Too Much of a Good Thing? A Comparison of Standard Versus Extended Dual Antiplatelet Therapy Following the Placement of Drug- Eluting Stents

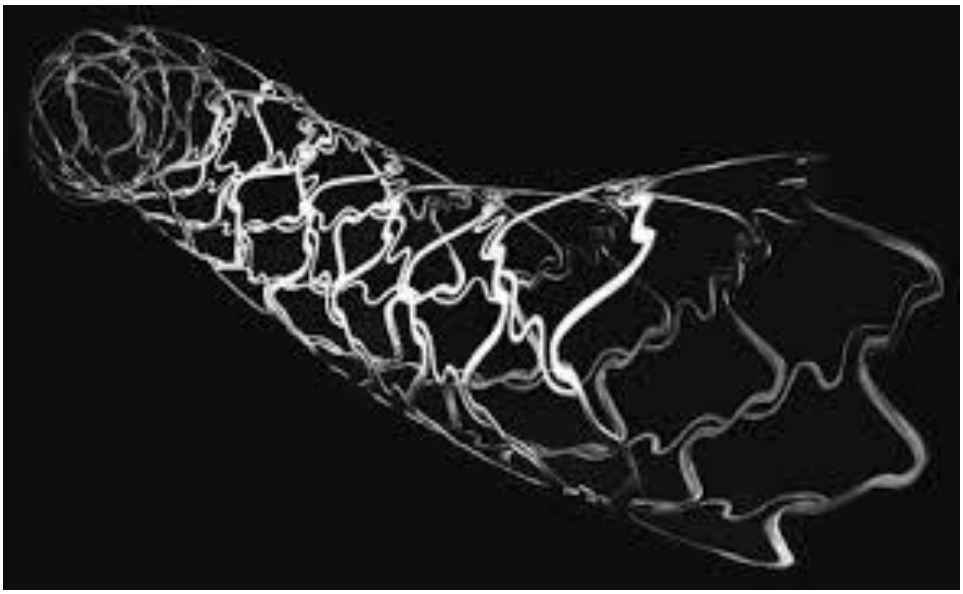

Illustration from Eur Heart J, Fall 2014

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Learning Objectives

1. Discuss the pathophysiology of coronary artery disease and indications for stent placement
2. List the antiplatelet therapy options that may be used following the placement of drug-eluting stents.
3. Analyze primary literature comparing 12 month to extended duration dual antiplatelet therapy
4. Identify patient specific factors that favor an extended duration of dual antiplatelet therapy

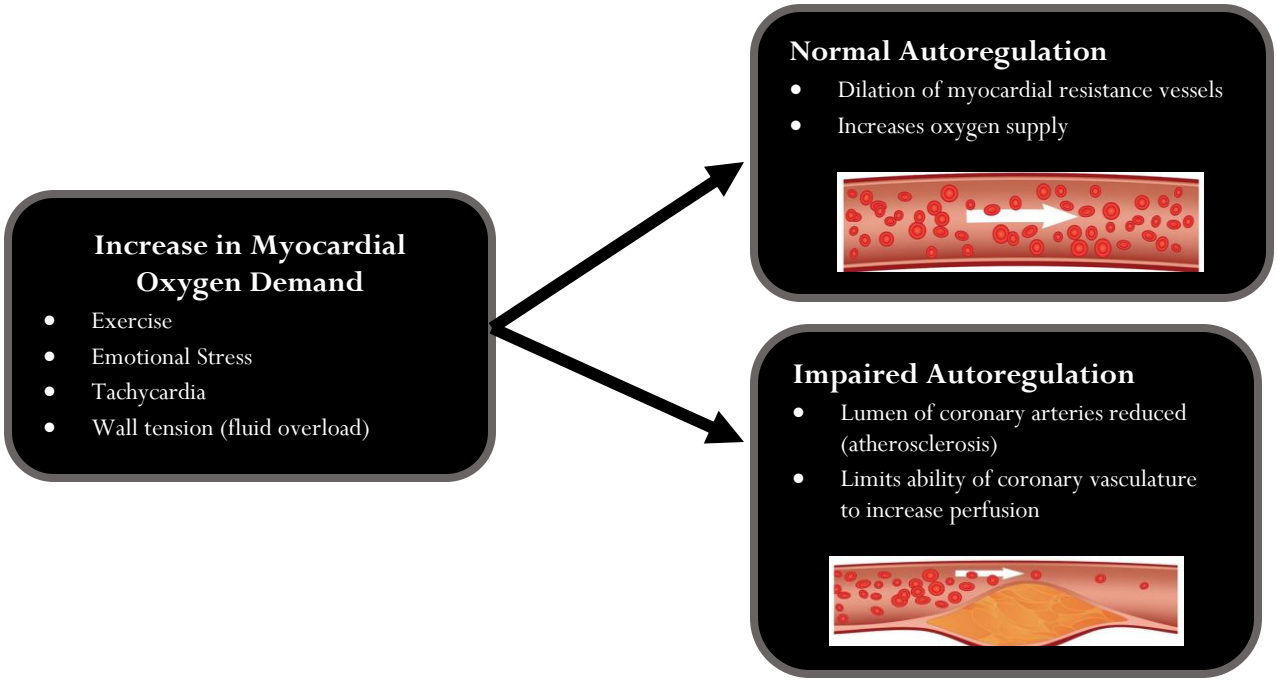
Coronary Artery Disease

Background and Pathophysiology

The Coronary Arteries

- Deliver oxygenated blood to the myocardial tissue, predominantly during diastole
- Coronary circulation driven by heart's oxygen demand (coronary vascular beds vary resistance)
- Largest determinants of oxygen demand: heart rate, myocardial contractility, and myocardial wall tension

Figure 1: Disease State Pathophysiology[1–3]



Consequences of Impaired Perfusion:[1,2,4,5]

- Symptoms
  - None (silent ischemia)
  - Chest pain (with or without exertion)
  - Pain in or radiating to the back, arm, neck, jaw, teeth, or epigastrium
- Myocardial Changes
  - Less severe presentation: minimal
  - More severe presentation: death of myocardial cells and increased markers of myocardial necrosis (troponin, CK-MB, myoglobin)
- Functional Changes
  - Less severe presentation: minimal
  - More severe presentation:
    - EKG changes, ventricular arrhythmias, cardiac arrest
    - Loss of left ventricular function, heart failure, cardiogenic shock

