



Controversies in Cardiac Pharmacology

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Disclosures

I have no relevant relationships with
commercial interests to disclose.

“Doc, do I really need to take all these medicines?”

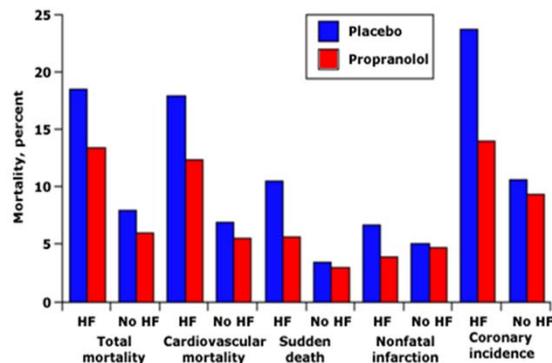
- Beta blockers in Coronary Heart Disease
 - Who, When and How long?
- Statins and LDL reduction
 - How low is too low?
- Antiplatelet Therapy
 - Risk/benefits of long term therapy
 - CHD, CVD and PAD

- Beta blockers in Coronary Heart Disease
 - Who, When and How long?

Beneficial effects of beta blockers in patients with Acute Myocardial Infarction (AMI)

- Decreased oxygen demand due to reduced heart rate, blood pressure and contractility
- Decreased automaticity & risk of ventricular fibrillation
- Increased coronary perfusion due to prolongation of diastole
- Improved ventricular “remodeling” and diastolic function
- Reduced progression of atherosclerosis

Benefit of propranolol after myocardial infarction



Beta blockers in Acute Myocardial Infarction

- Robust evidence for patients with STEMI treated without reperfusion (fibrinolysis or PCI)
 - Randomized trials performed **before** the use of reperfusion consistently showed a reduction in cardiovascular mortality of 10 to 25 percent.
 - Data are less well-defined for STEMI patients treated **with** reperfusion or for NSTEMI patients but still apply
 - Impact of routine use of antiplatelets and statins?
 - Regardless of revascularization, beta blockers reduce short-term complications and improve long-term survival in patients with Acute MI.
- All patients who have sustained an acute MI should be treated with oral beta blockers (No consistent evidence of benefit from **routine** use of IV beta blockers prior to primary PCI)

Beta blocker benefits and comorbidities

- COPD/asthma — Beta blockers are safe and effective post-MI with improved 3 year survival
 - Concerns about bronchospasm unfounded
- Diabetes mellitus - postinfarction benefit =/> nondiabetics
 - Concerns about masking hypoglycemia unfounded
- PAD
 - Beneficial with no adverse effect of beta-1 selective blockers on claudication symptoms
- AADT
 - all-cause mortality, cardiac death, arrhythmic deaths, and resuscitated cardiac arrest lower for patients receiving beta blockers along with amiodarone

ACC/AHA Recommendations for Beta blockers in Myocardial Infarction

Recommendation	Class of Recommendation	Level of Evidence
2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation ACS		
Initiate oral beta-blockers within the first 24 hours in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta-blockade.	I	A
Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for beta-blocker therapy with concomitant ACS without ST-segment elevation, stabilized HF, and reduced systolic function.	I	C
It is reasonable to continue beta-blocker therapy in patients with normal LV function with ACS without ST-segment elevation.	IIa	C
2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction		
Initiate oral beta-blockers within the first 24 hours in patients with ST-segment elevation MI in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta-blockade.	I	B
Beta-blockers should be continued during and after hospitalization for all patients with ST-segment elevation MI and with no contraindications to their use.	I	B

Beta blockers in Stable Ischemic Heart Disease

- Evidence supporting chronic beta blockade in stable ischemic heart disease is less robust
- REACH registry
 - Known CAD but no prior MI
 - No difference in composite of cardiovascular death, nonfatal myocardial infarction (MI), or nonfatal stroke @ **44 months** among those who were or were not taking beta blocker
- Outcomes from the National Cardiovascular Data Registry on 755,215 patients who had Percutaneous Coronary Intervention
 - Stable ischemic heart disease
 - No prior MI, no heart failure, EF >40%
 - No significant difference in adjusted all-cause mortality at **three years** between those discharged with beta blocker and those not.
- 26,793 patients with first CHD event (ACS or PCI)
 - 19,843 started beta blockers within seven days of discharge
 - Average **3.7 years** of follow-up, beta blocker treatment was associated with a 10 percent lower risk of death overall; however, among those without prior MI, there was no difference in the risk of death

