Dual Antiplatelet Therapy in CABG:
To Bleed? or Not To Bleed!!!

CV Surgery Symposium
January 14, 2017
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Linsey Krantz Hsieh, MPH
UVH CV Surgery TEAM.
Dual Antiplatelet Therapy in CABG: 
To Bleed? or Not To Bleed!!!

• Presentations
  – 30 mins or 50 mins?
  – Terrible time for this meeting:
    • Three weekends plus nights.
  – Expert?
    • Novice: P2Y12?
    • Not a pharmacist!
    • Not a hematologist!
    • Surgeon
      – Knife, suture, aspirin
  – Never enough room on a slide.
Dual Antiplatelet Therapy in CABG: To Bleed? or Not To Bleed!!!

• Objectives
  – Platelets: how, why
  – Antiplatelet therapy history
  – Antiplatelet therapy today
  – ACCF/AHA Guidelines in DAPT
    • Application to CABG(?)
  – CABG DAPT at our four Heart Programs
    • Brass knuckles or walk away?
  – Consider a strategy?
Dual Antiplatelet Therapy. Extrapolated points:

- The protection against ischemia afforded by DAPT in CABG for ACS comes at the price of increased risk of bleeding (small, but p<.05)
- Newer and more potent antiplatelet drugs are preferred over clopiogrel when possible, especially in first 90 days
- ACCF/AHA Guidelines recommend DAPT in CABG for ACS
- DAPT > 1 year now supported by the recent DAPT Study in PCI for ACS.
Why platelets?

• Platelets: first responders to acute vascular endothelial injury, producing both vasoactive and occlusive properties (vaso-occlusive).

• Acute Coronary Syndromes begin with fissuring or ulceration of a plaque, followed by thrombosis with or without occlusion mediated by platelet adhesion, activation, aggregation
  – Transient occlusion >> unstable angina or NSTEMI
  – Total occlusion >> STEMI
Adhesion

• Vessel endothelial injury exposes collagen and vWF to blood.
  – Collagen adheres plts through glycoproteins Ia,IIa, and VI receptors
  – vWF adheres plts through GP Ib-IX-V receptor
Activation

• Once adhered, plts become activated!
• Plts release ADP, serotonin, epinephrine, TXA2, COX 1, COX 2, etc, all activating the clotting cascade
  – Heparin, enoxaparin “Lovenox”, bivalirudin “Angiomax” inhibit intrinsic clotting cascade
  – GP IIb/IIIa inhibibitors: abciximab “ReoPro”, eptifibitide “Integrillin”, tirofiban “Aggrastat” inhibit fibrinogen>>fibrin
  – ADP binds to plt receptor P2Y12 >> activates GP IIb/IIIa, stimulating fibrinogen
  – Activated plts release COX 1 >> activates TXA 2 >> activates GP IIb/IIIa, stimulating fibrinogen
• Common endpoints with different pathways.
• Adhesion: collagen/vWF bind the plt
• Activation: bound plt releases ADP, TXA2, serotonin to stimulate GPIIbIIIa, and vasospasm
• Aggregation: activated GPIIbIIIa binds fibrinogen, clotting cascade
• Vicious propagating cycle initiated till white plug>>red plug>>thrombosis


ADP = adenosine diphosphate; GP = glycoprotein; TxA₂ = thromboxane A₂; vWF = von Willibrand factor
Aggregation >> Thrombosis

- So, tissue factor activates the clotting cascade, generating thrombin, which then further activates GPIIbIIIa, stimulating more platelet aggregation and binding of fibrinogen, to produce a stable platelet clot.
- White thrombus: initial platelet plug
- Red thrombus: platelet plug with activated fibrin with the clotting cascade, retains RBC’s
- Multiple pathways play synergistic roles in clot formation
Aggregation >> Thrombosis

- **White plug**
  - Predom platelets

- **Thrombus**
  - Activated clotting cascade with plts and RBCs

Definitions!!

- **GP IIbIIIa receptor:** plt receptor that binds fibrinogen & vWF, initiating clotting cascade
  - **Integrin complex receptor** = transmembranous receptors that are bridges for cell-cell and cell-extracellular matrix adhesions
  - Target for heparin, heparinoids, IIbIIIa inhibitors
- **P2Y receptor:** complex of eight purinergic glycoprotein platelet receptors stimulated by nucleotides like ATP, ADP
  - P2Y12 receptor specific to ADP activation
  - Activated P2Y12 receptor stimulates the GP IIbIIIa receptor above
  - Inhibited by thienopyridine blocking ADP-P2Y12 inhibitors
    - Clopidogrel, prasugrel, ticagrelor, ticlodipine (Ticlid)
    - Important: these four agents are all ADP blocking agents of the P2Y12 receptor, thus they are ADP antagonists, and P2Y12 receptor antagonists. The STS does not know this! Nor did I.
Antiplatelet agents:
Multiple pathways can be BLOCKED!

Aspirin

- Aspirin **irreversibly** inhibits cyclo-oxygenase 1 from converting arachidonic acid to thromboxane A2 (TXA2 is wicked stuff in CAD)
  - Blockage occurs in the platelet, TXA2 released outside of platelet
  - Decreases platelet activation, and vasoconstriction

- **In antiquity**
  - Greek/Chinese/Mesopotamians used willow tree bark for analgesia and anti-inflammatory properties; chewed, rubbed.

