammatory effects
- Stabilize unstable coronary plaques
- Reduce oxidative stress
- Improve endothelial function
- Effect on cytokine levels
Reperfusion Injury in Rats


Human Acute Settings


Surgical Data

• Noncardiac Vascular
• Carotid Endarterectomy
• Major Noncardiac (non-vasc)
<table>
<thead>
<tr>
<th>Study (# of pts)</th>
<th>Design</th>
<th>Type of Surgery</th>
<th>Primary Endpoint</th>
<th>Adjusted OR or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poldermans (2816) 0.22 04/03</td>
<td>Case-controlled</td>
<td>Vascular</td>
<td>In-hospital mortality</td>
<td>(0.10-0.47)</td>
</tr>
<tr>
<td>Kertai (570) 10/04</td>
<td>Retrospective, observational</td>
<td>Vascular</td>
<td>Thirty day perioperative mortality and MI</td>
<td>0.24 (0.10-0.70)</td>
</tr>
<tr>
<td>O’Neil-Callahan (1,163) 2/05</td>
<td>Retrospective, observational</td>
<td>Vascular</td>
<td>In-hospital perioperative cardiac complications</td>
<td>0.52 (0.35-0.77)</td>
</tr>
<tr>
<td>Ward (446) Thirty day complications 10/05</td>
<td>Retrospective, observational</td>
<td>Vascular</td>
<td>perioperative cardiovascular</td>
<td>0.36 (0.14-0.93)</td>
</tr>
<tr>
<td>Le Manach (669) 6/07</td>
<td>Prospective, cohort</td>
<td>Vascular</td>
<td>Myocardial necrosis in patients discontinuing versus continuing statins after surgery.</td>
<td>5.4 (1.2-25.3)</td>
</tr>
<tr>
<td>Study (# of pts)</td>
<td>Design</td>
<td>Type of Surgery</td>
<td>Primary Endpoint</td>
<td>Adjusted OR, RR, or HR (95% CI)</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------------------</td>
<td>-----------------</td>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>Barrett (3062)</td>
<td>Retrospective cohort</td>
<td>Vascular</td>
<td>Long-term mortality after vascular surgery</td>
<td>0.78 (0.67-0.92) NNT= 22</td>
</tr>
<tr>
<td>7/07</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Feringa (359)   | Prospective Observational dividing pts by statin dosing and LDL levels | Major Vascular | major cardiac events 30 days after sx and long-term                              | 30-day: 0.62 (.40-.96) with higher statin dose  
| 10/07           |                           |                 |                                                                                  | Late: 0.76(.65-.89) with higher statin dose |
| Welten (2126)   | retrospective study of prospectively collected data dividing pts by renal function | Major Vascular | All cause, cardiac, and cerebrovascular mortality 30 days after sx and long-term | 30-day: 0.27 (0.13-0.54)  
| 11/07           |                           |                 |                                                                                  | Late: 0.58 (0.48-0.69)           |
| Durazzo (100)   | RCT                       | Vascular        | At 6 months: death from cardiovascular causes, nonfatal AMI, ischemic stroke, or US | 0.31 p=0.031                     |
| 5/04            |                           |                 |                                                                                  |                                 |
Noncardiac Vascular Surgery

- Elective Vascular Procedures
- Randomized to statin or placebo an average of 2 weeks before surgery
- ITT, double-blind
- Total of 45 days of therapy
- Excluded for previous statin use
- Beta-blocker use was recommended “on the basis of current guidelines”
- Followed for 6 months

## Table IV. Primary end points for study group

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atorvastatin (n = 50)</th>
<th>Placebo (n = 50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiac causes</td>
<td>1 2.0</td>
<td>2 4.0</td>
<td>1.000</td>
</tr>
<tr>
<td>Nonfatal acute myocardial infarction</td>
<td>3 6.0</td>
<td>8 16.0</td>
<td>.199</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>—</td>
<td>1 2.0</td>
<td>1.000</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>—</td>
<td>2 4.0</td>
<td>.495</td>
</tr>
<tr>
<td>Combined end point</td>
<td>4 8.0</td>
<td>13 26.0</td>
<td>.031</td>
</tr>
</tbody>
</table>
Event-free Survival for 6 Months

13/17 cardiac events in first 10 days post-op

- Harm: 1 patient with rhabdo
## Carotid Endarterectomy

<table>
<thead>
<tr>
<th>Study (# of pts)</th>
<th>Design</th>
<th>Type of Surgery</th>
<th>Primary Endpoint</th>
<th>Adjusted OR or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy (3360)</td>
<td>Retrospective cohort</td>
<td>CEA</td>
<td>In-hospital mortality In-hospital stroke In-hospital cardiac event</td>
<td>0.25 (0.07-0.90) 0.55 (0.32-0.95) 0.87 (0.49-1.54)</td>
</tr>
<tr>
<td>10/05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McGirt (1566)</td>
<td>Retrospective cohort</td>
<td>CEA</td>
<td>Stroke Death</td>
<td>0.41(0.18-0.93) 0.21(0.05-0.96)</td>
</tr>
<tr>
<td>11/05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

McGirt- No benefit for asymptomatic patients with carotid stenosis
### Major Noncardiac Surgery