Duration of Beta blockade

- **LONG-TERM THERAPY** — Beta blockers reduce short-term complications and improve long-term survival in patients with Acute myocardial infarction (AMI).
- While all patients with AMI should receive long-term beta blocker therapy, the optimal duration, dose, and agent are not known.
- The evidence supports the use of beta blockers in patients **with MI for as long as three years**. The evidence supporting a longer duration, or indefinite therapy, is limited.
- Many patients have been treated indefinitely based on a 1999 meta-analysis that showed a 23 percent reduction in death; however, follow-up was only 1.4 years
- In **high risk** patients, such as those who present with cardiogenic shock, heart failure, or chronic kidney disease, treatment for longer than three years is reasonable
- Beta blockers have not been shown to improve survival or reduce the incidence of myocardial infarction in patients with chronic stable angina in the **absence of myocardial infarction or heart failure**.

AHA/ACCF Secondary Prevention Guidelines for Beta Blockade

- **Class I**
 - 1. Beta blocker therapy should be used in all patients with left ventricular systolic dysfunction (ejection fraction 40%) with heart failure or prior myocardial infarction, unless contraindicated. (Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce mortality.) (Level of Evidence: A)
 - 2. Beta blocker therapy should be started and continued for 3 years in all patients with normal left ventricular function who have had myocardial infarction or ACS. (Level of Evidence: B)
- **Class IIa**
 - 1. It is reasonable to continue -blockers beyond 3 years as chronic therapy in all patients with normal left ventricular function who have had myocardial infarction or ACS. (Level of Evidence: B)
 - 2. It is reasonable to give -blocker therapy in patients with left ventricular systolic dysfunction (ejection fraction 40%) without heart failure or prior myocardial infarction. (Level of Evidence: C)
- **Class IIb**
 - 1. Beta blockers may be considered as chronic therapy for all other patients with coronary or other vascular disease. (Level of Evidence: C)

- Statins and LDL reduction
 - How low is too low?

Primary Prevention: Statin Benefit

- The West of Scotland Coronary Prevention Study (WOSCOPS) showed that cholesterol lowering with pravastatin reduced nonfatal MI and CHD mortality in middle-aged men with LDL >155 mg/dl
- The JUPITER trial showed that treatment with rosuvastatin 20mg/daily in healthy men and women with elevated CRP and LDL < 130 mg/dl reduced CV events (nonfatal MI/stroke, hospitalization for unstable angina, arterial revascularization procedure, confirmed death from cardiovascular causes - HR 0.56) and reduced all cause mortality (HR 0.80). The trial was stopped early for benefit.

Secondary Prevention: Statin Benefit

- Patients with cardiovascular disease (CVD) are at high risk for CV events.
- In secondary prevention, statins have been shown to reduce CV events and all-cause mortality.
- Meta-analysis of clinical trials in high-risk patients found that PCSK9 inhibitors also decrease CV events and mortality.
- Trials of other lipid-lowering agents have generally only shown reductions in CV events.

Targeted vs. Level of Intensity Therapy

- Prior recommendations were “Target” driven
 - LDL <100
 - LDL <70
- New recommendations are based on the Intensity of therapy:
 - High, moderate and low intensity

Targeted vs. Level of Intensity Therapy

- High-intensity therapy (atorvastatin 40 mg to 80 mg) reduces ASCVD risk more than moderate-intensity therapy (atorvastatin 10 mg, pravastatin 40 mg, or simvastatin 20 mg to 40 mg bid)
- High-intensity statin therapy on average lowers LDL by approximately $\geq 50\%$, moderate-intensity statin therapy lowers LDL by approximately 30%

Secondary Prevention with High-Intensity Statin Therapy

- PROVE IT-TIMI 22 Trial
 - Patients with an acute coronary syndrome treated with intensive lipid-lowering therapy (atorvastatin 80 mg) had fewer clinical events compared to standard therapy (pravastatin 40 mg).
 - The benefit began within 30 days, and increased over time (primary end point significantly lower with atorvastatin - 22.4 vs. 26.3 percent @ 2 years).
 - Patients treated with atorvastatin had a decrease in mortality (relative risk 0.72)
 - All patients with coronary heart disease, including those with an acute coronary syndrome (ACS), should receive long-term, intensive statin therapy.