- **1758: first recorded clinical trial in history(!)**
  - Rev Edward Stone of the Royal Society of London, efficacy of ground dried English willow bark to treat thrombosis associated with malaria (salicylic acid)
Antiplatelet agents.
Multiple pathways can be BLOCKED!
Aspirin

- Aspirin
  - 1904: purification of salicylic acid to acetylsalicylic acid
    ASA reduced nasty side effects, and use as a NSAID
  - 1971: found to be a COX 1 inhibitor and prevented platelet aggregation
  - Biggest drawback: GI and intracranial bleeding
  - 1988: Lancet: Int’l Study of Infarct Survival (ISIS 2) Trial:
    - ASA use reduced reinfarct rate, stroke, 5 wk mortality, and all cause mortality after MI
      - 1986: Puel and Sigwart place first coronary stent

SV Ittaman, 2014
Antiplatelet agents.

P2Y12 receptor antagonists.

- Clopidogrel and prasugrel irreversibly inhibit the P2Y12 receptor, inhibiting plt activation and aggregation
- Prasugrel 10X more potent than clopidogrel (one less pass through the liver) and faster onset
- Ticagrelor reversibly inhibits P2Y12 receptor, no hepatic conversion, faster onset than prasugrel
- Cangrelor reversibly inhibits P2Y12 receptor, IV only, very fast, FDA approved June 2015. Not in use at UVH.
Thienopyridines
# Platelet Inhibitor Qualities

<table>
<thead>
<tr>
<th>Platelet Inhibitor</th>
<th>Aspirin</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
<th>Cangrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand</strong></td>
<td>Ubiquitous</td>
<td>Plavix</td>
<td>Effiant</td>
<td>Brilinta</td>
<td>Kengreal (Non-formulary)</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>162-325 mg load, 81 – 100 mg per day</td>
<td>150-600 mg po load* 75 mg po per day</td>
<td>30-60 mg load 10 mg per day</td>
<td>90-180 mg load 60-90 mg BID</td>
<td>4 ug/kg/min IV</td>
</tr>
<tr>
<td><strong>Metabolic Activation</strong></td>
<td>Gastrointestinal mucosal esterases</td>
<td>CyP450</td>
<td>CyP450</td>
<td>None.</td>
<td>None</td>
</tr>
<tr>
<td><strong>Time to Peak Activity</strong></td>
<td>1-2 hours</td>
<td>2-6 hours</td>
<td>0.5-4 hours</td>
<td>0.5-2 hours</td>
<td>2-30 mins</td>
</tr>
<tr>
<td><strong>Elimination half life</strong></td>
<td>3 hours</td>
<td>6 hours</td>
<td>2-15 hours</td>
<td>7-9 hours</td>
<td>0-30 mins</td>
</tr>
<tr>
<td><strong>ACC/AHA Class I rec for surgery delay</strong></td>
<td>None.</td>
<td>5-6 days</td>
<td>6-7 days</td>
<td>5 days (not in guideline)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Renal impairment adjustment</strong></td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td><strong>Cost per tablet</strong></td>
<td>$0.02</td>
<td>75 mg range $0.10 – $0.77</td>
<td>60 mg = $67.67 10 mg = $11.28</td>
<td>180 mg = $9.73 90 mg = $4.87 (BID)</td>
<td>50 mg vial = $700</td>
</tr>
<tr>
<td><strong>Charge to patient</strong></td>
<td>$0.40</td>
<td>75 mg = $5.76 - $9.73</td>
<td>60 mg = $133.77 10 mg = $60.46</td>
<td>180 mg = $52.88 90 mg = $29.03 (BID)</td>
<td>50 mg vial = $1100</td>
</tr>
<tr>
<td><strong>Aspirin</strong></td>
<td>81-100 mg</td>
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<td>81-100 mg</td>
<td>81-100 mg &gt; 100 mg diminishes P2Y12 inhibition.</td>
<td>81-100 mg</td>
</tr>
</tbody>
</table>

**Thieno-pyridines***

***Pyrimidine

**ATP analogue**

Definitions

- SIHD: Stable ischemic heart disease (2014 ACC/AHA Guideline for SIHD)
  - Stable known or stable suspected ischemic heart disease (IHD)
  - New onset chest pain; ie, “low risk” unstable angina (UA)
  - Stable pain syndromes
  - Asymptomatic IHD with appropriate medical therapy
  - Stable patients after PCI
  - Stable patients after CABG
Definitions

**ACS**: Acute Coronary Syndrome

- *By definition*, begins with disruption of the fibrous luminal plaque with initiation of thrombogenesis; ie, platelet activation, and vaso-occlusive progression.

- Non occlusion: NSTEMI (positive enzymes >> NQwMI or rarely QwMI), rest angina, high risk unstable angina (negative enzymes), crescendo angina
  - Canadian Cardiovascular Association class III and class IV angina

- Occlusion: STEMI, mostly resulting in QwMI, less frequently in NQMI

- Thus, 3 presentations make up **ACS**
  - **High risk unstable angina**
  - **NSTEMI**
  - **STEMI**

2014 ACC/AHA Guideline for ACS
Acute Coronary Syndromes

Lipid rich plaque formation

SIHD

ACS

2014 ACC/AHA Guideline for ACS
Acute Coronary Syndromes

**Presentation**

- Working Dx
- ECG
- Cardiac Biomarker

**Ischemic Discomfort**

- ACS
  - No ST Elevation
  - ST Elevation

**Diagnosis**

- NSTE-ACS
- STEMI

**Etiologies**

- Unstable Angina
- NSTEMI
- STEMI
- QwMI

2014 ACC/AHA Guideline for ACS
Why DAPT in PCI?
Early Short-term (30 day) trials support alternatives to ASA monotherapy, primarily DAPT: ASA + P2Y12.

Surgeons: this is all MI and PCI data!!!

