DUAL ANTI-PLATELET THERAPY AFTER CORONARY EVENTS AND INTERVENTIONS

An Update on Intensity, Duration and Strategies

Internal Medicine Grand Rounds January 17, 2020

University of Texas Southwestern Medical Center

***This is to acknowledge that Tayo A. Addo, M.D. has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Addo will be discussing off-label uses in his presentation*.**

Tayo A. Addo, MD

Director, Interventional Cardiology Fellowship

Medical Director, Cardiac Catheterization Lab, Parkland Health & Hospital System

Associate Professor of Medicine

UT Southwestern Medical Center

Clinical Interests: Coronary and lower extremity percutaneous arterial revascularization

Research Activities: Interventional therapy for hypertension via renal arterial denervation

Contact: tayo.addo@utsouthwestern.edu

Purpose & Overview:

To provide an update on the extent and duration of intense anti-platelet therapy after atherosclerotic coronary events

Objectives

1. Identify antiplatelet therapy options indicated for patients following myocardial infarction or percutaneous coronary interventions
2. Assess the benefits and the risks associated with antiplatelet therapy for these indications
3. Identify those most likely to benefit as well those who are poor candidates for treatment
4. Determine treatment duration and methods to reduce risks associated with treatment

Abbreviations

ACS Acute coronary ischemic syndromes

CABG Coronary artery bypass grafting

CV Cardiovascular

DAPT Dual anti-platelet therapy

MI Myocardial Infarction

PCI Percutaneous coronary interventions

Anti-platelet therapy has been a cornerstone in the management of patients with coronary heart disease for decades. Long-term therapy with aspirin showed reduction in cardiovascular mortality in wide range of patients with established cardiovascular disease, mediated by reductions in future myocardial infarction and stroke (1). Twenty-five years ago, the addition of PY12 antagonists improved short-term outcomes when added to aspirin in patients undergoing percutaneous revascularization (2). The combination appeared safe and led to the concept of dual-antiplatelet therapy (DAPT). The CURE trial first tested long-term DAPT by adding Clopidogrel to aspirin in patients with acute coronary syndromes (3). In this trial, 12,562 patients with non ST-elevation ACS randomly received Clopidoprel or placebo on admission and continued for up to 12 months. The trial showed a significant 20% relative and 2.1% absolute risk reduction in the composite risk of CV death, MI, and stroke. The outcome was driven by a reduction in recurrent MI, and the benefit also evident in the patients who received PCI and continued long-term therapy (4). Clopidogrel did increase the absolute risk of major bleeding by 1%. Short-term benefits of DAPT were soon evident in patients with ST-elevation myocardial infarction, making the treatment applicable to all patients with acute coronary syndromes (5, 6).

Patients with coronary disease undergoing PCI outside of acute coronary syndromes were also at risk for stent-related thrombotic complications. While the efficacy of a short-course of DAPT was already established, the Introduction of 1st generation drug eluting stents led to delays in coronary endothelial healing and was associated with higher rates of rare late stent-related thrombotic events (7). These stents were also been increasingly used in patients with more complex coronary disease that is associated with higher stent related thrombotic events (8). In light of data from acute coronary syndromes, guideline committees soon recommended all patients undergoing PCI receive DAPT for 12 months if tolerable (10). The widespread recommendation of DAPT however quickly posed challenges for the medical community. Clopidogrel at the time was not generically available and so affordability and access were problematic in large patient cohorts. There was no guarantee of compliance and so patients receiving drug-eluting stents appeared to carry a new treatment-related risk. There is a common need to interrupt anti-platelet for surgical procedures. Finally, bleeding complications was been appreciated clinically, as use expanded beyond healthier patients enrolled in clinical trials. Elderly patients as well as others at high risk of bleeding were of concern. These issues will serve basis for multiple trials testing the safety of shorter course DAPT discussed later.