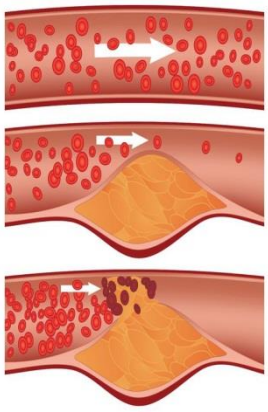
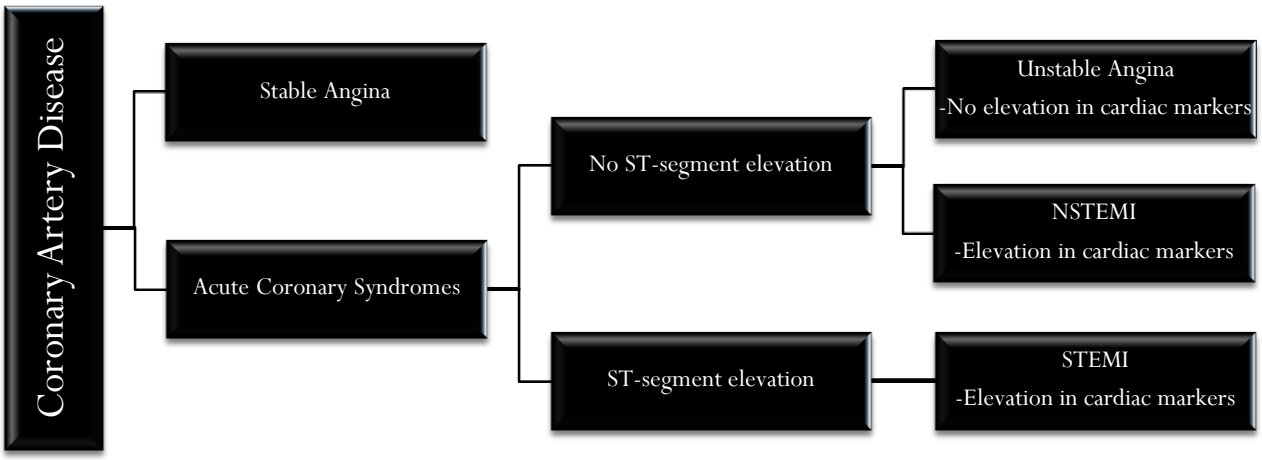


Figure 2: Classifications of Coronary Artery Disease[6–8]



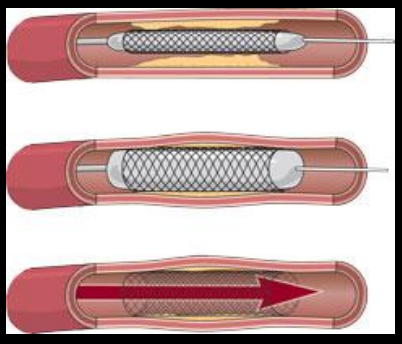
Guideline Recommended Treatment Options[6–8]

- **Stable Angina**
  - Guideline-Directed Medical Therapy (GDMT)
  - Coronary revascularization
    - If myocardial imaging indicates high-risk lesions
    - If symptoms persist despite optimized GDMT
- **Acute Coronary Syndromes**
  - Ischemia-Guided Strategy (GDMT)
  - Reperfusion Strategy
    - Coronary revascularization
    - Pharmacologic reperfusion with fibrinolytic (STEMI only)

Figure 3: Comparison of Coronary Revascularization Approaches[3]

Percutaneous Coronary Intervention (PCI)

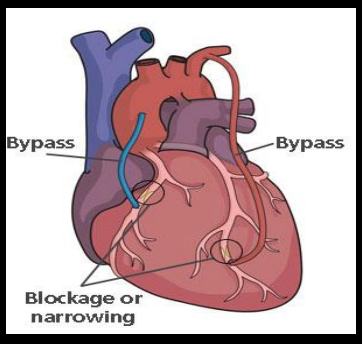
- Non-surgical procedure
- Catheter guided mechanical widening
- Reperfusion often via stent placement



Increasing Invasiveness

Coronary Artery Bypass Graft (CABG)

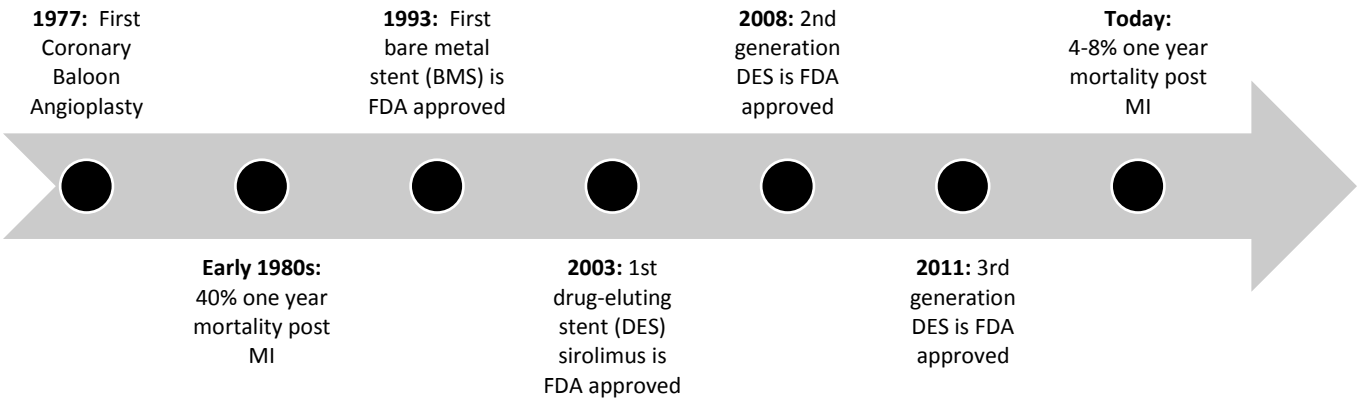
- Open heart surgery
- Grafting veins to bypass occluded artery
- Often reserved for multivessel disease



Percutaneous Coronary Intervention

Progression of Stent Development

Figure 4: Timeline of Advancements in PCI[9]



Challenges Faced as Stents Advanced[10–12]

Balloon Angioplasty
- Lack structural support; arterial recoil and restenosis (vessel narrowing)
- High rates of restenosis of coronary artery (30-40%)

Bare Metal Stents
- Structural support prevents abrupt and chronic recoil
- Neointimal hyperplasia (cell proliferation) thickens areterial walls; restenosis of 20-30%

Drug-Eluting Stents
- Antiproliferative drugs reduce hyperplasia; restenosis rates of 5-7%
- Impaired arterial healing maintains a prothrombogenic environment (increased late in-stent thrombosis)