<table>
<thead>
<tr>
<th>RCT Study Name</th>
<th>Test</th>
<th>Outcome</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPRIE: Lancet. 1996</td>
<td>ASA vs clopidogrel monotherapy in MI reduction</td>
<td>clopidogrel decreased MI rate and mortality</td>
<td>Aspirin is good, clopidogrel is better.</td>
</tr>
<tr>
<td>ISAR: NEJM. 1996</td>
<td>ASA + ticlodipine vs ASA + Coumadin after PCI</td>
<td>ASA+ticlodipine &gt; marked decrease in MI, and bleeding</td>
<td>DAPT better than ASA + coumadin</td>
</tr>
<tr>
<td>STARS: NEJM. 1998</td>
<td>ASA + ticlod vs ASA + Coumadin vs ASA only, after PCI</td>
<td>Marked decrease in stent rethrombosis with ASA + ticlod</td>
<td>Bleeding least with ASA alone, same rate for other two</td>
</tr>
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Long term trials (3-12 months) support DAPT!

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<tr>
<td>CURE: NEJM, 2001</td>
<td>NSTEMI patients: ASA + clopidogrel vs ASA + placebo for 3 to 12 months</td>
<td>MACCE signif lower in DAPT vs placebo, in both PCI and non-PCI treated pts.</td>
<td>Clopidogrel pretreatment and post tx &gt; 9 mos magnified beneficial results.</td>
</tr>
<tr>
<td>CREDO: JAMA, 2002</td>
<td>PCI for ACS patients: ASA mono vs ASA + clopidogrel for one year</td>
<td>Prolonged DAPT signif reduce MACCE at 1 yr.</td>
<td>Outcome even better when DAPT started pre treatment</td>
</tr>
</tbody>
</table>

Sigh, then came the onslaught of Cardiology throwing any concern of BLEEDING into the wind! You had a cold? Rx: CLOPIDOGREL!
RCT’s of DAPT in PCI for 12 + months.

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<tr>
<th>Trial (No. of patients)</th>
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<td>DAPT³ (9,961)</td>
<td>DAPT vs aspirin alone beyond 12 months</td>
<td>18 months</td>
<td>0.4% vs 1.4% a</td>
<td>4.3% vs 5.9% a</td>
<td>2.5% vs 1.6% a</td>
<td>DAPT &gt; 1 year decreased risk of stent thrombosis and MACE</td>
</tr>
<tr>
<td>ARCTIC- Interruption⁴⁶ (1,259)</td>
<td>DAPT vs aspirin alone beyond 12 months</td>
<td>17 months</td>
<td>0% vs 1%</td>
<td>4% vs 4%</td>
<td>1% vs &lt; 0.5%</td>
<td>No benefit of DAPT beyond 12 months</td>
</tr>
<tr>
<td>DES-LATE⁴⁷ (5,045)</td>
<td>DAPT vs aspirin alone beyond 12 months</td>
<td>24 months</td>
<td>0.5% vs 0.3%</td>
<td>2.4 vs 2.6%</td>
<td>1.1% vs 1.4%</td>
<td>No benefit of DAPT for 24 more months at end of 1 year</td>
</tr>
<tr>
<td>CREDO⁴⁰ (2,116)</td>
<td>DAPT vs aspirin and placebo up to 12 months</td>
<td>12 months</td>
<td>Not reported</td>
<td>8.5% vs 11.5% a</td>
<td>8.8% vs 6.7% a,b</td>
<td>Significant benefit of DAPT vs placebo at 1 year</td>
</tr>
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<td>OPTIMIZE⁴² (3,118)</td>
<td>DAPT for 3 vs 12 months</td>
<td>12 months</td>
<td>0.3% vs 0.1%</td>
<td>2.6% vs 2.6%</td>
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<td>EXCELLENT⁴¹ (1,493)</td>
<td>DAPT for 6 vs 12 months</td>
<td>12 months</td>
<td>0.9% vs 0.1%</td>
<td>8% vs 8.5%</td>
<td>0.3% vs 0.6%</td>
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<td>PRODIGY⁴⁵ (1,970)</td>
<td>DAPT for 6 vs 12 months</td>
<td>12 months</td>
<td>3.9% vs 4.7%</td>
<td>10.1% vs 10%</td>
<td>1.6% vs 0.6% a</td>
<td>No significant benefit of 24 vs 6 months of DAPT with clopidogrel</td>
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<td>SECURITY⁴⁰ (1,399)</td>
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P < .05.
DAPT = dual antiplatelet therapy; MACE = major adverse cardiac event
RCT’s of DAPT in PCI for 12 + months.

Multiple small RCT’s failed to demonstrate MACE benefit of DAPT beyond 1 year, many revealed noninferiority only between 6 months of therapy or 12 months of therapy, but not BETTER.

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**“DAPT” Study: Mauri et al. NEJM 2014; 371:2155-2166**
- multicenter, dbl blind RCT, placebo controlled
- examined DAPT (thienopyridine) vs ASA monotx after 1 yr in 9961 PCI patients
- followed an additional 18 mos after original 12 mos
- efficacy endpoints were stent thrombosis and MACE
- safety endpoint was moderate to severe bleeding


$^a$ P < .05.
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DAPT after all cause PCI.

Summary

- DAPT for at least 6 months, up to 12 months (I-IIa, B): PRODIGY does not support > 12 months.
  - ASA (81 mg) a given (I, A).
- Ticagrelor = prasugrel > clopidogrel for mortality, stent thrombosis
- Bleeding greatest in DAPT with ticagrelor (2.6%) least with clopidogrel (1.4%), p<.05.
- Consider ticagrelor for 30 days, then clopidogrel, for better compliance.
- Patients needing surgeries on DAPT: Interrupt DAPT after 30 days if possible (5% after vs 30% stent rethrombosis rate), resume as soon as possible after bleeding risk normalized (PEGASUS, CHARISMA).

