DAPT Management in Bleeding Events: To Continue or Not to Continue?

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Learning Objectives:

1. Describe the role and purpose for the use of DAPT.
2. Identify patients who are candidates for shortened durations of DAPT.
3. Discuss the reasoning and selection of monotherapy in select patients previously on DAPT.
4. Identify patients on DAPT who are candidates for the addition of PPI therapy.

Acronyms:

ACS: acute coronary syndrome
ADP: adenosine diphosphate
BMS: bare metal stent
CABG: coronary artery bypass surgery
CAD: coronary artery disease
CI: confidence interval
COX: cyclo-oxygenase
CYP: cytochrome
DAPT: dual antiplatelet therapy
DES: drug eluting stent
GI: gastrointestinal
GP: glycoprotein
H-K-ATPase: hydrogen – potassium-adenosine triphosphatase
HR: hazard ratio
MACE: major adverse cardiac events
MI: myocardial infarction
NACCE: net adverse clinical and cerebral events
PCI: percutaneous coronary intervention
PPI: proton pump inhibitor
SIHD: stable ischemic heart disease
STEMI: ST-segment elevation myocardial infarction

Background

Dual Antiplatelet Therapy [1,2]

- Purpose
  - Prevention of clot formation leading to cardiovascular events
- Components
  - Aspirin
  - P2Y12 Inhibitor
- Commonly used following:
  - MI
  - Stent
  - CABG
- Recommended duration
  - At least 12 months following ACS
  - At least 6 months in SIHD with DES
  - At least 1 month in SIHD with BMS

Aspirin [3]

- Mechanism
    - Irreversible inhibitor of COX-1 and 2
- Maintenance dosing
    - 75 to 100 mg daily
- Side effects
    - GI ulcers or mucosal damage
    - Heartburn
    - Nausea
    - Vomiting
    - Increased liver enzymes

P2Y12 Inhibitors [4-6]

- Class members
    - Clopidogrel
        - Maintenance: 75 mg daily
    - Ticagrelor
        - Maintenance: 90 mg twice daily
    - Prasugrel
        - Weight based maintenance dosing: 10 mg (≥60 kg) or 5 mg (<60 kg) daily
- Mechanism
    - Blocks the P2Y12 component of ADP receptors on the platelet surface, preventing activation of GPIIb/IIIa receptor complex
- Side effects
    - Bleeding
    - Thrombotic thrombocytopenia purpura

P2Y12 Inhibitor	Related CYP Pathways	Prodrug?
Clopidogrel	2C19	Yes
Ticagrelor	3A4, 3A5	No
Prasugrel	3A4, 2B6	Yes

Active Learning:

What is the purpose of DAPT?

a) To dissolve active blood clots
b) To lower blood pressure levels
c) To prevent the formation of blood clots
d) To decrease heart rate

Possibility of GI Injury [7]

- Aspirin
    - Causes topical injury to the mucosa and systemic effects induced by prostaglandin depletion
- P2Y12 Inhibitors
    - Prevent angiogenesis, which is needed for the repair of GI mucosal disruptions
- When used together, these agents can cause prolonged GI injury

GI Bleeding [8, 9]

- GI bleeding results in:
    - 500,000 hospital admissions per year
    - 2 million hospital days per year
    - $5 billion in direct costs
- A main cause of GI bleeding:
    - Peptic Ulcers

Defining Bleed-Risk: HAS-BLED [10]

Letter	Clinical Characteristic	Points
H	Hypertension	1
A	Abnormal renal or liver function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly	1
D	Drugs and alcohol	1 or 2

Total Score	Interpretation
1	Low-risk
2	Moderate-risk
3-5	High-risk
6-9	Very high-risk

Defining Bleed Types: BARC [11]

Classification	Description	
Type 1	Bleeding that is not actionable	Minor Bleeding
Type 2	Any overt, actionable sign of bleeding	
Type 3A	Overt bleeding with hemoglobin drop of 3-5 g/dL or any transfusion	
Type 3B	Overt bleeding with hemoglobin drop of $\geq$ 5 g/dL, bleeding requiring vasopressors, surgical intervention or due to tamponade	Major Bleeding
Type 3C	Intra-ocular or intracranial	
Type 4	CABG-related bleeding: transfusion of $\geq$ 5 units blood, repeat sternotomy and chest tube output $\geq$ 2 liters within 24 hours	
Type 5	Fatal bleeding	

<u>Question</u>: How should patients on DAPT have their therapy managed after a bleeding event?