Table 1: Classifications of Drug-Eluting Stents [3,14]

Generation	Characteristics	Examples
First	• Stainless Steel platform • Sirolimus or paclitaxel	• Cypher, Taxus Express, Taxus Liberte
Second	• Cobalt chromium platform • Everolimus or zotarolimus	• Endevor, Xience V/Prime, Promus, Resolute Integrity
Third	• Platinum chromium platform • Everolimus or sirolimus	• Promus Element and Taxus Element
Fourth	• Bioabsorbable and polymer-free devices • BA9 or Amphilimus (sirolimus + organic acid)	• BioFreedom and Cre8

Table 2: Recommendations for Stent Selection During PCI[15]

Stent	Indication for Use
Bare Metal Stent	• Patients unable to tolerate or comply with DAPT • Anticipated surgery requiring discontinuation of DAPT • High risk of bleeding
Drug-Eluting Stents	• Generally considered first line • Preferred over BMS in patients with diabetes, multiple and long lesions, left main disease, and in-stent restenosis

Dual Antiplatelet Therapy

Following Percutaneous Coronary Intervention

Guideline Recommendations for Antiplatelet Therapy Following Stent Placement[7,8,15]

- Recommend dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ inhibitor

Aspirin
- 81 mg (range of 75-100 mg)
- Previous guidelines have recommended 81-325 mg
- Continued indefinitely

+

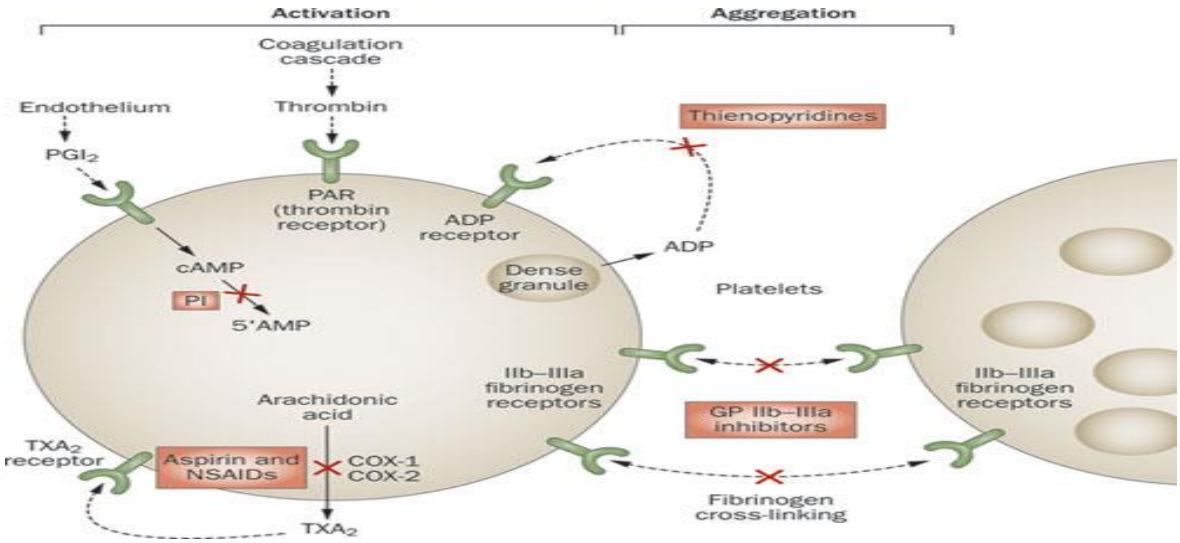
$P2Y_{12}$ Inhibitors
- Clopidogrel: 75 mg daily
- Prasugrel: 10 mg daily
- Ticagrelor: 90 mg twice daily
- Varied duration

Table 3: Comparison of Oral $P2Y_{12}$ Inhibitors[17–19]

	Onset of Action	Duration of Action	Metabolism	Cost per 30 days
Irreversible Binding				
Clopidogrel (Plavix)	• Dose dependent • 2 hours	• Return to baseline 5 days after discontinuation	Prodrug: CYP2C19 mediated oxidation to active metabolite	• $208.80 (75 mg)
Prasugrel (Effient)	• Dose dependent • < 1 hour	• Return to baseline 5-9 days after discontinuation	Prodrug: esterase mediated hydrolysis and CYP oxidation to active metabolite	• $501.12 (10 mg)
Reversible Binding				
Ticagrelor (Brilinta)	• Dose dependent • < 30 minutes	• Return to baseline 3-4 days after discontinuation	CYP metabolism to active metabolites	• $399.54 (90 mg)

*Cost per GoodRx for San Antonio area: clopidogrel: $10-$75.82, prasugrel: $435.55-$447, ticagrelor: $348.96-$364.59

Figure 5: Mechanisms of Antiplatelet Agents[16]



Clinical Controversy

How Long Should Dual Antiplatelet Therapy be Continued?

Table 4: Guideline Recommendations for Duration of $P2Y_{12}$ Inhibitor Following Stent Placement

Stent Indication	Stent Type	2011 PCI Guideline[20]	2016 Update on Duration of DAPT[15]
Stable Angina	BMS	• 1 to 12 months (2 weeks if increased bleeding risk)	• At least 1 month • Consider continuation beyond 1 month
	DES	• At least 12 months	• At least 6 months (3 months if increased bleeding risk • Consider continuation beyond 6 months
		2011 PCI Guideline[20] 2013 ST-Elevation MI Guideline[8] 2014 Non-ST-Elevation Guideline[7]	**2016 Update on Duration of DAPT[15]**
Acute Coronary Syndromes	BMS	• At least 12 months	• At least 12 months (6 months if increased bleeding risk • Consider continuation beyond 12 months
	DES	• At least 12 months • Consider continuation beyond 1 year	• At least 12 months (6 months if increased bleeding risk • Consider continuation beyond 12 months

Table 5: Early Trials Establishing Recommendations for Duration of DAPT Following PCI

Study	Population	Findings	Duration
PCI-CURE (2001)[21]	• Compared aspirin to aspirin plus clopidogrel in patients with non-STEMI acute coronary syndromes (ACS) who underwent PCI • Stent types not reported	• Clopidogrel plus aspirin significantly reduced risk of MI and increased risk of minor bleeding	• Mean: 8 months • Target: 12 months
TRITON-TIMI 38 (2007)[22]	• Compared aspirin plus clopidogrel to aspirin plus prasugrel in ACS patients who underwent PCI • 99% underwent PCI: 48% BMS, 47% DES	• Prasugrel plus aspirin significantly reduced risk of MI • Major, life-threatening, and fatal bleeding significantly increased with prasugrel	• Median: 14.5 months • Target: 6 -15 months
PLATO (2009)[23]	• Compared aspirin plus clopidogrel to aspirin plus ticagrelor in ACS patients who underwent PCI • 64% underwent PCI: 42% BMS, 19% DES	• Ticagrelor plus aspirin significantly reduced risk of MI and death from vascular causes • No difference in major, life-threatening, and fatal bleeding	• Mean: 9.2 months • Target: 12 months