More Potent DAPT in Acute Coronary Disease

In spite of the efficacy noted and increased bleeding seen with Clopidogrel, several shortcomings were widely known with this drug. Significant variation in anti-platelet response had been evident from pharmacodynamic and pharmacokinetic studies. Large groups of patients remained relatively resistant including those with acute coronary syndrome, diabetes, and poor genetic metabolizers of Clopidogrel (11-12). Moreover, recurrent thrombotic rates remained significantly high after acute coronary syndromes, suggesting more potent and consistent anti-platelet therapy will further reduce events. The TRITON-TIMI 38 trial enrolled 13,608 patients with acute coronary syndromes scheduled to undergo PCI and randomized them to DAPT with Aspirin and Clopidogrel or to Aspirin and the more potent P2Y12 antagonist Prasugrel (13). Through a median follow up of 14.5 months, there was a reduction in the composite endpoint of CV death, MI and stroke in favor of those assigned to Prasugrel. The 19% relative (2.2% absolute) risk reduction was associated by a further 0.6% absolute increase in major bleeding. The risk reduction was driven by reduction in recurrent MI, but also seen was reduction in stent thrombosis.

The PLATO trial next tested DAPT with Ticagrelor versus Clopidogrel in 18,624 patients hospitalized with acute coronary syndromes, undergoing an invasive management strategy (14). More than 60% received PCI and 10% CABG. The rate of CV death, MI and stroke was significantly reduced in the Ticagrelor arm, with 16% relative and 1.9% absolute reductions noted. The benefit appeared consistent whether the patient received invasive management or not. Noted also was a significant reduction in CV mortality in addition to MI and stent thrombosis. A 0.7% absolute increase in non-CABG related major bleeding was observed compared with Clopidogrel. Taken together, these data were sufficient to recommend these potent DAPT regimens in patients with ACS undergoing invasive management. Updated guidelines also suggested preference to these regimens over Clopidogrel when feasible (15). Treatment duration of 12 months was set as an ideal regimen based on the trial durations although there was no evidence benefits stopped at 12 months. A further attempt to push potent anti-platelet therapy in acute coronary disease came with the introduction of Vorapaxar, a non-P2Y12 antagonist that inhibited platelets via blocking the platelet thrombin receptor PAR-1. In the TRACER trial, Vorapaxar was added to a background of Aspirin and Clopidogrel in 12,944 patients with acute coronary syndrome (16). The trial ended early due to safety concerns after median follow up of 16 months. While the rate of CV death, MI and stroke was reduced another 11% (1.7% absolute), major bleeding further increased, reaching 7%, including a more then 3-fold increase in intra-cranial bleeding. Vorapaxar therefore never received recommendation as added therapy for acute coronary syndromes.

Long-duration DAPT in Chronic Coronary Disease

The CHARISMA trial first tested the concept of DAPT with Clopidogrel in 15,603 patients who had not recently suffered myocardial infarction (17). This study included patients with established coronary disease and those with multiple CV risk factors. After a median follow-up of 28 months, there was no significant reduction in the outcome of CV death, MI and stroke in this trial. However, among patients with established myocardial infarction or other prior thrombotic events, the primary endpoint was reduced, driven by reductions in new myocardial infarction (18). Vorapaxar also underwent evaluation in stable patients with established cardiovascular disease including prior myocardial infarction. The TRA 2P TIMI 50 trial enrolled 26,449 patients with 2/3rds having had a prior myocardial infarction and 2/3rds already on Clopidogrel (19). At 2 years, the combined endpoint of CV death, MI and stroke was reduced by 13% (1.2% absolute) along with a 1% absolute further increase in major bleeding. Of note, patients with prior strokes were later excluded from the trial due to concerns about intra-cranial bleeding. Vorapaxar is available for use in reducing atherothrombotic events in patients such as enrolled in TRA 2P, however widespread use has been tempered by bleeding risks including intra-cranial hemorrhage which was 2-fold higher. Long-term therapy using Ticagrelor in addition to aspirin in stable patients was tested in the PEGASUS TIMI 50 trial (20). In this study, more than 21,000 patients who had suffered myocardial infarction 1-3 years ago were randomized to DAPT using Ticagrelor or to aspirin alone. Following a median of 33 months, there was a significant reduction (15% relative, 1.3% absolute) in the composite endpoint of CV death, MI and stroke. All components of the endpoint were redued and the benefit was primarily in those who had suffered MI 1-2 years previously. An absolute increase in major bleeds by 1.5% was noted over this treatment period. A meta-analysis of trials of stable patients with prior myocardial infarction including subgroups from broader trials show that major adverse cardiac events is reduced by 20% (absolute 2.1%), including CV mortality (21). A nearly 1% absolute increase in major bleeding complication is seen however with long-term DAPT therapy. Most recently, DAPT using Ticagrelor was studied in diabetics with coronary disease but no prior myocardial infarction (22). The

THEMIS trial enrolled 19,220 patients with a median follow up of 39 months to study this. The primary endpoint of CV death, myocardial infarction and stoke was reduced 10% (0.8% absolute), driven by reductions in myocardial infarction and stroke. There was however an absolute 1% increase in major bleeding complication over this period.