Number needed to treat to benefit!
PEGASUS TIMI 54

- Bittl et al.
  - Best case scenario:
  - P2Y12 (ticagrelor) for 12 mos or > therapy after newer gen DES tx
    - 1,000 post MI pts with ticagrelor 60-90 mg BID
    - >> 4 fewer MI, CVA, death
  - Caused 3 major bleeds
  - DAPT made NO difference though in 970 patients treated with monotherapy
    - 30 events in control group,
    - DAPT with ticagrelor had 26 events
CONCLUSION of DAPT in PCI?

Madorsky, Melanie.
With permission, please?
So WHEN do the Surgeons get on board!

• 2011: ACCF/AFA/STS Guideline for CABG
  – NO COMMENT!
  – No surgeon on the committee either.
• Maybe we’ben on dis longer than you think!
DAPT after CABG.

The History.

- ASA improves 1 year graft patency, 1 year re-MI rate, stroke, mortality. NEJM 1984;310. Circ 1988;77.

- DAPT by 2010.
  - Only one RCT: (Gao G. JACC 2010;56) Clopidogrel + ASA (113) vs ASA (111)
  - Improved 3 month VG patency p<.05

- DAPT by 2013
  - Meta analysis: (Deo SV. J Card Surg 2013;28) 5 RCT’s and 6 observ. studies. Clopidogrel + ASA vs ASA.
    - 25,728 pts
    - 90 day vein graft occlusion reduced 40%, p=.05
    - 30 d mortality DAPT 0.8% vs ASA 1.9%, p<.0001
    - 30 d MI rate comparable p=.31
    - Major bleeding increased 17%, p=.05

- UVH: DAPT in 15-20% of CABG for > 5 years.
  - All coronary endarterectomies
  - Selected high risk cases: that is, crap targets!
    - Efficacy: praying the grafts don’t go down!!!
DAPT after CABG: 2015

  – Meta analysis. Queried all RCT’s (only) through Aug 2015 of CABG comparing dual vs mono therapy, or higher vs lower intensity DAPT
  – 9 RCTs included: 5 elective CABG, 4 ACS CABG subgroups
  – Excluded: (most surveyed studies are PCI subset studies)
    • CHARISMA, DISPERSE, COMMIT, TRILOGY ACS, JUMBO-TIMI 26: no f/u on CABG pts
    • CLARITY-TIMI 28, CURRENT OASIS 7: patients did not receive DAPT after CABG
    • CAPRIE: no reporting on CABG patients
    • TRACER: randomized patients to non P2Y12 agents, so not included

Meta analysis characteristics:

### SIHD

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Patients</th>
<th>No. of Centres</th>
<th>Enrolment period</th>
<th>Treatment Follow Up Post Randomization</th>
<th>Median Time to CABG Post Randomization</th>
<th>Treatment Follow Up Post CABG</th>
<th>Funding</th>
<th>Patients</th>
<th>Mean Age (years)</th>
<th>% Male</th>
<th>BMI</th>
<th>Diabetes</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>Done (mg/d)</td>
<td>325 then 81</td>
<td>1</td>
<td>Nov 2006 - Feb 2008</td>
<td>30 (all)/49 (median)</td>
<td>(Randomized At Time of CABG)</td>
<td>30 (all)/49 (median)</td>
<td>Public</td>
<td>224</td>
<td>65</td>
<td>90</td>
<td>31</td>
<td>35%</td>
<td>70%</td>
</tr>
<tr>
<td>Clopidogrel 300 mg/d vs placebo</td>
<td>100</td>
<td>12</td>
<td>Dec 2007 - Dec 2008</td>
<td>3 months (all)</td>
<td>12 months (all)</td>
<td>n/a (not included)</td>
<td>n/a (not included)</td>
<td>Public / Industry</td>
<td>113</td>
<td>67</td>
<td>59</td>
<td>26</td>
<td>40%</td>
<td>59%</td>
</tr>
<tr>
<td>Clopidogrel 75 mg/d vs placebo</td>
<td>300</td>
<td>2</td>
<td>May 2006 - Oct 2007</td>
<td>12 months (all)</td>
<td>6 months (all)</td>
<td>n/a (not included)</td>
<td>n/a (not included)</td>
<td>Public / Industry</td>
<td>300</td>
<td>65</td>
<td>74</td>
<td>26</td>
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<td>46%</td>
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<tr>
<td>Clopidogrel 75 mg/d vs 75 mg/d</td>
<td>305</td>
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<td>Jun 2010 - Feb 2013</td>
<td>12 months (all)</td>
<td>12 months (all)</td>
<td>n/a (not included)</td>
<td>n/a (not included)</td>
<td>Public / Industry</td>
<td>310</td>
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<td>96%</td>
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<tr>
<td>Clopidogrel 300 mg/d then 75 mg/d vs placebo</td>
<td>335</td>
<td>1</td>
<td>Jun 1999 - Apr 2001</td>
<td>9 months (mean)</td>
<td>9 months (mean)</td>
<td>255 days (IQR 12-70.5)</td>
<td>-20 days</td>
<td>n/a (not included)</td>
<td>219</td>
<td>64</td>
<td>74</td>
<td>26</td>
<td>22%</td>
<td>96%</td>
</tr>
<tr>
<td>Clopidogrel 300 mg/d then 75 mg/d vs 75 mg/d</td>
<td>335</td>
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<td>Dec 1998 - Sep 2000</td>
<td>9 months (mean)</td>
<td>9 months (mean)</td>
<td>255 days (IQR 12-70.5)</td>
<td>-20 days</td>
<td>n/a (not included)</td>
<td>219</td>
<td>64</td>
<td>74</td>
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<td>96%</td>
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<td>Ticagrelor 180 then 90 mg bid vs Clopidogrel 300 then 75 mg/d</td>
<td>75-100</td>
<td>1</td>
<td>Oct 2006 - Jul 2008</td>
<td>14 months (mean)</td>
<td>14 months (mean)</td>
<td>255 days (IQR 12-70.5)</td>
<td>-20 days</td>
<td>n/a (not included)</td>
<td>219</td>
<td>64</td>
<td>74</td>
<td>26</td>
<td>22%</td>
<td>96%</td>
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<tr>
<td>Pravasol 60 then 10 mg/d vs Clopidogrel 300 then 75 mg/d</td>
<td>75-100</td>
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<td>Nov 2004 - Jan 2007</td>
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<td>14 months (mean)</td>
<td>255 days (IQR 12-70.5)</td>
<td>-20 days</td>
<td>n/a (not included)</td>
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<td>22%</td>
<td>96%</td>
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</table>