Targeted vs. Level of Intensity Therapy

- No good evidence to support titrating cholesterol-lowering drug therapy to achieve optimal LDL or non-HDL levels
- No recommendations are made for or against specific LDL or non-HDL goals for the primary or secondary prevention of ASCVD
- Rather than LDL or non-HDL targets, current Guidelines recommend the Intensity of statin therapy as the goal of treatment.
- Patients with known CVD (or at similar risk) should be treated with moderate to high intensity therapy regardless of the baseline LDL.
- All patients with an Acute Coronary Syndrome should receive long-term, high-intensity statin therapy.

How Low is Too Low?

- Epidemiologic studies as well as rare congenital conditions (e.g., hypobetalipoproteinemia) have shown that very low LDL cholesterol (<70 mg/dL) levels are associated with a very low risk of cardiovascular disease.
- In patients with total deficiency of proprotein convertase subtilisin-like/kexin type 9 (PCSK9) LDL levels can be in the range of 15 mg/dL with no adverse clinical effects.
- In patients treated with the PCSK9 inhibitor alirocumab who attained LDL levels <25 mg/dL, adverse events were no greater than with placebo (except possible cataracts?).
- Randomized clinical trials have shown a lower risk of cardiovascular disease without an increase in adverse events among those with very low LDL (<40 mg/dL).

How Low is Too Low?

- Patients in the PROVE IT-TIMI 22 study treated with atorvastatin were divided into 5 groups:
 - LDL >100, 80 to 100, 60 to 80, 40 to 60, and <40 mg/dl.
- The <40 mg/dl and 40 to 60 mg/dl groups had fewer major cardiac events (death, MI, stroke, recurrent ischemia, revascularization).
- No significant differences in safety (muscle, liver, or retinal abnormalities, intracranial hemorrhage, or death) was seen in the very low LDL groups compared to patients with an LDL 80 to 100 mg/dl
- Other studies have shown lowering LDL-cholesterol levels to very low levels results in a significant reduction in cardiovascular events (LDL <50 mg/dL had a significantly lower risk of MACE than LDL levels 50 to 75 mg/dL and 75 to <100 mg/dL).
- These data identify clear benefit and no intrinsic safety concerns of low LDL.
- A strategy of High-Intensity treatment need not be altered in patients achieving very low LDL levels.

Statins and Low LDL - Summary

- Unequivocal benefit of statin therapy in both Primary and Secondary Prevention of ASCVD
- Intensity of Therapy is preferred to Targeted Therapy
- Lowering LDL-cholesterol to very low levels results in a significant reduction in cardiovascular events and incremental benefits compared to standard therapy.
- Low LDL levels pose no intrinsic safety concerns
- A strategy of High-Intensity treatment need not be altered in patients achieving very low LDL levels (although some experts recommend considering a reduction of statin dose in patients who achieve an LDL <25 mg/dl.)