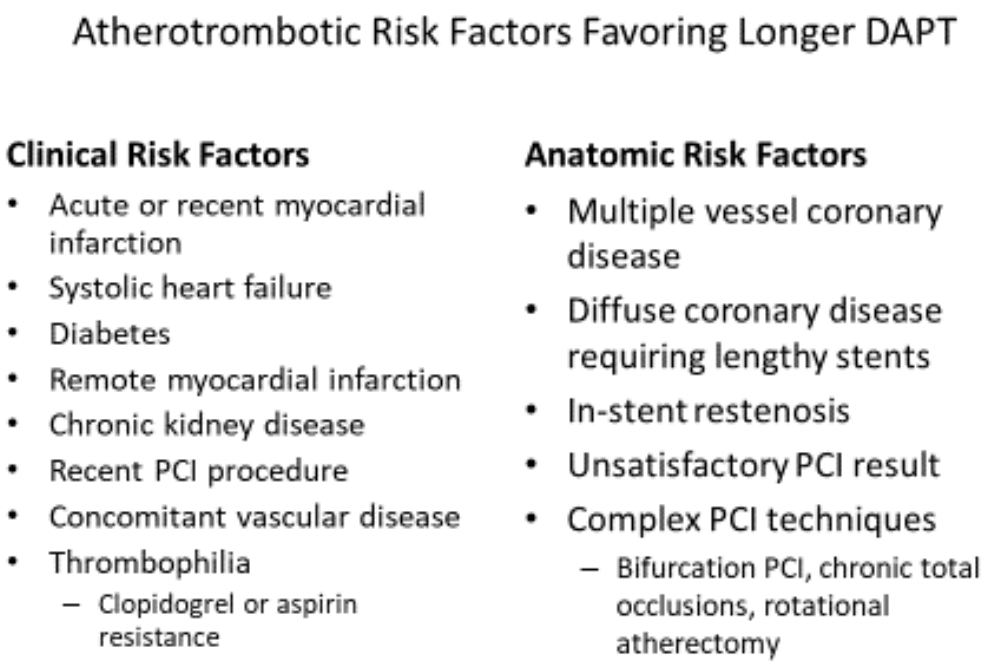
Trials in Patients undergoing PCI

Patients undergoing PCI with stents present a large opportunity for study. The self-imposed 12-month DAPT for patients receiving drug eluting stents created numerous difficulties for patients and providers, and so there was a need to assess shorter regimens. On the other hand, ongoing therapy with DAPT may continue to reduce thrombotic events either stent-related or not, making a case for longer treatment. Several trials beginning in 2009 tested the concept of shorter-course DAPT versus 12 months, first in stable elective PCI and more recently after acute coronary syndromes. Advances in drug-eluting coronary stent technology had also reduced the risk of stent thrombosis, allowing clinical equipoise (23). In meta-analysis of studies assessing shorter (3-6 month) DAPT regimens, there were lower rates of bleeding complications universally but a modest increase in ischemic events, limited to those presenting with ACS (24). Shorter duration (3-6 months) DAPT therefore has become an option for those at higher bleeding risk, those who cannot tolerate treatment due to bleeding and those who need to interrupt for surgical procedures (25). To test the other concept of DAPT beyond 12 months, the DAPT trial assigned 9,961 patients who previously undergone PCI 12 months ago to further therapy with DAPT for 18 months or to aspirin alone (26). Continuing DAPT reduced the rates of myocardial infarction (2.1 vs 4.1%) and stent thrombosis (0.4 vs 1.4%). The benefit was also larger in those who originally presented with ACS. Moderate to severe bleeding however increased from 1.6% to 2.5%. In a meta-analysis including similar trials, longer DAPT resulted in a 40% reduction in recurrent MI and 63% reduction in stent thrombosis (27). No difference in all-cause mortality was seen. Again, the benefit is most prominent in those that presented with ACS, while the bleeding risk increased regardless of presentation. Those presenting initially with ACS derived a net clinical advantage.