### ACS

<table>
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<tr>
<th>Drug</th>
<th>Study</th>
<th>Patients</th>
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<th>Enrolment period</th>
<th>Treatment Follow Up Post Randomization</th>
<th>Median Time to CABG Post Randomization</th>
<th>Treatment Follow Up Post CABG</th>
<th>Funding</th>
<th>Patients</th>
<th>Mean Age (years)</th>
<th>% Male</th>
<th>BMI</th>
<th>Diabetes</th>
<th>Hypertension</th>
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<td>(Randomized At Time of CABG)</td>
<td>30 (all)/49 (median)</td>
<td>Public</td>
<td>224</td>
<td>65</td>
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<td>35%</td>
<td>70%</td>
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<tr>
<td>Goso et al.</td>
<td>[13]</td>
<td>113</td>
<td>2</td>
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<td>n/a (not included)</td>
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<td>40%</td>
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<tr>
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<tr>
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<td>22%</td>
</tr>
<tr>
<td>Grepachronic</td>
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<td>Jun 1999 - Apr 2001</td>
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<td>74</td>
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<td>22%</td>
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<tr>
<td>CREDO</td>
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<td>Dec 1998 - Sep 2000</td>
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<td>255 days (IQR 12-70.5)</td>
<td>-20 days</td>
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<td>22%</td>
</tr>
<tr>
<td>CURE</td>
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<td>Oct 2006 - Jul 2008</td>
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<td>255 days (IQR 12-70.5)</td>
<td>-20 days</td>
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<td>22%</td>
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<tr>
<td>PLATO</td>
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<tr>
<td>TRITON-TIMI 38</td>
<td>[21]</td>
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<td>255 days (IQR 12-70.5)</td>
<td>-20 days</td>
<td>n/a (not included)</td>
<td>219</td>
<td>64</td>
<td>74</td>
<td>26</td>
<td>22%</td>
</tr>
</tbody>
</table>

Mortality: DAPT generally better than monotx

1. Mortality equal between low intensity DAPT and ASA monotherapy
2. Mortality strongly improved by high intensity DAPT over low intensity DAPT

MI: DAPT no better than monotherapy, high vs low intensity, ACS vs elective.

Stroke: DAPT no better than monotherapy, high vs low intensity, ACS vs elective.

Composite Mortality, MI, Stroke: DAPT slightly better, no benefit high vs low intensity.

**Bleeding:** DAPT slightly increases risk over monotx, no difference high vs low intensity.

Verma: Meta analysis conclusions

• High intensity DAPT in the post CABG ACS patients reduces mortality 50% at up to 12 months
  • This does NOT hold up for clopidogrel
• Very small pools of patients in both high intensity and low intensity groups
• TRITON TIMI 3: mortality reduced, but risk of bleeding increased
  • Prasugrel used in this study
• Ticagrelor is a reversible P2Y12
  • PLATO: ticagrelor vs clopidogrel reduced mortality 20% in the PCI group and 50% in CABG group, but no difference in bleeding whether CABG or PCI

• Limitations
  • Small CABG populations
  • Follow up for elective (SIHD) CABG 1.5 – 12 months, ACS CABG 6-12 months.
  • Remarkably, in the ACS CABG cohort (4 RCT’s) only 66% of patients even resumed DAPT, suggesting strong bias in that group. The sicker 34% likely did not receive DAPT post op.

• This meta analysis was NOT included in the ACCF/AHA Guideline on DAPT.

Verma Conclusion

• Resumption of higher intensity DAPT but not lower intensity DAPT reduces all-cause mortality by 50% in the ACS CABG patient
• Net clinical benefit (efficacy vs bleeding) favors use of ticagrelor
• No significant benefit or harm in DAPT after SIHD CABG patient
• RCT’s so small that results may be inconclusive
• Bleeding slightly increased in DAPT vs ASA monotherapy
• Large prospective RCT ‘s needed!

So NOW the Surgeons get on board?

- 2011: ACCF/AHA Guideline for CABG
  - NO COMMENT!
- 2016

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines


Developed in Collaboration With the American Association for Thoracic Surgery, American Society of Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons
Breaking News
subgroup analysis

• **Future REvascularization Evaluation in patients with Diabetes Mellitus**
  – 544 CABG pts rec’d DAPT vs 251 CABG pts rec’d ASA
    • International, multicenter, type II diabetics, CLOPIDOGREL
  – Nonrandomized, POD 30 evaluation for DAPT or not.
    • Median duration of DAPT post op = .98 years.
  – Primary analysis: 5 years post CABG outcomes
    • All cause mortality, MI, stroke. Looking for long term benefit.
  – Secondary analysis: 1 year post CABG outcomes
    • Individual component death, vascular death, CV hospitalization. Looking for short term benefit.
  – Safety analysis: bleeding, bleeding hospitalizations
  – Any patient that DIED within 30 days of CABG was excluded!

Patient demographics:

- Two groups similar except
  - DAPT were younger, non-Caucasian.