<table>
<thead>
<tr>
<th>Study (# of pts)</th>
<th>Design</th>
<th>Type of Surgery</th>
<th>Primary Endpoint</th>
<th>Adjusted OR or RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lindenauer (780,591)</td>
<td>Retrospective, cohort</td>
<td>Major Noncardiac</td>
<td>In-hospital mortality</td>
<td>0.62 (0.58-0.67)</td>
</tr>
</tbody>
</table>

### Perioperative Deaths

- 2.13% (1640) in statin group
- 3.05% (21,460) in the statin naïve group

<table>
<thead>
<tr>
<th>Revised Cardiac Risk Index Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Patients, No. (%)</td>
</tr>
<tr>
<td>45371 (34)</td>
</tr>
<tr>
<td>43756 (33)</td>
</tr>
<tr>
<td>27853 (21)</td>
</tr>
<tr>
<td>11706 (9)</td>
</tr>
<tr>
<td>3149 (2)</td>
</tr>
<tr>
<td>131835 (100)</td>
</tr>
<tr>
<td>In-hospital mortality, No. (%)</td>
</tr>
<tr>
<td>647 (1.43)</td>
</tr>
<tr>
<td>1136 (2.60)</td>
</tr>
<tr>
<td>1253 (4.50)</td>
</tr>
<tr>
<td>828 (7.07)</td>
</tr>
<tr>
<td>294 (9.34)</td>
</tr>
<tr>
<td>4158 (3.15)</td>
</tr>
<tr>
<td>NNT (95% CI)†</td>
</tr>
<tr>
<td>186 (168-214)</td>
</tr>
<tr>
<td>103 (93-119)</td>
</tr>
<tr>
<td>60 (54-69)</td>
</tr>
<tr>
<td>39 (35-45)</td>
</tr>
<tr>
<td>30 (27-35)</td>
</tr>
<tr>
<td>85 (77-98)</td>
</tr>
</tbody>
</table>
Surgical Data Lessons

- Most look at CABG or non-cardiac vascular surgery
- Retrospective studies all show odds are in the favor of statin users
- None are clear on whether statin use day of surgery or 4 weeks before surgery is best
- None can tell if statin withdrawal is harmful
- None quantify risks of statin use
Risks
Prospective Observational Study

- Major elective vascular surgery – 981 screened
- Pretreatment started approx 40 days before surgery for pts with elevated cholesterol
  - 44 patients (5%)
- Patients continued on chronic therapy
  - 182 (19%)
- Perioperative death and MI composite
  - 22 (8.8%) of statin users
  - 111 (14.7%) of the non-users

Harms

**TABLE 4** Postoperative Creatinine Phosphokinase (CPK) Levels in Statin Users and Nonusers*

<table>
<thead>
<tr>
<th>Postoperative CPK Levels</th>
<th>Statin User</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (95% CI)</td>
</tr>
<tr>
<td>≤1 × ULN</td>
<td>40 (33–47)</td>
</tr>
<tr>
<td>&gt;1 ×, ≤5 × ULN</td>
<td>43 (36–50)</td>
</tr>
<tr>
<td>&gt;5 ×, ≤10 × ULN</td>
<td>9 (5–13)</td>
</tr>
<tr>
<td>&gt;10 × ULN</td>
<td>8 (4–12)</td>
</tr>
</tbody>
</table>

*Levels are divided into normal (≤1 × upper limit of normal [ULN]), mildly elevated (>1 ×, ≤5 × ULN), moderately elevated (>5 ×, ≤10 × ULN), and severely elevated CPK levels (>10 × ULN).

Cl = confidence interval.

- Length of surgery was the only predictor of myopathy
- No case of rhabdomyolysis occurred
Harm Caveats

- Almost no studies have targeted harms as a primary outcome. Studies are not powered for this.
- Harms not assessed in patients who develop sepsis, acute renal failure, or hepatitis after surgery.
The Future & CONCLUSIONS
DECREASE-IV Study

- 4-year multi-armed placebo controlled study
- Evaluating the use of a statin and beta-blocker separately and together
- Patients > 40 years old
- Undergoing elective noncardiac surgery
- Have an estimated risk of cardiovascular death of more than 1%
- Have not used statins previously
- Do not have elevated cholesterol

My Recommendations

- Evaluate all patients for need for chronic statin therapy based on NCEP guidelines
- If not on chronic therapy but should be, start ASAP before surgery - pretreatment is probably better
- When seen inpatient, start statin ASAP if the patient should be receiving statin chronically
- Do not withhold statin from chronic users
- Consider statins in patients with multiple risk factors having moderate risk surgery
- Advise surgeons to follow LFTs and CPKs especially if the clinical condition changes
“for patients undergoing vascular surgery with or without clinical risk factors, statin use is reasonable.

patients with a risk factor who are undergoing intermediate-risk procedures could consider statin therapy

patients who already receiving statins and are undergoing noncardiac surgery should not have their statin discontinued
Benefit for moderate risk patients undergoing moderate risk surgery

When therapy should be started - 2 weeks, 1 month

Should therapy be started on the day of surgery if it was not started earlier

Which statin and what doses

How long should therapy be continued in patients who would not otherwise qualify for them

What are the risks of perioperative statin therapy