Guideline Recommendations for Duration of DAPT in Patients at High Risk of Bleeding[15]

- Shorter durations for patients who have experienced bleeding on DAPT or are considered high bleeding risk

Table 6: Trials Comparing 12 Months of DAPT to Shorter Durations Following DES

Study	Population	Findings	Limitations
RESET (2012)[24]	• Compared 3 months of DAPT + zotarolimus DES (ZES) to 12 months + other DES • 45% stable angina (SA), 40% unstable angina (UA), 14% acute MI	• 3 months non-inferior to 12 • ACS: more revascularization with 3 months • No difference in major or minor bleeding	• Event rates did not match previous trials • Could be underpowered • Conducted in Korea
EXCELLENT (2012)[25]	• Compared 6 months to 12 months of DAPT in patients receiving DES • Excluded MI within 72 hours • 48% SA, 48% UA, 3% STEMI	• 6 months non-inferior to 12 • DM: higher rates of primary endpoint with 6 months • No difference in TIMI major bleeding or any bleeding	• Underpowered to detect death or MI (low event rate) • Conducted in Korea
OPTIMIZE (2013)[26]	• Compared 3 months to 12 months of DAPT in stable CAD and low risk ACS patients undergoing PCI with ZES • Excluded acute MI or previous DES • 59% SA, 36% ACS within 30 days	• 3 months non-inferior to 12 • No difference in any bleeding or major bleeding	• Underpowered to detect ischemic or bleeding events (low event rate) • Conducted in Brazil
SECURITY (2014)[27]	• Compared 6 months to 12 months of DAPT in patients with 2nd generation DES • Excluded NSTEMI or STEMI within 48 hours of procedure • 61% SA, 38% UA	• 6 months non-inferior to 12 • No difference in BARC type 3 or 5 bleeding	• Did not meet power due to low event rates
ISAR-SAFE (2015)[28]	• Compared 6 months to 12 months of DAPT in patients receiving DES • 48% SA, 22% UA, 10% NSTEMI, 8% STEMI, 10% silent ischemia	• 6 months non-inferior to 12 • No difference in TIMI bleeding. BARC higher with 12 months (65% Type 1 or 2)	• Stopped early (low recruitment and event rates)

*Primary endpoints were all composites of ischemic events and/or bleeding events, including CV death, all-cause death, MI, stent thrombosis, stroke, revascularization, and major bleeding.

Guideline Recommendations for Duration of DAPT in Patients Not at High Risk for Bleeding[15]

- Longer duration can be considered; weigh risk of bleeding against risk of ischemic event

Increased Ischemic Risk	Increased Stent Thrombosis Risk	Increased Bleeding Risk
•Advanced age •ACS presentation •Multiple prior MIs •Extensive CAD •Diabetes •Chronic kidney disease (CKD)	•ACS presentation •Diabetes •Left ventricular EF < 40% •1st generation DES •Stent undersizing •Small stent diameter •Greater stent length •bifurcation stents •In-stent restenosis	•History of prior bleeding •Oral anticoagulant therapy •Female gender •Advanced age •Low body weight •CKD •Diabetes •Anemia •Chronic steroid or NSAID use

Literature Review

Comparison of 12 Months to Extended Durations of DAPT Following DES

Table 7: DES-LATE
Lee CW, Ahn J, Park D, et al. Optimal Duration of Dual Antiplatelet Therapy after Drug-Eluting Stent Implantation: A Randomized Controlled Trial. Circulation. 2014;129(3):304-12.

<table>
<tr><td>Objective</td><td colspan="2">To determine if 36 months of dual antiplatelet therapy following the placement of a DES significantly differs in regards to safety or efficacy when compared to 12 months</td></tr>
<tr><td colspan="3">Methods</td></tr>
<tr><td>Study Design</td><td colspan="2">Multicenter, randomized, open-label, trial conducted in Korea (N= 5,045)</td></tr>
<tr><td>Patient Selection</td><td><u>Inclusion criteria</u>
• Implantation with a DES at least 12 months prior
• No major adverse cardiovascular or bleeding events since implantation
• Receiving DAPT at enrollment</td><td><u>Exclusion criteria</u>
• Contraindications to antiplatelet drugs
• Vascular disease requiring long-term use of clopidogrel
• Life expectancy less than 1 year</td></tr>
<tr><td>Intervention</td><td colspan="2">• 36 month group: aspirin 100 -200 mg daily plus clopidogrel 75 mg daily
• 12 month group: aspirin 100-200 mg daily</td></tr>
<tr><td>Outcomes</td><td><u>Primary Endpoint</u>
• Composite of death from cardiovascular (CV) causes, myocardial infarction (MI), or stroke 24 months after randomization</td><td><u>Secondary Endpoints</u>
• Death from any cause, MI, stroke, stent thrombosis, repeat revascularization
• Multiple composites including death from CV cause, death from any cause, MI, stroke, stent thrombosis, and TIMI major bleeding
• TIMI major bleeding</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">• Intention to treat
• 5,000 for 80% power (assuming primary endpoint incidence of 1.3% and 2.7% for the aspirin-alone group and aspirin plus clopidogrel group, respectively), two-sided alpha of 0.05
• Student's t-test and chi-squared for between group differences; Kaplan-Meier for event rates
• Homogeneity test run between two cohorts to determine if populations were similar</td></tr>
<tr><td colspan="3">Results</td></tr>
<tr><td>Baseline</td><td colspan="2">
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<tr><td colspan="2">Demographics</td></tr>
<tr><td>Age</td><td>62</td></tr>
<tr><td>Male gender</td><td>69.4%</td></tr>
<tr><td colspan="2">Past Medical History</td></tr>
<tr><td>Diabetes</td><td>28.1%</td></tr>
<tr><td>Hypertension</td><td>57.5%</td></tr>
<tr><td colspan="2">Cardiovascular History</td></tr>
<tr><td>Previous angioplasty</td><td>11.7%</td></tr>
<tr><td>Previous MI</td><td>3.9%</td></tr>
</table>
<table>
<tr><td colspan="2">PCI Details</td></tr>
<tr><td>Indication</td><td>39% for SA, 37.7% UA, 10.6% NSTEMI, and 12.5% STEMI</td></tr>
<tr><td>Multivessel Intervention</td><td>31.8%</td></tr>
<tr><td>Bifurcation</td><td>13.4%</td></tr>
<tr><td>Stents per lesion</td><td>1.2</td></tr>
<tr><td>Stent Type</td><td>43.9% sirolimus, 20.4% paclitaxel, 19% zotarolimus, 11.2 % everolimus, 5.7% other</td></tr>
<tr><td colspan="2">Medications</td></tr>
<tr><td>Discharge medications</td><td>50.6% ACE inhibitor, 65.6% beta blocker, 82.3% statin</td></tr>
</table>
</td></tr>
</table>