High Thrombotic Risk

The ideal patients for long-term DAPT are those with highest rate of future thrombotic events. Those with higher rates receive a greater absolute reduction in events with longer or more potent drugs. Extensive literature has identified patients at risk for future events, and as risk factors add up, the greater the benefit. Patients with acute coronary syndrome or prior myocardial infarction are at higher risk, and so show benefits with DAPT as described above. Other clinical risk factors for thrombosis include patients with diabetes, systolic heart failure, renal disease, concomitant vascular disease, and thrombophilia. Several sub-studies in trials of DAPT show the benefits of targeting these populations (28). Having multiple risk factors such as acute myocardial infarction and diabetes for example would predict a group more likely to benefit from long-term and more potent DAPT. In addition to clinical risk factors, coronary anatomic risk factors also predict patients at higher risk for events and thus benefit of DAPT. Patients with multiple vessel coronary disease, complex revascularization procedures or previous failed stents are at increased risk for recurrent events. Studies such as Guistino et al. (29), Yeh et al. (30), and Costa et al (31) show complex anatomy or procedures predict benefit from longer DAPT. Having both clinical and anatomic risk factors appears to be an effective way to select candidates for long-term DAPT.

Figure 1

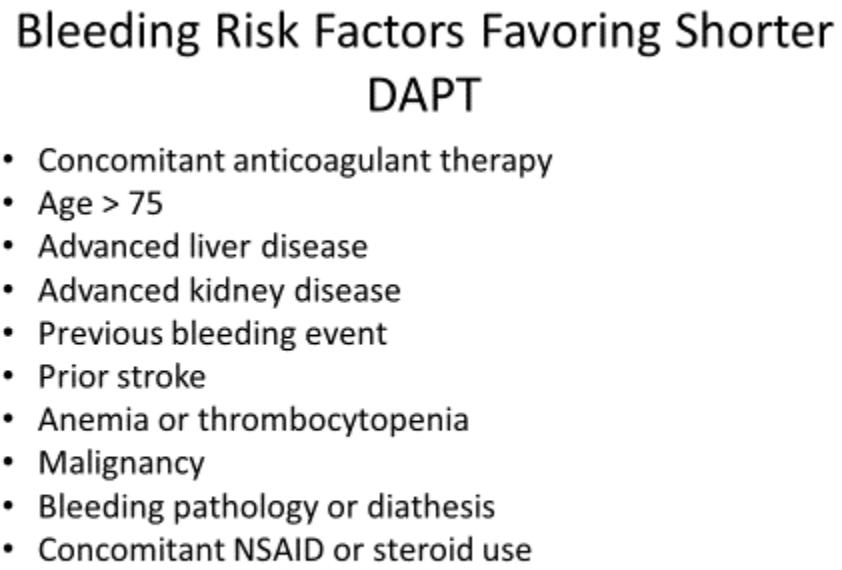


Bleeding risk on DAPT

Bleeding complications remain the greatest challenge to long-term anti-platelet therapy and the risk continues to accrue over the period of treatment. Major bleeding is a serious complication that typically requires hospitalization, blood transfusion, medical stabilization and occasionally surgical or other procedural interventions. Acute hemodynamic and metabolic derangement can occur, and bleeding can be fatal when rapid and uncontrollable or result in permanent disability when it occurs in a critical space. Bleeding also frequently causes disruption of important cardiovascular medications. Importantly, major bleeding in patients on DAPT has been associated with an increase in all cause as well as cardiovascular mortality (33, 34). The risk associated with a bleeding event occurs early after the event and can exceed risks associated with recurrent myocardial infarction. In essentially all trials of DAPT, the reduction in MACE events is tempered by increases in the absolute increase in major bleeding. As such, cardiovascular and all-cause mortality must be determined and should directionally favor anti-platelet therapy to be considered net beneficial. As with thrombotic risk, several risk factors identified from several datasets predict risk. These include advanced age, concomitant anticoagulant therapy, bleeding disorders, cirrhosis, frailty, anemia, underlying malignancy, cerebrovascular disease, and end-stage renal disease. Major risk factors and multiple minor risk factors further increase risk, and scoring systems are

helpful in estimating risk (35). Current guidelines now endorse an estimation of bleeding risk when selecting DAPT drugs and treatment duration (36) with Clopidogrel preferred in patients with higher bleeding risk. Among patients with acute coronary syndromes initially prescribed potent P2Y-12 antagonists such as Prasugrel or Ticagrelor, de-escalation to clopidogrel was safe and effective at reducing bleeding after a short (1-3 month) treatment period (37).