- Interesting:
  - ACS 29-36%
  - SIHD 68-73%
  - Hgb 13.9 mg/dl
  - LVEF 60%
  - HgbA1c 7.3%
  - Mean grafts: 3
  - Endarterectomy: 6.3% DAPT vs 3.6% mono

Primary endpoints: 5 year
Secondary endpoints: 1 year

Summary:
- NO endpoints met significance!
- 5 yr and 1 yr mortality better with DAPT
- 1 year MI better with mono
- No difference in bleeds
- Disappointing!

Summary Review

- DAPT appropriate for most CABG patients: decreased mortality, improved graft patency
  - Therapy for 1 year
  - Exclusions: bleeding risk
- ASA 81 mg po QD for all CABG patients (not 325)
- ASA/clopidogrel for CABG in SIHD.
- Controversy: Which P2Y12 inhibitor for CABG in ACS is better?
  - Ticagrelor = prasugrel >> clopidogrel in mortality, graft patency
  - Prasugrel increases risk of CVA in prior stroke patients, bleeding in prior bleed patients
  - TRITON TIMI 3 revealed higher bleeding risk in ticagrelor (14%) vs clopidogrel (4%)
- Clopidogrel generic, the other two are not, and are expensive.
Increased Ischemic Risk/Risk of Stent Thrombosis (may favor longer-duration DAPT)

- Increased ischemic risk
  - History of prior bleeding
  - Advanced age
  - Oral anticoagulant therapy
  - ACS presentation
  - Female sex
  - Multiple prior MIs
  - Advanced age
  - Extensive CAD
  - Low body weight
  - Diabetes mellitus
  - CKD
  - CKD
  - Diabetes mellitus
- Increased risk of stent thrombosis
  - Anemia
  - ACS presentation
  - Chronic steroid or NSAID therapy
  - Diabetes mellitus
  - Left ventricular ejection fraction <40%
  - First-generation drug-eluting stent
  - Stent undersizing
  - Stent underdeployment
  - Small stent diameter
  - Greater stent length
  - Bifurcation stents
  - In-stent restenosis

Increased Bleeding Risk (may favor shorter-duration DAPT)

- Increased bleeding risk
  - History of prior bleeding
  - Advanced age
  - Female sex
  - Low body weight
  - Diabetes mellitus
  - CKD
  - Diabetes mellitus
  - Left ventricular ejection fraction <40%
  - First-generation drug-eluting stent
  - Stent undersizing
  - Stent underdeployment
  - Small stent diameter
  - Greater stent length
  - Bifurcation stents
  - In-stent restenosis
Factors to calculate the DAPT Score

- Derived for the **DAPT Study**
  - A score \( \geq 2 \): favorable benefit/risk ratio for prolonged DAPT (greater than 1 year)
    - Decreased MI rate and stent thrombosis
    - Bleeding risk NOT increased
  - A score \(< 2\): unfavorable benefit/risk ratio for prolonged DAPT
    - Stop DAPT per guideline indication
    - Increased bleeding risk with prolongation
    - MI and stent thrombosis are NOT improved

<table>
<thead>
<tr>
<th>Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ( \geq 75 \text{ y} )</td>
<td>-2</td>
</tr>
<tr>
<td>Age 65 to (&lt; 75 \text{ y} )</td>
<td>-1</td>
</tr>
<tr>
<td>Age (&lt; 65 \text{ y} )</td>
<td>0</td>
</tr>
<tr>
<td>Current cigarette smoker</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>Stent diameter (&lt; 3 \text{ mm} )</td>
<td>1</td>
</tr>
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<td>Paclitaxel-eluting stent</td>
<td>1</td>
</tr>
<tr>
<td>CHF or LVEF (&lt; 30% )</td>
<td>2</td>
</tr>
<tr>
<td>Saphenous vein graft PCI</td>
<td>2</td>
</tr>
</tbody>
</table>

Yew RW. JAMA. In press.
Triple Therapy?

- 2-3 fold increase in bleeding complications
- Appropriate in limited patient populations:
  - CABG (PCI) patient (ACS) with atrial fib &/or valve
- Multiple trials underway: DAPT vs Triple Tx.
  - Clopidogrel and Coumadin
    vs.
  - Clopidogrel and Coumadin and Aspirin

**TABLE 6**

<table>
<thead>
<tr>
<th>Summary and Synthesis of Guideline, Expert Consensus Documents, and Comprehensive Review Article Recommendations on the Management of Patients Treated With Triple Therapy (14,88,91-93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assess ischemic and bleeding risks using validated risk predictors (e.g., CHA\textsubscript{2}DS\textsubscript{2}-VASc, HAS-BLED)</td>
</tr>
<tr>
<td>Keep triple therapy duration as short as possible; dual therapy only (oral anticoagulant and clopidogrel) may be considered in select patients</td>
</tr>
<tr>
<td>Consider a target INR of 2.0-2.5 when warfarin is used</td>
</tr>
<tr>
<td>Clopidogrel is the P2Y\textsubscript{12} inhibitor of choice</td>
</tr>
<tr>
<td>Use low-dose (=100 mg daily) aspirin</td>
</tr>
<tr>
<td>PPIs should be used in patients with a history of gastrointestinal bleeding and are reasonable to use in patients with increased risk of gastrointestinal bleeding</td>
</tr>
</tbody>
</table>