DAPT

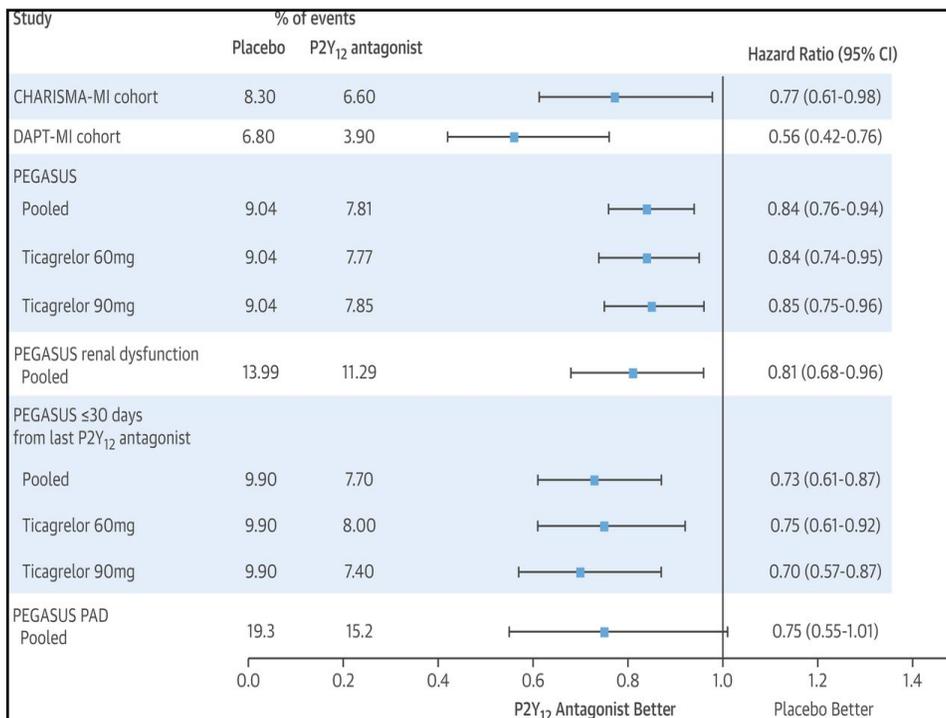
- Dual Antiplatelet Therapy in CHD, CVD and PAD
 - Risk/benefits of long term therapy
 - Which patients?
 - Which agents?
 - How long?

DAPT: Who and why?

- **STEMI:** There is strong evidence to support the early initiation of dual antiplatelet therapy (DAPT) with ASA and a P2Y₁₂ receptor blocker, irrespective of treatment strategy (fibrinolysis, primary percutaneous coronary intervention [PCI], or medical therapy), in patients with acute ST-elevation myocardial infarction
- **NSTEMI:** All patients with non-ST elevation acute coronary syndrome should receive (DAPT) with ASA and a P2Y₁₂ receptor blocker, as opposed to single antiplatelet therapy
- **FOLLOWING PCI:** The risks of stent thrombosis & myocardial infarction or death are diminished by the use of DAPT compared to ASA monotherapy and may prevent ischemic events remote from the stented area.
- **HOW LONG?** 1 month vs. 6 months vs. 12 months vs. longer