Figure 2



Strategies to Reduce Bleeding and Maximize DAPT

Proton pump Inhibitors

Gastrointestinal bleeding is the most common cause of major bleeding during long-term anti-platelet therapy, and a pathology commonly seen is gastrointestinal mucosal erosions or exacerbation of peptic ulcer disease (38, 39). Proton pump inhibitors by reducing gastric acidity, reduces the risk of GI bleeding. The COGENT trial tested the addition of Omeprazole to patients taking DAPT in 3783 patients (40). There was a significant reduction in GI bleeding complications from 2.9% to 1.0, including episodes of major bleeding. There was no increase in thrombotic events with this strategy even through Omeprazole may affect the anti-platelet effect of Clopidogrel via its hepatic metabolism. A proton pump inhibitor is useful in all patients at high bleeding risk and recommended in patients with known peptic ulcer disease or history of upper GI bleeding.

Shorter Duration of DAPT

As described above, several trials have tested 3-6 month regimens of DAPT. Bleeding events are lower and ischemic events similar in patients with stable coronary disease. Ischemic events are modestly higher is those presenting with ACS but there no difference in all-cause mortality by network meta-analysis (24). Newer studies are now evaluating DAPT courses as short as 1 month in patients with high bleeding risk receiving DES. Both LEADERS FREE and the SENIOR trial evaluated this regimen in patients receiving DES or bare metal stents. In both trials, outcomes with DES were superior to bare metal stents.

Elimination of aspirin from DAPT

Finally, a new strategy is emerging that may allow ongoing therapy with a lower bleeding risk. While aspirin is a core component of all studies mentioned thus far, its use likely contributed to overall bleeding risk. Aspirin increases bleeding by both anti-platelet effects and gastrointestinal mucosal injury. Low dose aspirin reduces gastrointestinal injury while preserving anti-platelet effects and is now the recommended dose in managing cardiovascular disease. Nonetheless, low dose aspirin still increases bleeding and effects more pronounced in patients at high bleeding risk. Trials are now testing the elimination of aspirin to determine if ischemic protection is preserved and bleeding reduced. Patients receiving concomitant oral anticoagulants for conditions such as atrial fibrillation first underwent evaluation. In patients receiving warfarin, early elimination of aspirin significant reduced bleeding events (41). The PIONEER AF and the RE-DUAL PCI trials (42, 43) studied stable patients undergoing PCI and receiving new oral anticoagulants Dabigatran and Rivaroxaban respectively. In both trials, arms taking a P2-Y12 without aspirin experienced lower bleeding complications. More recently, the AUGUSTUS trial evaluated the strategy of eliminating aspirin among PCI patients receiving Apixaban (44). The study of 4600 patients comprised stable and unstable patients. Again, there was a significant reduction in bleeding complications and no increase in ischemic complications without aspirin. Bleeding risk is also lower with a NOAC compared with warfarin. There is now sufficient data to recommend Clopidogrel alone along with a NOAC as treatment of choice for all patients undergoing PCI who have an indication for chronic anticoagulation (45). Outside of atrial fibrillation, the SMART-CHOICE trial, 2993 patients with stable and unstable coronary disease undergoing PCI received either a 12-month course of DAPT or 3 months followed by monotherapy with a P2Y12 antagonist (46). There was a reduction in bleeding events but no increase in ischemic events. The STOP DAPT-2 trial similarly randomized 3045 patients with stable and unstable coronary disease undergoing PCI to a 12-month course of DAPT or 1 month followed by monotherapy with a P2Y12 antagonist (47). Again bleeding was lower without an increase in ischemic complications. Both trials however enrolled lower risk patients. Finally, in the largest trial to date, the TWILIGHT trial enrolled 9000 patients undergoing PCI who were at increased risk of thrombotic events based on clinical and anatomic criteria (48). Patients received DAPT with Ticagrelor and then at 3 months, 7119 patients free of events underwent randomization to Ticagrelor monotherapy or continued DAPT for another 12 months. The results showed a reduction in moderate and major bleeding complications from 7.1% to 4.0% including 1% absolute reduction in major bleeds. There was no increase in ischemic events with this strategy and this was true even in patients who has presented with acute coronary syndromes. The early elimination of aspirin from DAPT therefore appears to be a good strategy at reducing bleeding while preserving benefit in patients needing treatment for increased thrombotic risk.