2014 ACC/AHA Guideline for NSTE ACS
Master Algorithm for Duration of P2Y12 Inhibitor Tx in Patients with CAD

### CABG Recommendations

<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>C-EO</td>
<td>In patients treated with DAPT after coronary stent implantation who subsequently undergo CABG, P2Y₁₂ inhibitor therapy should be resumed postoperatively so that DAPT continues until the recommended duration of therapy is completed.</td>
</tr>
<tr>
<td>I</td>
<td>C-LD</td>
<td>In patients with ACS (NSTEMI or STEMI) being treated with DAPT who undergo CABG, P2Y₁₂ inhibitor therapy should be resumed after CABG to complete 12 months of DAPT therapy after ACS (52-54,118-120).</td>
</tr>
<tr>
<td>I</td>
<td>B-NR</td>
<td>In patients treated with DAPT, a daily aspirin dose of 81 mg (range, 75 mg to 100 mg) is recommended (56-60,75-78).</td>
</tr>
<tr>
<td>IIb</td>
<td>B-NR</td>
<td>In patients with SIHD, DAPT (with clopidogrel initiated early postoperatively) for 12 months after CABG may be reasonable to improve vein graft patency (121-125).</td>
</tr>
</tbody>
</table>

The Definition of Dual Anti-Platelet Therapy in STS is Unclear

<table>
<thead>
<tr>
<th>Medication(s) Prescribed:</th>
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<td>Antiplatelets</td>
<td>Aspirin</td>
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<tr>
<td></td>
<td>P2Y12 Antagonists</td>
<td>□ Yes □ No □ Contraindicated</td>
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<td></td>
<td>ADP Inhibitor</td>
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<tr>
<td></td>
<td>Other Antiplatelet</td>
<td>□ Yes □ No □ Contraindicated</td>
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</table>
This Has Led to Problematic Data Collection

<table>
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<td>ADP Inhibitors</td>
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<td>Among Eligible Cases</td>
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<td>5.5%</td>
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<td>Among Eligible Cases</td>
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<td>13.2%</td>
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<td>28.2%</td>
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<td>Among Eligible Cases</td>
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<td>2.0%</td>
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<td>0.9%</td>
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## ADP and P2Y12 at Discharge for Isolated CABG Patients

**STS Harvest Report**  
**January 2016 - June 2016**

<table>
<thead>
<tr>
<th></th>
<th>Dixie</th>
<th>McKay</th>
<th>UVH</th>
<th>Like STS</th>
<th>IMED</th>
<th>IMED Like STS</th>
<th>All STS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual Anti-Platelet</td>
<td>4.1%</td>
<td>0.0%</td>
<td>18.0%</td>
<td>36.3%</td>
<td>4.5%</td>
<td>37.0%</td>
<td>36.5%</td>
</tr>
</tbody>
</table>
MI <= 7 Days Prior to Surgery Isolated CABG Patients
STS Harvest Report
January 2016 - June 2016

<table>
<thead>
<tr>
<th>MI &lt;= 7 Days</th>
<th>Dixie</th>
<th>McKay</th>
<th>UVH</th>
<th>Like STS</th>
<th>IMED</th>
<th>IMED Like STS</th>
<th>All STS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI &lt;= 7 Days</td>
<td>45.6%</td>
<td>40.4%</td>
<td>56.9%</td>
<td>30.6%</td>
<td>36.7%</td>
<td>24.7%</td>
<td>29.2%</td>
</tr>
</tbody>
</table>
Percent of All Patients with Any CABG Procedure Discharged on Dual Anti-Platelet Therapy
1/1/2013-9/30/2016

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Average 2013</th>
<th>2013 Q2</th>
<th>2013 Q4</th>
<th>2014 Q2</th>
<th>2014 Q4</th>
<th>2015 Q2</th>
<th>2015 Q4</th>
<th>2016 Q2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIXIE</td>
<td>6%</td>
<td>10.0%</td>
<td>14.9%</td>
<td>12.5%</td>
<td>9.3%</td>
<td>7.5%</td>
<td>0.0%</td>
<td>3.8%</td>
</tr>
<tr>
<td>MCKAY</td>
<td>7%</td>
<td>21.1%</td>
<td>8.1%</td>
<td>11.4%</td>
<td>11.9%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>UVH</td>
<td>19%</td>
<td>21.9%</td>
<td>18.9%</td>
<td>23.5%</td>
<td>11.1%</td>
<td>18.4%</td>
<td>15.9%</td>
<td>17.4%</td>
</tr>
<tr>
<td>IMED</td>
<td>5%</td>
<td>7.3%</td>
<td>0.0%</td>
<td>7.8%</td>
<td>12.5%</td>
<td>3.1%</td>
<td>6.6%</td>
<td>8.9%</td>
</tr>
</tbody>
</table>
### Isolated CABG from Total Heart Surgery By Facility 1/1/2013-9/30/2016

<table>
<thead>
<tr>
<th>Facility</th>
<th>Patients with Isolated CABG</th>
<th>Number of Cases</th>
<th>Rate of Patients with Isolated CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIXIE</td>
<td>605</td>
<td>759</td>
<td>79.7%</td>
</tr>
<tr>
<td>MCKAY</td>
<td>397</td>
<td>603</td>
<td>65.8%</td>
</tr>
<tr>
<td>UVH</td>
<td>431</td>
<td>532</td>
<td>81.0%</td>
</tr>
<tr>
<td>IMED</td>
<td>617</td>
<td>870</td>
<td>70.9%</td>
</tr>
</tbody>
</table>
Patients with Acute Coronary Syndrome (ACS) Receiving Any Type of CABG Surgery
1/1/2013 – 9/30/2016

<table>
<thead>
<tr>
<th>Facility</th>
<th>Patients with ACS</th>
<th>Number of Cases</th>
<th>% of Patients with ACS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIXIE</td>
<td>482</td>
<td>759</td>
<td>63.5%</td>
</tr>
<tr>
<td>MCKAY</td>
<td>395</td>
<td>603</td>
<td>65.5%</td>
</tr>
<tr>
<td>UVH</td>
<td>367</td>
<td>532</td>
<td>69.0%</td>
</tr>
<tr>
<td>IMED</td>
<td>518</td>
<td>870</td>
<td>59.5%</td>
</tr>
</tbody>
</table>