- If DAPT is stopped or shortened, what length of therapy is appropriate?
- Could DAPT be changed to a single agent, and if so which agent do we keep?
- If we add a PPI to DAPT, will a PPI and clopidogrel work together effectively or should we choose alternatives?

<u>Current State of Guidance: 2008 ACC/AHA/ACG Consensus Statement</u> [7]

- Aspirin
    - Dose should not exceed 81 mg
    - Formulation has shown no difference in trials
    - Consider discontinuing until problem has resolved
- Addition of a PPI
    - All patients on DAPT suggested to receive PPI
        - All studies had doses of aspirin of 100 mg or more
        - Unknown how this recommendation would work with P2Y12 inhibitors

PPI Refresher [12-17]

- Class Members
    - Dexlansoprazole
    - Esomeprazole
    - Lansoprazole
    - Omeprazole
    - Pantoprazole
    - Rabeprazole
- Mechanism
    - Inhibit H-K-ATPase in order to prevent gastric acid secretion by parietal cells
- Side effects
    - GI- abdominal pain, diarrhea, flatulence
    - Malabsorption of vitamins and minerals
    - Acute interstitial nephritis
    - Fracture risk
    - Infections

PPI	Primary Pathway	Secondary Pathway
Omeprazole	CYP2C19	CYP3A4
Lansoprazole	CYP3A4	CYP2C19
Rabeprazole	CYP2C19	CYP3A4
Pantoprazole	CYP2C19	CYP3A4
Esomeprazole	CYP2C19	CYP3A4

Literature Review

Question 1: If DAPT is stopped or shortened, what length of therapy is appropriate?

***Study 1*: Three vs Twelve Months of Dual Antiplatelet Therapy After Zotarolimus-Eluting Stent** [18]

Background

- Study Design
    - Open-label
    - Active-controlled
    - Randomized
    - Multi-center
    - Non-inferiority trial
- Purpose
    - Assess clinical non-inferiority of short term versus long term DAPT in patients undergoing PCI with a zotarolimus-eluting stent

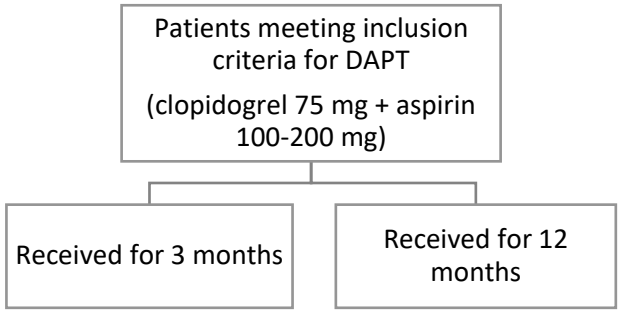
Objectives

- Primary outcome
    - NACCE
- Secondary outcomes
    - Stent thrombosis
    - Target-lesion and target-vessel revascularization
    - MACE
    - Bleeding

Inclusion and Exclusion Criteria

- Inclusion Criteria
    - Symptoms of stable angina or silent ischemia
    - Symptoms of low-risk ACS
- Exclusion Criteria
    - STEMI presenting for primary or rescue PCI
    - PCI with bare-metal stent in non-target lesions less than 6 months prior to the index procedure
    - Previous treatment with any drug-eluting stent
    - Scheduled elective surgery within 12 months after the index procedure
    - Contraindication, intolerance, or known hypersensitivity to aspirin, clopidogrel, or both
    - Lesion located in a saphenous vein graft
    - In-stent restenosis of a drug-eluting stent

Methods



Statistical Analysis

- Sample size goal of 1404 in each group
    - Increased to 1544 per group based on loss to follow-up expectation
- Non-inferiority fixed margin of 2.7%
- Intent-to-treat principle
- Baseline characteristics and secondary outcomes reported as descriptive statistics
- Categorical variables reported as Chi-square test
- Continuous variables reported as means and compared using the 2-sample t-test
- $P < 0.05$ (2-sided) was considered significant