Study Outcomes	**<u>Primary Outcome:</u> (12 month vs. 36 months)** • Composite (death from CV causes, MI, or stroke): 2.4% vs. 2.6% (p=0.75) • Remained non-significant after adjusting for age, gender, and pre-specified subgroups **<u>Secondary Outcomes</u> (12 month vs. 36 months)** • TIMI major bleeding at 36 months: 1.1% vs. 1.4% (p=0.20) • TIMI major bleeding at 48 months: 1.8% vs. 3.2% (p=0.045) • No difference in death, MI, stroke, or repeat revascularization at 36 or 48 months • No difference in safety outcomes of fatal bleeding or intracranial bleeding at 36 or 48 months • At the end of the follow up period, increased bleeding risk with DAPT (p=0.026) • Net clinical benefit (death from CV causes, MI, stent thrombosis, stroke, or TIMI major bleeding): 3.2% vs. 3.8% (p=0.26)
Critique	
Author's Conclusion	Among patients receiving drug-eluting stents, continued treatment with clopidogrel and aspirin beyond 1 year, did not reduce the risk of cardiac death, MI, or stroke.
Strengths	• Randomized, multicenter • Investigator initiated with no company involvement in design or analysis • Continued to follow patients for 48 months • Compliance assessed • Clinical event adjudicated by independent committee • Data analyzed by independent statistician

Limitations	• Open label
	• Conducted in Korea
	• Clopidogrel adherence at 36 months was 79.4% in the aspirin plus clopidogrel group
	• Adherence to aspirin was significantly lower at 36 months for the DAPT group compared to the aspirin-alone group (95.7% vs. 97.2%), may not be clinically significant
	• 8.1% of patients in the aspirin-alone group were taking DAPT at 36 months.
	• Time from index procedure to randomization ranged considerably
	  ○ 81% 12-18 months
	  ○ 12% >18-24 months
	  ○ 7% > 24 months.
	• Low risk population: majority were indicated for PCI due to stable angina or unstable angina, predominantly single-vessel interventions, and low rates of previous coronary angioplasty or MI
	• Only included clopidogrel, cannot extend findings to other P2Y12 inhibitors
	• Majority of stents were first generation (64%)
	• Many patients were not taking other medications recommended for patients with coronary artery disease: ACE inhibitors, beta blockers, statins
	• Claimed that study was underpowered because did not reach 2.7% event in DAPT group

Take Away Summary	
• In patients receiving drug-eluting stents, who do not experience major bleeding or cardiovascular events during the initial 12 months of DAPT, there is no benefit in reduction of death from cardiac causes, MI, or stroke seen with continuing DAPT to 36 months, rates of TIMI major bleeding also did not significantly differ at 36 months.	

Table 8: DAPT

Mauri L, Kereiakes D, Yeh R, et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. N Engl J Med 2014;371:2155-66.

<table>
<tr><td>Objective</td><td colspan="2">To determine if 30 months of dual antiplatelet therapy significantly differs in regards to safety or efficacy when compared to the standard 1 year duration.</td></tr>
<tr><td colspan="3">Methods</td></tr>
<tr><td>Study Design</td><td colspan="2">International, multicenter, randomized, placebo-controlled trial (N = 9,961)</td></tr>
<tr><td>Patient Selection</td><td><u>Inclusion criteria</u>
• Undergone PCI with stent placement (or PCI within 3 days)
• Event free after 12 months of DAPT and no contraindications to DAPT
• Compliance during first 12 month (taking 80-120% of drug and interruptions ≤ 14 days)</td><td><u>Exclusion criteria</u>
• Stent diameter <2.25mm or > 4.0 mm
• Planned surgery requiring discontinuation of antiplatelet therapy (>14 days) within 30 months
• Life expectancy ≤ 3 years
• Long-term anticoagulant therapy
• Received DES and BMS during the index procedure
• Switched thienopyridine type or dose within 6 months
• PCI or cardiac surgery between index procedure and randomization</td></tr>
<tr><td>Intervention</td><td colspan="2">• Both groups: aspirin 75-162 mg daily plus clopidogrel 75 mg or prasugrel 10 mg daily for 12 months
• 30 month group: aspirin 75-162 mg daily plus clopidogrel 75 mg daily or prasugrel 10 mg daily for additional 18 months
• 12 month group: aspirin 75-162 mg daily plus placebo for additional 18 months</td></tr>
<tr><td>Outcomes</td><td><u>Primary Endpoints</u>
• Incidence of stent thrombosis
• Composite of death, MI, or stroke (MACCE)
• GUSTO moderate or severe bleeding</td><td><u>Secondary Endpoints</u>
• All-cause mortality, MI, and stroke
• BARC type 2, 3, or 5</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">• Intention to treat
• Sample size of 9,800 for 85% power to detect superiority, superiority analysis using log-rank test, two-sided, error rate of 0.05 (primary efficacy analysis). Sample size of 9960 for 80% power to detect non-inferiority, one-sided alpha of 0.025 (primary safety analysis)
• Cox proportional hazards regression used for co-primary efficacy and primary safety endpoints
• Kaplan-Meier used to estimate major adverse cardiovascular and cerebrovascular events</td></tr>
<tr><td colspan="3">Results</td></tr>
<tr><td>Baseline</td><td colspan="2">
<table>
<tr><td colspan="2">Demographics</td></tr>
<tr><td>Age</td><td>61.7</td></tr>
<tr><td>Male gender</td><td>74.7%</td></tr>
<tr><td>BMI</td><td>30.6</td></tr>
<tr><td>North American</td><td>89.6%</td></tr>
<tr><td colspan="2">Past Medical History</td></tr>
<tr><td>Current or recent smoker</td><td>24.7%</td></tr>
<tr><td>Diabetes</td><td>30.6%</td></tr>
<tr><td>Hypertension</td><td>73.9%</td></tr>
<tr><td colspan="2">Cardiovascular History</td></tr>
<tr><td>Previous PCI</td><td>30.7%</td></tr>
<tr><td>Previous MI</td><td>21.6%</td></tr>
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<table>
<tr><td colspan="2">PCI Details</td></tr>
<tr><td>Indication</td><td>37.7% for SA, 16.7% UA, 15.5% NSTEMI, and 10.5% STEMI, 19.7% other</td></tr>
<tr><td>Multivessel Intervention</td><td>32%</td></tr>
<tr><td>Treated lesions</td><td>1.3</td></tr>
<tr><td>Treated vessels</td><td>1.12</td></tr>
<tr><td>Number of stents</td><td>1.5</td></tr>
<tr><td>Stent Type</td><td>11.2% sirolimus, 26.8% paclitaxel, 12.7% zotarolimus, 47.2% everolimus, 2.1% ≥ 1 type</td></tr>
<tr><td colspan="2">Medications</td></tr>
<tr><td>Thienopyridine</td><td>65.3% clopidogrel, 34.7% prasugrel</td></tr>
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Study Outcomes	**<u>Primary Outcome:</u> (12 month vs. 30 months)**
	• Stent thrombosis: 1.4% vs. 0.4% (p<0.001; NNT 100)
	• MACCE: 5.9% vs. 4.3% (p<0.001; NNT 62)
	• GUSTO moderate or severe bleeding 1.6% vs. 2.5% (p=0.001; NNH 111)
	• GUSTO moderate bleeding: 1.0% vs. 1.7% (p=0.004; NNH 143)
	• GUSTO severe bleeding was not significant: 0.6% vs. 0.8% (p=0.15)
	