Acute Coronary Syndrome is defined using the STS database to include: Prior MI in <= 7 days, NYHA Class III or IV within 2 weeks, cardiogenic shock at time of procedure or prior 24 hours, or unstable angina, STEMI or Non-STEMI MI at time of admission or time of surgery.
Percent of Patients with ACS with Isolated CABG Procedure Discharged on Dual Anti-Platelet Therapy 1/1/2013-9/30/2016
30-Day Mortality for All Patients with Any CABG Procedure
1/1/2013 – 9/30/2016

<table>
<thead>
<tr>
<th></th>
<th>Patients who Died within 30 Days</th>
<th>Number of Cases</th>
<th>Rate of Patients who Died within 30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIXIE</td>
<td>No Dual Anti-Platelet</td>
<td>27</td>
<td>3.8%</td>
</tr>
<tr>
<td></td>
<td>On Dual Anti-Platelet</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>MCKAY</td>
<td>No Dual Anti-Platelet</td>
<td>26</td>
<td>4.6%</td>
</tr>
<tr>
<td></td>
<td>On Dual Anti-Platelet</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>UVH</td>
<td>No Dual Anti-Platelet</td>
<td>17</td>
<td>3.9%</td>
</tr>
<tr>
<td></td>
<td>On Dual Anti-Platelet</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>IMED</td>
<td>No Dual Anti-Platelet</td>
<td>30</td>
<td>3.6%</td>
</tr>
<tr>
<td></td>
<td>On Dual Anti-Platelet</td>
<td>0</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

After controlling for differences in age, sex and STS risk score for morbidity and mortality, the likelihood of 30-day mortality was not significantly different whether or not the patient received dual anti-platelet therapy.
After controlling for differences in age, sex and STS risk score for morbidity and mortality, the likelihood of reoperation for bleeding in 30 days was not significantly different whether or not the patient received dual anti-platelet therapy.
Non-Surgical Intervention for Bleeding within 30 Days for All Patients with CABG 1/1/2013 – 9/30/2016

<table>
<thead>
<tr>
<th></th>
<th>Patients with Non-Surgical Complications</th>
<th>Number of Cases</th>
<th>Rate of Non-Surgical Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIXIE</td>
<td>No Dual Anti-Platelet 39</td>
<td>712</td>
<td>5.5%</td>
</tr>
<tr>
<td></td>
<td>On Dual Anti-Platelet 2</td>
<td>47</td>
<td>4.3%</td>
</tr>
<tr>
<td>MCKAY</td>
<td>No Dual Anti-Platelet 30</td>
<td>560</td>
<td>5.4%</td>
</tr>
<tr>
<td></td>
<td>On Dual Anti-Platelet 2</td>
<td>43</td>
<td>4.7%</td>
</tr>
<tr>
<td>UVH</td>
<td>No Dual Anti-Platelet 5</td>
<td>432</td>
<td>1.2%</td>
</tr>
<tr>
<td></td>
<td>On Dual Anti-Platelet 2</td>
<td>100</td>
<td>2.0%</td>
</tr>
<tr>
<td>IMED</td>
<td>No Dual Anti-Platelet 17</td>
<td>824</td>
<td>2.1%</td>
</tr>
<tr>
<td></td>
<td>On Dual Anti-Platelet 2</td>
<td>46</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

After controlling for age, sex, and STS risk of morbidity and mortality, there was no significant difference in risk of non-surgical intervention for bleeding in patients on dual anti-platelet therapy vs. those not on dual anti-platelet therapy.
30-Day Combined Mortality and Complication Rate for All Patients at All Facilities with any CABG Procedure 1/1/2013-9/30/2016

<table>
<thead>
<tr>
<th></th>
<th>Patients with Complication/Death</th>
<th>Number of Cases</th>
<th>Rate of Complication/Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Dual Anti-Platelet</td>
<td>253</td>
<td>2,528</td>
<td>10.0%</td>
</tr>
<tr>
<td>On Dual Anti-Platelet</td>
<td>13</td>
<td>236</td>
<td>5.5%</td>
</tr>
</tbody>
</table>

After controlling for sex, age, and STS risk of morbidity and mortality there was no difference in any complication for patients on dual anti-platelet therapy compared to those who were not on dual anti-platelet therapy. (Complications included: 30-day mortality, surgery due to bleeding, and non-surgical interventions and readmissions due to bleeding.)
Intermountain CV Surgery Summary

• We are not employing the ACCF/AHA Guidelines for DAPT after CABG
  • In our system, nor in comparison to the STS.

• There was no significant difference in bleeding complications or death within 30 days of surgery between patients on DAPT and patients not on DAPT after controlling for sex, age, and STS Risk Score for Morbidity and Mortality.

• We have not evaluated for long-term benefits for patients on DAPT, but we only started treating significant numbers of CABG patients with DAPT in Quarter 3 2016.

• Future work in 1-5 years will continue to monitor risk and measure long-term benefit.

• UVH data support following the ACC/AHA guideline for dual anti-platelet therapy after CABG.
  • This will generate the potential benefit expected by the guidelines.
  • But confirms the low risk expressed by the guidelines.
  • For those reasons, expected benefit exceeds recognized risks.
Summary Proposal:

Utah Valley Hospital

- Follow the guidelines.
- ASA 81 mg po Q day to include evening of surgery
- ACS: ticagrelor + ASA for 30 days, then clopidogrel + ASA to 1 year
- SIHD: clopidogrel + ASA for 1 year
  - 15% nonresponders
- P2Y12 and ASA start evening of surgery
  - Load? Yes.
  - Cut or pull wires?