Baseline Characteristics

Characteristic	3 month (n=1563)	12 month (n=1556)
Age (mean)	61.3 (10.4)	61.9 (10.6)
Women (%)	571 (36.5)	574 (36.9)
Cardiovascular Risk		
Diabetes Mellitus (%)	554 (35.4)	549 (35.3)
Hypertension (%)	1350 (86.4)	1371 (88.2)
Dyslipidemia (%)	953 (63.2)	952 (63.7)
Current Smoker (%)	290 (18.6)	269 (17.3)
Renal Insufficiency (%)	114 (7.4)	89 (5.8)
Cardiac Heart Failure (%)	67 (4.3)	64 (4.2)
Previous MI (%)	541 (34.6)	542 (34.8)
Previous PCI (%)	327 (20.9)	297 (19.1)
History of Bleeding (%)	10 (0.6)	9 (0.6)
Clinical Presentation		
Silent Ischemia (%)	134 (8.6)	143 (9.2)
Stable Angina (%)	935 (59.8)	911 (58.6)
Recent ACS (%)	494 (31.6)	502 (32.3)

Results

Power Met

Clinical Outcome	3 month (n=1563)	12 month (n=1556)	HR (95% CI)	P value
NACCE	93 (6.0)	90 (5.8)	1.03 (0.77-1.38)	0.84
Stent Thrombosis	13 (0.8)	12 (0.8)	1.08 (0.49-2.36)	0.86
MACE	128 (8.3)	114 (7.4)	1.12 (0.87-1.45)	0.36
Target-lesion Revascularization	53 (3.5)	49 (3.2)	1.08 (0.73-1.59)	0.70
Target-vessel Revascularization	70 (4.6)	57 (3.8)	1.23 (0.87-1.75)	0.25
Bleeding	35 (2.3)	45 (2.9)	0.77 (0.50-1.20)	0.25

All data presented as n (%)

Strengths and Limitations

- Strengths
  - Multi-center
  - Randomized
  - Similar populations
  - Power met
- Limitations
  - Generalizability
    - 1 country
    - 1 DES
    - Only low-risk ACS

Conclusions

- Authors' Conclusions
  - Among patients undergoing PCI with implantation of zotarolimus-eluting stent, short-term DAPT was non-inferior to long-term DAPT for the effect of death, MI, stroke, or major bleeding
- Personal Conclusion
  - In select patients who are considered to have had low-risk ACS, it is reasonable to consider discontinuing DAPT therapy after 3 months of therapy

Active Learning:

Based on the findings from Feres and colleagues, which patient would be appropriate for stopping DAPT?

a) 60 year old male who has completed 4 months of DAPT following PCI for stable angina
b) 87 year old male who has completed 4 months of DAPT following PCI for STEMI
c) 74 year old female who has completed 1 month of DAPT following PCI for silent ischemia
d) 50 year old female who has completed 7 months of DAPT following their second PCI for NSTEMI

Question 2: Could DAPT be changed to a single agent, and if so which agent do we keep?

<u>Study 2</u>: The Safety and Efficacy of Aspirin Discontinuation on a Background of a P2Y12 Inhibitor in Patients After Percutaneous Coronary Intervention [19]

Background

- Study Design
    - Systematic Review and Meta-Analysis
    - Included 5 trials
- Purpose
    - To determine the relative risk of MACE when aspirin is discontinued for patients on DAPT

Objectives

- Primary Outcomes
    - MACE
    - Bleeding
- Additional Outcomes
    - Death
    - MI
    - Stroke
    - Major bleeding

Methods

- Computerized literature search
    - 2001 to March 2020
    - Medline, PubMed, Cochrane, Embase, and clinicaltrials.gov

Inclusion Criteria	Exclusion Criteria
Strategy of P2Y12 inhibitor versus DAPT in patients after PCI with an indication of either stable CAD or ACS	Patients with anticoagulant therapy
MACE outcome	Duplicative studies
Bleeding outcome	Observational studies
Minimum follow up of 6 months	Crossover study design
	Non-random allocation method

Statistical Analysis

- Random effects model for each outcome extracted based on published data
- Heterogeneity across trials assessed by Cochran Q statistics and I^2
- Hazard ratios with 95% confidence intervals
- All tests are two-sided with $P < 0.05$ considered significant

Trial Background

Trial Name	GLOBAL LEADERS	SMART CHOICE	STOPDAPT -2	TWILIGHT	TICO
Blinding	Open label	Open label	Open label	Double-blind	Open label
Population	ACS or stable CAD after DES	ACS or stable CAD after DES	ACS or stable CAD after DES	NSTE-ACS or stable CAD after DES	ACS after DES
Intervention	Ticagrelor alone after 1 month	Any P2Y12 inhibitor alone after 3 months	Clopidogrel alone after 1 month	Ticagrelor alone after 3 months	Ticagrelor alone after 3 months
Control	Ticagrelor or clopidogrel + Aspirin (75-100 mg)	Any P2Y12 inhibitor + Aspirin (100 mg)	Clopidogrel + Aspirin (81-200 mg)	Ticagrelor + Aspirin (81-100 mg)	Ticagrelor + Aspirin (100 mg)
Sample Size	15,968	2,993	3,045	7,119	3,056
Bleeding End Point	BARC 3 or 5	BARC 2 to 5	TIMI major or minor bleeding	BARC 2, 3, or 5	TIMI major bleeding
Cardiovascular End Point	All-cause death or MI	All-cause death, MI, or stroke	Cardio-vascular death, MI, stroke, or stent thrombosis	All-cause death, MI, or stroke	All-cause death, MI, stroke, stent thrombosis, or target vessel revascular-ization