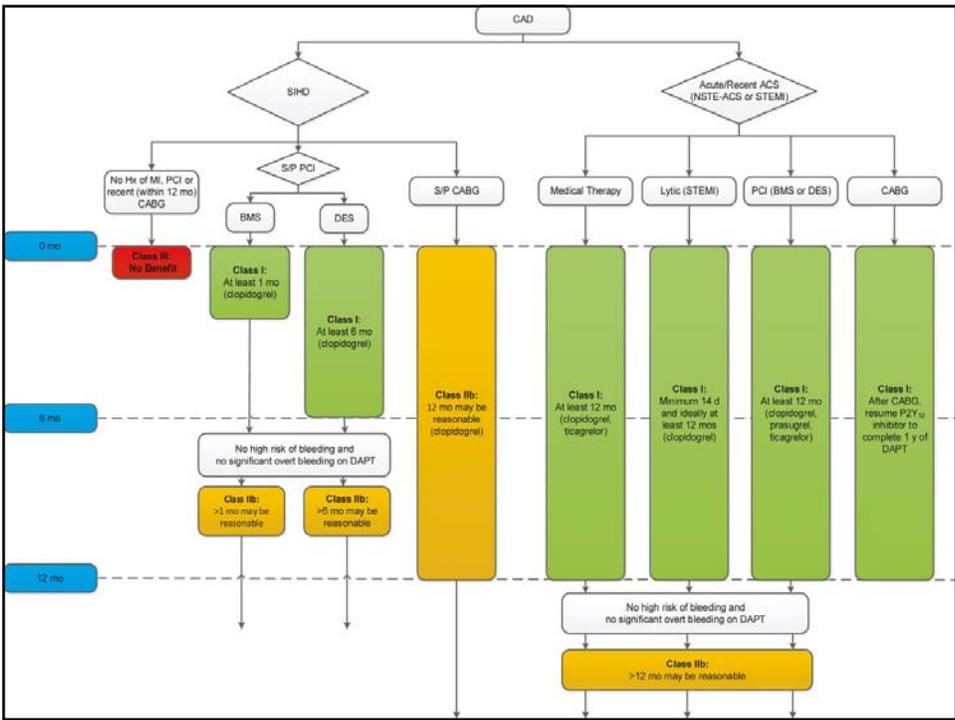
Studies of Prolonged DAPT

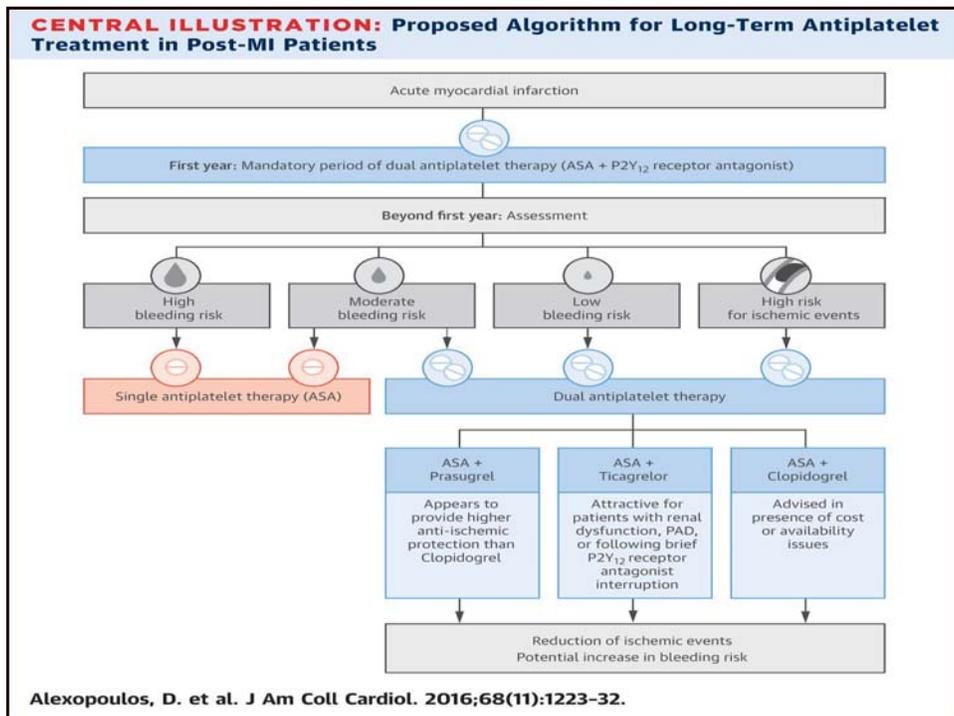
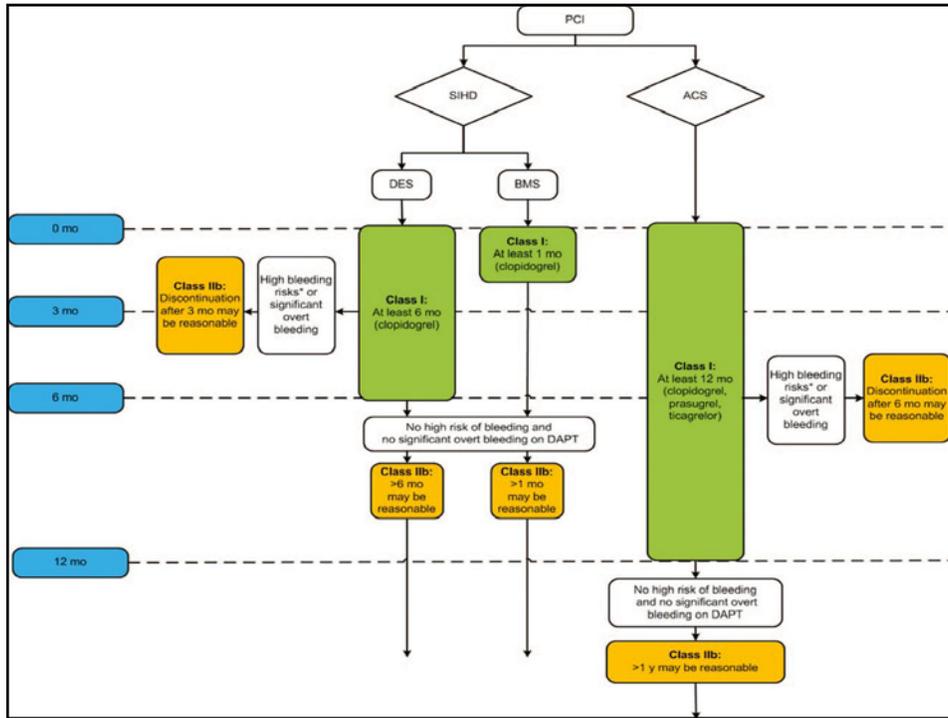
- **CHARISMA**
 - Stable patients with either atherothrombotic disease or with multiple risk factors for atherothrombotic dz
 - ASA plus clopidogrel or placebo
- **DAPT**
 - Post PCI with DES
 - ASA plus clopidogrel vs. prasugrel vs. placebo (18 mos)
- **PEGASUS-TIMI 54**
 - Stable patients w/ MI 1 to 3 years prior to enrollment
 - ASA + ticagrelor 90 or 60 mg BID, or placebo