	<u>Secondary Outcomes</u> (12 month vs. 30 months)
	• TIMI major bleeding at 36 months: 1.1% vs. 1.4% (p=0.20)
	• All-cause mortality 1.5% vs. 2.0% (p=0.05)
	  ○ Cardiac and vascular deaths not significant
	  ○ Non-CV death: 0.5% vs. 1.0% (p=0.002)
	  ▪ Not significant for bleeding or trauma related death
	  ▪ Cancer related death: 0.28% vs. 0.62% (P=0.02)
	• MI: 4.1% vs. 2.1% (p<0.001)
	• Stroke: 0.9% vs. 0.8% (p=0.32), no significant difference in ischemic or hemorrhagic
	• BARC Bleeding: 2.9% vs. 5.6% (p<0.001)
	  ○ Type 2: 1.5% vs. 3.1% (p<0.001)
	  ○ Type 3: 1.5% vs. 2.6% (p<0.001)
	  ○ Type 5: 0.1% vs. 0.1% (p=0.38)

Critique	
Author's Conclusion	Among patients receiving drug-eluting stents, continued treatment with a thienopyridine and aspirin beyond 1 year reduced the risk of stent thrombosis and MACCE driven by a reduction in MI. GUSTO moderate bleeding and BARC type 2 and 3 bleeding did significantly increase, but there was no difference in severe or life-threatening bleeds.
Strengths	• Adequately powered and placebo controlled • Use of multiple thienopyridines • Allowed a range for acceptable adherence, 80%-120% of drug taken • Followed patients additional 3 months after DAPT stopped • Large portion of population from North America

Limitations	• Choice of thienopyridine not blinded
	  ○ Subgroup analysis of MACCE showed greater reduction with prasugrel
	  ○ Subgroup analysis of MI and stent thrombosis no difference between agents
	• Many patients lower risk,
	• 1st generation DES
	• Unknown indications for the "others" that were not SA or ACS
	• Cannot apply results to non-thienopyridine P2Y12 inhibitors (ticagrelor)
	• No review of other mortality reducing agents patients were taking (ACE-I/ARB, BB, statin, etc)

Take Away Summary	
• In patients receiving drug-eluting stents, who do not experience major bleeding or cardiovascular events during the initial 12 months of DAPT, there is a benefit in terms of MI and stent thrombosis reduction seen with continuing DAPT to 30 months, at the expense of increased rates of non-fatal bleeding.	

Table 9: OPTIDUAL

Helft G, Steg PG, Le Feuvre C, et al. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. Eur Heart J 2016; 37(4): 365-374.

Objective	To determine if 48 months of dual antiplatelet therapy following the placement of a DES significantly differs in regards to safety or efficacy when compared to 12 months	
Methods		
Study Design	Multicenter, randomized, open-label, trial conducted in France (N= 1,385)	
Patient Selection	**Inclusion criteria** • Symptoms of SA, silent ischemia, or ACS • At least 1 lesion with stenosis > 50% in a native vessel > 225 mm in diameter • Received ≥ 1 DES of any type	**Exclusion criteria** • Requirement for oral anticoagulation • Implantation in unprotected left main coronary artery • Life expectancy < 2 years.
Intervention	• 48 month group: aspirin 75-160 mg daily plus clopidogrel 75 mg daily • 12 month group: aspirin 75-160 mg daily	
Outcomes	**Primary Endpoint** • Net adverse clinical events: composite of all-cause mortality, non-fatal MI, stroke, or major bleeding defined according to ISTH	**Secondary Endpoints** • All-cause mortality, MI, stroke, major bleeding, stent thrombosis, repeat revascularization of the treated vessel, bleeding defined according to ISTH, GUSTO, TIMI, and BARC
Statistical Analysis	• Intention to treat • Sample size of 983 patients for 80% power, assuming a reduction in the primary outcome of 7% with aspirin alone and 4% with extended DAPT (planned for 1,966 patients to be enrolled) • Two-sided alpha level of 0.05 • Cox model used for primary and secondary outcome • Kaplan-Meier used for survival status • Chi-squared or Fisher's exact test for other secondary outcomes	
Results		

Baseline

Demographics	
Age	64.2
Male gender	80.5%
Past Medical History	
Current or recent smoker	59.5%
Diabetes	31.41%
Hypertension	58.5%
Cardiovascular History	
Previous PCI	26.5%
Previous MI	17.4%

* Age over 75 and LAD as the target vessel were significantly higher in the 12 month group