Baseline Characteristics

	GLOBAL LEADERS	SMART CHOICE	STOP DAPT-2	TWILIGHT	TICO	Pooled Population
Age (mean)	64.6	64.5	68.6	65.1	61.0	64.7
Female (%)	23.3	26.6	22.3	23.9	20.5	23.4
Diabetes (%)	25.3	37.5	38.5	36.8	27.3	30.4
Smoking (%)	26.1	26.4	23.6	21.7	37.4	26.0
Hypertension (%)	73.4	61.5	73.8	72.4	50.4	69.9
Hyperlipidemia (%)	67.4	45.2	74.6	60.4	-	64.2
Previous MI (%)	23.3	4.2	13.5	28.7	3.7	19.9
Reason for presentation						
ACS (%)	46.9	58.2	38.2	64.8	100	56.1
Stable CAD (%)	53.1	41.8	61.8	35.2	0	43.8

Results

Outcome	P2Y12 Inhibitor Monotherapy (n=16,057)	DAPT (n=16,088)	HR (95% CI)
Primary Bleeding	317 (2.0)	503 (3.1)	0.60 (0.45-0.79)
Major Bleeding (BARC 3 or 5)	196 (1.2)	291 (1.8)	0.60 (0.42-0.86)
MACE	438 (2.7)	499 (3.1)	0.88 (0.77-1.02)

All data presented as n (%)

Strengths and Limitations

- Strengths
  - Multiple options for treatment arms
  - Large variety of patients
- Limitations
  - Many open label
  - Selection bias not analyzed
  - Multiple options for treatment arms

Conclusions

- Authors' Conclusion
  - The strategy of stopping aspirin 1 to 3 months after PCI with continued use of P2Y12 inhibitor reduces the risk of bleeding with no apparent increase in risk of MACE when compared to traditional DAPT.

- Personal Conclusion
    - It is reasonable to discontinue aspirin therapy in patients with concerns for future bleeding at 3 months following a PCI.

Active Learning:

When considering monotherapy for patients previously on DAPT, which agent is discontinued and why?

a) Aspirin because it prevents angiogenesis
b) Aspirin because it causes topical injury to the mucosa and systemic effects leading to peptic ulcers
c) P2Y12 Inhibitors because they prevents angiogenesis
d) P2Y12 Inhibitors because they causes topical injury to the mucosa and systemic effects leading to peptic ulcers

Question 3: If we add a PPI to DAPT, will a PPI and clopidogrel work together effectively or should we choose alternatives?

***Study 3*: Clopidogrel with or without Omeprazole in Coronary Artery Disease** [20]

Background

- Study Design
    - International
    - Randomized
    - Double-blind
    - Placebo-controlled
    - Parallel-group
- Purpose
    - To assess the efficacy and safety of concomitant administration of clopidogrel and PPIs in patients with CAD who are receiving DAPT.

Outcomes

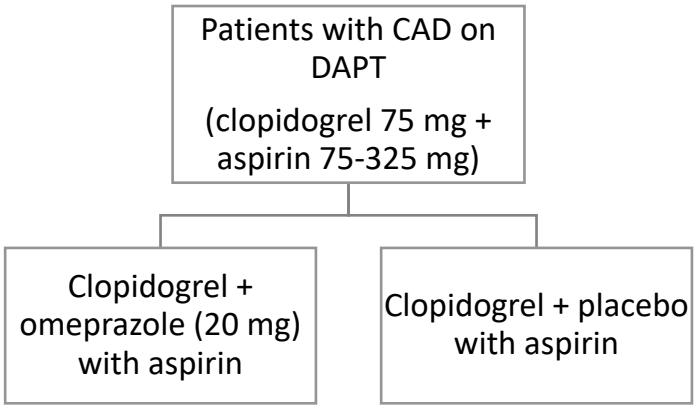
- Primary Outcomes
    - First occurrence of a composite of upper GI clinical events
    - Cardiovascular composite safety endpoint