Studies of Prolonged DAPT

- **CHARISMA:**
 - Primary efficacy endpoint: CV death, MI, or stroke:
Clopidogrel, 6.6%, Placebo, 8.3% (HR: 0.774 (95% CI: 0.613–0.978); p = 0.031)
- **DAPT:**
 - Stent thrombosis: Thienopyridine, 0.5%, Placebo, 1.9% (HR: 0.27 (95% CI: 0.13–0.57), p < 0.001)
 - MACCE: Thienopyridine: 3.9% Placebo, 6.8% (HR 0.56 (95% CI: 0.42–0.76), p < 0.001)
- **PEGASUS–TIMI 54 (CV death, MI, or stroke)**
 - Ticagrelor, 90 mg: 7.85%; Ticagrelor, 60 mg: 7.77%; Placebo, 9.04%
 - Ticagrelor 90 mg vs. placebo: HR: 0.85 (95% CI: 0.75–0.96), p = 0.008
 - Ticagrelor, 60 mg vs. placebo: HR: 0.84 (95% CI: 0.74–0.95), p = 0.004





DAPT Score

- Age \geq 75 y -2
- Age 65 to <75 y -1
- Age <65 y 0
- Current cigarette smoker 1
- Diabetes mellitus 1
- MI at presentation 1
- Prior PCI or prior MI 1
- Stent diameter <3 mm ` 1
- Paclitaxel-eluting stent 1
- CHF or LVEF <30% 2
- Saphenous vein graft PCI 2
- A score of >2 is associated with a favorable benefit/risk ratio for prolonged DAPT
- A score of <2 is associated with an unfavorable benefit/risk ratio.

DAPT - Recommendations

- Class of Recommendation (COR) and Level of Evidence (LOE)
- I A
 - In patients with SIHD treated with DAPT after BMS implantation, P2Y12 inhibitor therapy should be given for a minimum of 1 month.
- I B
 - In patients with SIHD treated with DAPT after DES implantation, P2Y12 inhibitor therapy should be given for at least 6 months.
- II A
 - In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT with or without PCI it is reasonable to use ticagrelor in preference to clopidogrel for maintenance P2Y12 inhibitor therapy.
 - In patients with ACS (NSTEMI-ACS or STEMI) treated with DAPT after coronary stent implantation who are not at high risk for bleeding complications and who do not have a history of stroke or TIA, it is reasonable to choose prasugrel
- IIb
 - In patients with SIHD treated with DAPT after BMS or DES implantation who have tolerated DAPT without a bleeding complication and who are not at high bleeding risk (e.g., prior bleeding on DAPT, coagulopathy, oral anticoagulant use), continuation of DAPT for longer than 1 month in patients treated with BMS or longer than 6 months in patients treated with DES may be reasonable.
- IIb
 - In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g., treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g., major intracranial surgery), or develop significant overt bleeding, discontinuation of P2Y12 inhibitor therapy after 3 months may be reasonable

Thank You