Figure 3

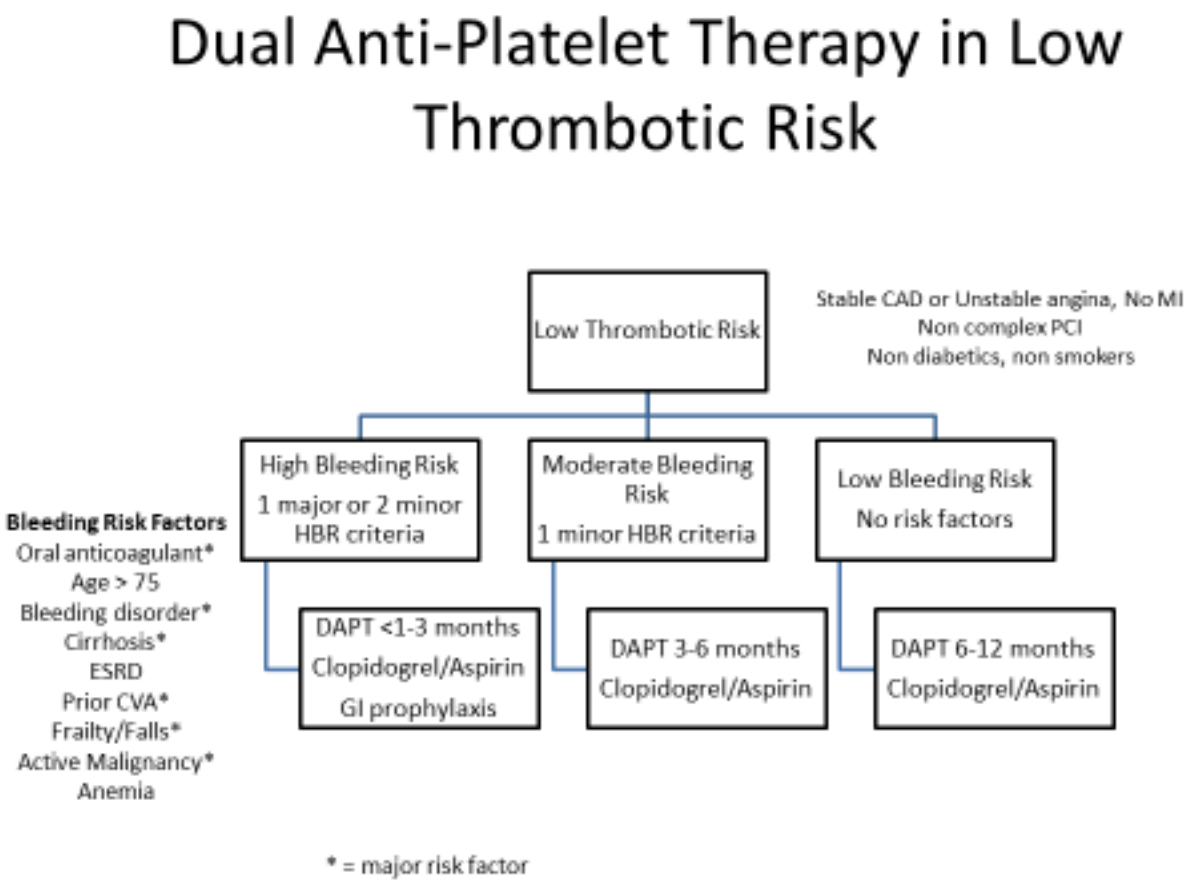
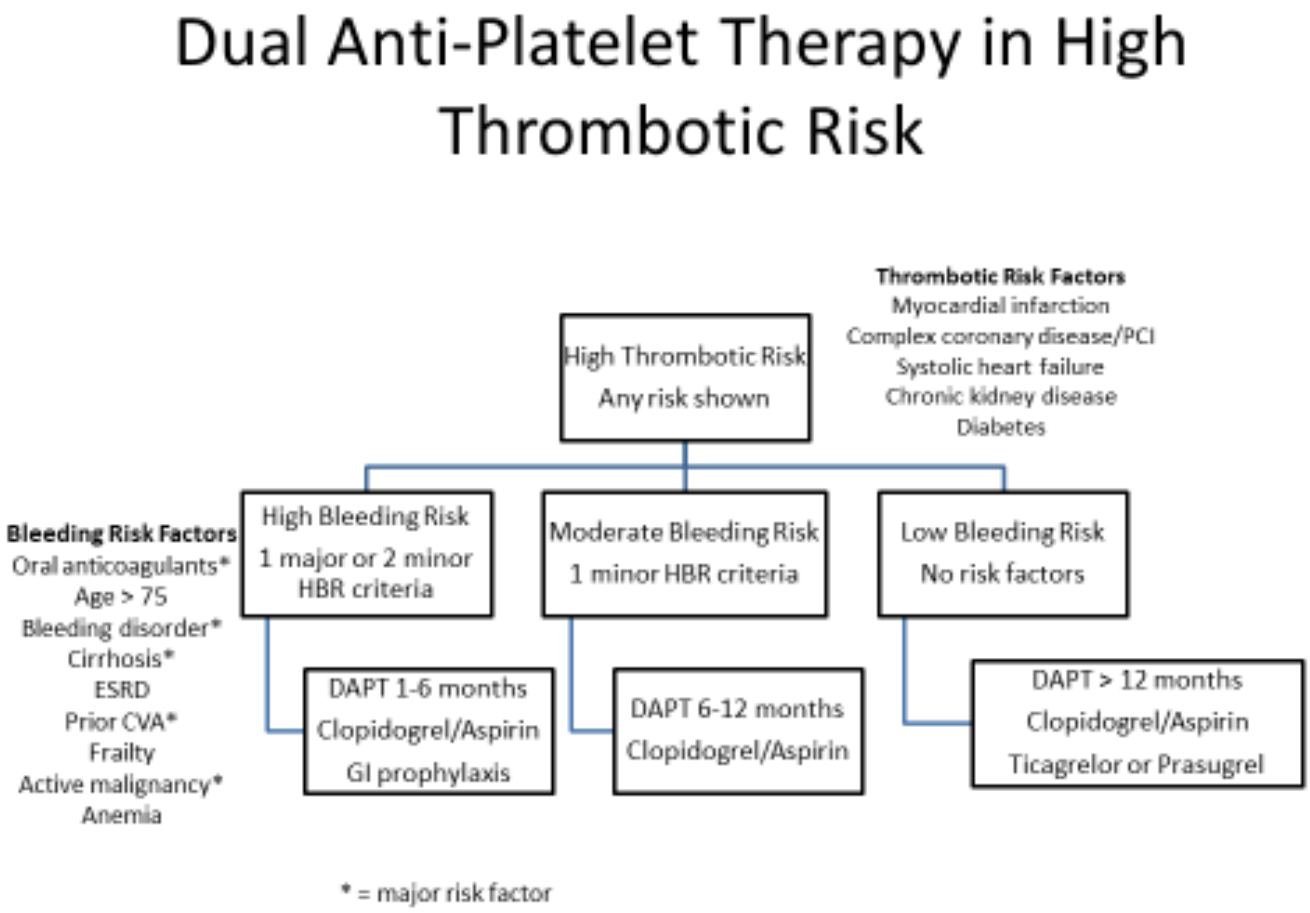