PCI Details	
Indication	32.3% SA, 9.3% UA, 15.6% NSTEMI, 11.3% STEMI, 20.9% silent ischemia, 10.7% other
Multivessel disease	54.7%
Diseased vessels	45.3% one, 33.7% two, 21% three
Treated vessels	60.9% one, 26.1% two, 12.6% three
Number of stents	1.5
Stent Type	18.5% sirolimus, 15.6% paclitaxel, 9.6% zotarolimus, 49.7% everolimus, 6.5% other
Medications	
Aspirin dose at randomization	78.4% on dose ≤ 100 mg, 21.6% on dose of 101-300 mg
Medications at randomization	74.7% ACE inhibitor, 79.8% beta blocker, 93.9% statin, 48.3% proton pump inhibitor

Study Outcomes	**<u>Primary Outcome:</u> (12 month vs. 48 months)** • Composite (all-cause mortality, MI, stroke, and ISTH major bleeding): 7.5% vs. 5.8% (p=0.17) **<u>Secondary Outcomes</u> (12 month vs. 36 months)** • All-cause mortality: 3.5% vs. 2.3% (p=0.18), CV mortality and non-CV mortality did not differ • Non-fatal MI: 2.3% vs. 1.6% (P=0.31) • No difference in stroke, stent thrombosis, or target vessel revascularization • ISTH major bleeding: 2% vs. 2% (P=0.95) • No significant difference in GUSTO (moderate or severe), BARC (type 2, 3, or 5), TIMI major or minor), or ISTH (major or moderate) bleeding between groups
Critique	
Author's Conclusion	Among patients receiving drug-eluting stents, continued treatment with clopidogrel and aspirin for a median of 22 months, did not reduce the risk of all-cause mortality, MI, or stroke compared to 12 months of therapy. Bleeding rates did not significantly differ between groups.
Strengths	• Randomized, multicenter • Majority of stents were second generation • At randomization, most patients were on guideline recommended medications for CAD and ACS • Used multiple definitions of bleeding for analysis
Limitations	• Open label, conducted in France • Terminated early due to a lack of resources and slow enrollment • 43.7% achieved max 36 month follow-up, all achieved minimum 6 month follow-up • Actual duration of DAPT varies and is unclear (median of 22 months, mean not reported). • Only included clopidogrel, cannot extend findings to other P2Y12 inhibitors • Did not monitor 48 month group immediately following DAPT discontinuation.
Take Away Summary	
• In patients receiving drug-eluting stents, who do not experience major bleeding or cardiovascular events during the initial 12 months of DAPT, there is no benefit in reduction of all-cause mortality, MI, or stroke seen with continuing DAPT to a median of 22 months. There was also no difference in rates of bleeding, regardless of the definition used.	

Table 10: Other Trials Comparing 12 Months of DAPT or Less to Extended Durations Following DES

Study	Population	Findings/Limitations	Duration
REAL-LATE + ZEST-LATE (2010)[29]	• Compared 12 months of DAPT to extended durations following DES • 37% SA, 41% UA, 11% NTEMI & 11% STEMI	• No difference in MI or death or TIMI major bleeding • <u>Underpowered</u> & conducted in Korea	• Median: 33.2 months • Target: 28-37 months
ARCTIC-Interruption (2014)[30]	• Compared 12 months of DAPT to extended durations following DES • Unknown indications; excluded STEMI pts	• No difference in composite of death, MI, stroke, or revascularization. • STEEPLE major or minor bleeding higher with DAPT, no difference individually • Underpowered, conducted in France	• Median: 29 months • Target: 18-30 months
ITALIC (2015)[31]	• Compared 6 months to 24 months of DAPT following everolimus DES • 41% SA, 16.9% silent ischemia, 17% UA, 7% NSTEMI, 0.2% STEMI	• 6 months non-inferior composite of death, MI, revascularization, stroke, major bleeding • <u>Prematurely terminated (poor enrollment)</u> • Conducted in Europe and the Middle East	• 24 months

Conclusion and Recommendations

Comparison of 12 Months to Extended Durations of DAPT Following DES

Summary of Primary Literature Comparing 12 Month to Extended DAPT Following DES[29–34]

Extended DAPT benefit is unclear:

- Most studies did not find a benefit
- Majority of studies are open label and under powered
- DAPT (2014) did show a benefit and is the largest placebo controlled study available

Extent of bleeding risk is unclear:

- Many studies show increased bleeding with DAPT but studies vary in type of bleeding and extent
- Limited studies of prasugrel and ticagrelor; unclear if $P2Y_{12}$ inhibitor impacts risk

Limitations of available studies:

- Little data on more potent $P2Y_{12}$ inhibitors
- Durations of extended DAPT vary between studies
- Various stent generations
- Low ischemic risk populations

Recommendation Based on Literature

- The benefits of extending DAPT beyond 12 months not supported by enough evidence to recommend their use for the majority of patients who receive DES
- Selecting the duration of DAPT should be based on overall ischemic risk and bleeding risk
- Extended durations of DAPT should be reserved for patients at high ischemic risk, if bleeding risk is low and they have tolerated 12 months of DAPT without any bleeding events.

Guideline Recommended Assessment of Bleeding Risk and Ischemic Risk[15,35]

- The DAPT Score is risk score that assesses the risk/benefit ratio of extended DAPT
- Score ≥ 2: favorable risk/benefit ratio for extended DAPT
- Score < 2: unfavorable risk/benefit ratio for extended DAPT