Inclusion and Exclusion Criteria

- Inclusion Criteria
    - 21 years of age or older
    - Use of DAPT anticipated for at least the next 12 months
    - Patients presenting with ACS or undergoing stent placement

- Exclusion Criteria
    - Hospitalized patients whom discharge within 48 hours was not anticipated
    - Need for short or long-term PPI, H2-receptor antagonist, sucralfate, or misoprostol
    - Pre-existing erosive esophagitis, esophageal or gastric variceal disease, or previous non-endoscopic gastric surgery
    - Received clopidogrel or other class members for more than 21 days before randomization
    - Oral anticoagulation therapy
    - Recent fibrinolytic therapy

Methods



Statistical Analysis

- Sample size goal of 5000 patients total
    - Original sample size goal was 3200
- Medians and IQR reported for continuous variables
- Counts and percentages reported for categorical data
- Analysis of time-to-event variables were performed with log-rank statistics, Kaplan-Meier survival curves, and Cox proportional-hazards models
- Hazard ratios with 95% confidence intervals
- P values < 0.05 were considered to indicate statistical significance

Baseline Characteristics

	Omeprazole (n=1876)	Placebo (n=1885)
Age (median)	68.5	68.7
Male (%)	66.9	69.5
White (%)	93.5	93.9
Body-mass index (median)	28.4	28.3
PCI (%)	71.7	71.4
ACS (%)	42.2	42.6
Hypertension (%)	80.1	81.4
Diabetes (%)	31.7	28.6
Hypercholesteremia (%)	79.1	77.1
Current smoking (%)	12.5	14.1
History of GI bleed or ulcer (%)	4.2	4.1

Results

Power NOT Met

	Omeprazole (n=1876)	Placebo (n=1885)	P-value
Composite of GI events	13 (0.7)	38 (2.0)	< 0.001
Overt gastroduodenal bleeding	1 (0.05)	8 (0.4)	0.03
Overt upper GI bleeding of unknown origin	1 (0.05)	7 (0.4)	0.03
Composite cardiovascular events	55 (2.9)	54 (2.7)	0.98
MI	14 (0.7)	15 (0.8)	0.83
Revascularization	42 (2.2)	45 (2.4)	0.70
Stroke	4 (0.2)	2 (0.1)	0.43
Death from cardiovascular causes	5 (0.3)	3 (0.2)	0.49

All data presented as n (%)

No statistical difference related to serious adverse effects

Strengths and Limitations

- Strengths
  - Randomized
  - International
  - Blinded
- Limitations
  - Trial termination
  - Power not met
  - Single-pill formulation

Conclusions

- Authors' Conclusions
    - This trial provides reassurance that there is no clinically significant cardiovascular interaction between PPIs and clopidogrel. This combination also resulted in a significant reduction in GI bleeding when compared to placebo.
- Personal Conclusion
    - PPI therapy should be used in patients in receiving DAPT in order to prevent GI events. This combination does not appear to have a significant drug interaction and appears to have no statistical impact on cardiovascular outcomes.

Active Learning:

Which patient would be appropriate for adding PPI therapy to their DAPT regimen?

a) 50 year old female who has completed 7 months of DAPT following their second PCI for NSTEMI with no known allergies and past medical history of diabetes
b) 87 year old male who has completed 4 months of DAPT following PCI for STEMI with an allergy to penicillin and past medical history of hypertension and hyperlipidemia
c) 74 year old female who has completed 1 month of DAPT following PCI for silent ischemia with an allergy to codeine and past medical history of hypertension, chronic kidney disease, and hypothyroidism
d) All of the above

<u>Recommendations</u>

- Low-risk ACS/CAD following GI bleed
    - DAPT $\geq$ 3 months
        - Consider DAPT discontinuation
        - OR follow < 3 month option
    - DAPT < 3 months
        - Temporarily discontinue aspirin
        - Restart aspirin and add PPI for remainder of DAPT
- Moderate to high-risk ACS/CAD following GI bleed
    - Temporarily discontinue aspirin
    - Restart aspirin and add PPI for remainder of DAPT
- Prevention
    - HAS-BLED score $\geq$ 2
    - Add a PPI for duration of DAPT

Future Areas for Investigation

- Clarification in regards to discontinuing DAPT therapy early in patients considered to be of moderate or high risk
- Determination of timing for resumption of aspirin therapy following a GI event
- Studies regarding DAPT following bleeding events other than GI bleeds

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