Dual Anti-Platelet Therapy in Low Thrombotic Risk
Low Thrombotic Risk
Stable CAD or Unstable angina, No MI
Non complex PCI
Non diabetics, non smokers
High Bleeding Risk
1 major or 2 minor HBR criteria
Moderate Bleeding Risk
1 minor HBR criteria
Low Bleeding Risk
No risk factors
Bleeding Risk Factors
Oral anticoagulant*
Age > 75
Bleeding disorder*
Cirrhosis*
ESRD
Prior CVA*
Frailty/Falls*
Active Malignancy*
Anemia
DAPT <1-3 months
Clopidogrel/Aspirin
GI prophylaxis
DAPT 3-6 months
Clopidogrel/Aspirin
DAPT 6-12 months
Clopidogrel/Aspirin
* = major risk factor

Figure 4



Conclusions

DAPT therapy has evolved substantially in the past several years. We now have a variety of treatment regimens to maximize treatment benefit and reduce treatment risk. Improvements in PCI has shifted the focus of longer-term DAPT from stent thrombosis to prevention of future myocardial infarction. Treatment duration and intensity comes at a cost of major bleeding which carries serious implications. Determination of thrombotic and bleeding risk factors is useful in guiding treatment. When bleeding risk is low and thrombotic risk significant, long-term DAPT, well beyond a year reduces future ischemic events. When bleeding risk is elevated, short courses, <3-6 months is recommended. The elimination of aspirin from DAPT lowers bleeding risk yet preserves benefit conferred by DAPT. This may emerge as the best strategy for many of our patients.

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