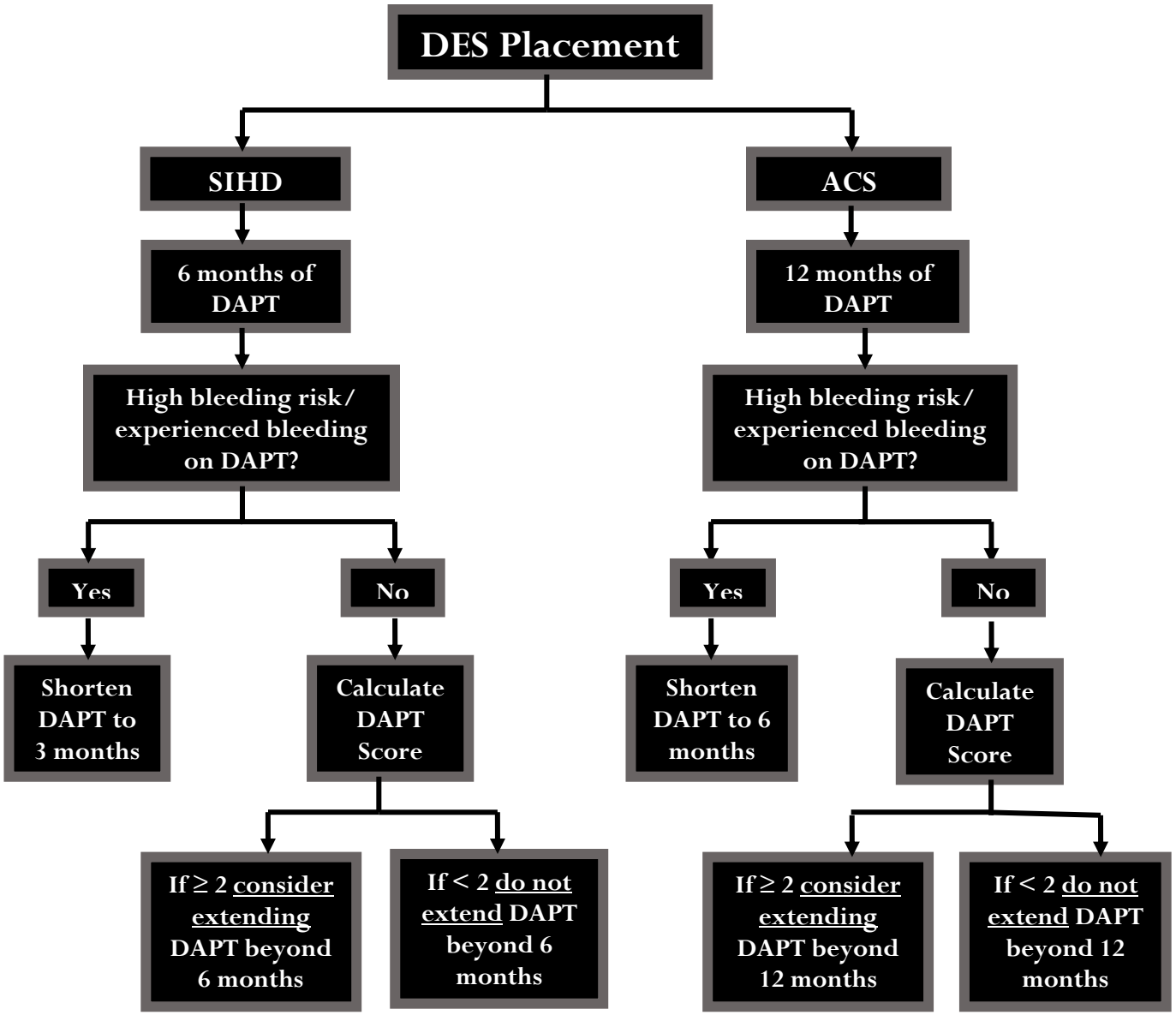
Table 11: Calculating a DAPT Score

Variable	Points
Age ≥ 75	-2
Age 65 to < 75	-1
Age < 65	0
Current cigarette smoker	1
Diabetes	1
MI at presentation	1
Prior PCI or prior MI	1
Stent diameter < 3 mm	1
Paclitaxel-eluting stent	1
Congestive heart failure (CHF) or LVEF < 30%	2
Saphenous vein graft PCI	2

Score ≥ 2 favorable for extended DAPT

Score < 2 unfavorable for extended DAPT

Treatment Algorithm for DAPT Duration Following Drug-Eluting Stents[15,35]



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Appendices

Appendix A: Criteria for BARC Bleeding Definition[36]	
Definition	**Criteria**
BARC	Type 0 • No bleeding Type 1 • Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional Type 2 • Any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation Type 3a • Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed) • Any transfusion with overt bleeding Type 3b • Overt bleeding plus hemoglobin drop ≥ 5 g/dL* (provided hemoglobin drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring intravenous vasoactive agents Type 3c • Intracranial hemorrhage • Subcategories confirmed by autopsy or imaging or lumbar puncture • Intraocular bleed compromising vision Type 4: CABG-related bleeding • Perioperative intracranial bleeding within 48 h • Reoperation after closure of sternotomy for the purpose of controlling bleeding • Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period • Chest tube output ≥2L within a 24-h period Type 5: Fatal bleeding • Type 5a: probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious • Type 5b: definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Appendix B: Criteria for GUSTO Bleeding Definition[36]	
Definition	**Criteria**
GUSTO	Severe or life-threatening: • Intracerebral hemorrhage • Resulting in substantial hemodynamic compromise requiring treatment Moderate • Requiring blood transfusion but not resulting in hemodynamic compromise Mild

Appendix C: Criteria for ISTH Bleeding Definition[36]	
Definition	**Criteria**
ISTH	Major bleeding in non-surgical patients • Fatal bleeding • Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome • Bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells. Major bleeding in surgical patients • Fatal bleeding • Bleeding that is symptomatic and occurs in a critical area or organ, assessed in consultation with the surgeon • Extrasurgical site bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of blood or PRBC, within 24–48 h to the bleeding • Surgical site bleeding that requires a second intervention (open, arthroscopic, endovascular) or a hemarthrosis of sufficient size as to interfere with rehabilitation by delaying mobilization or delayed wound healing, resulting in prolonged hospitalization or a deep wound infection. • Surgical site bleeding that is unexpected and prolonged and/ or sufficiently large to cause hemodynamic instability, as assessed by the surgeon. There should be a fall in hemoglobin level of at least 2 g/dL (1.24 mmol/L), or transfusion, indicated by the bleeding, of at least two units of blood or PRBC, within 24 h. • The period for collection of these data is from start of surgery until five half-lives after the last dose of the drug with the longest half-life and with the longest treatment period • The population is those who have received at least one dose of the study drug. Minor bleeding • All non-major bleeds will be considered minor bleeds. Minor bleeds will be further divided into those that are clinically relevant and those that are not.

Appendix D: Criteria for TIMI Bleeding Definition[36]	
Definition	**Criteria**

TIMI	**Non-CABG related bleeding:**
	• Major
	  ○ Any intracranial bleeding (excluding microhemorrhages < 10 mm evident only on MRI)
	  ○ Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥ 5 g/dL
	  ○ Fatal bleeding (bleeding that directly results in death within 7 d)
	• Minor
	  ○ Clinically overt (including imaging), resulting in hemoglobin drop of 3 to < 5 g/dL
	• Requiring medical attention
	  ○ Any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above
	  ○ Requiring intervention, leading to or prolonging hospitalization, or prompting evaluation
	• Minimal
	  ○ Any overt bleeding event that does not meet the criteria above
	Bleeding in the setting of CABG:
	• Fatal bleeding
	• Perioperative intracranial bleeding
	• Reoperation after closure of the sternotomy incision for the purpose of controlling bleeding
	• Transfusion of ≥ 5 units PRBCs or whole blood within a 48-h period
	• Chest tube output > 2 L within a 24-h period