Duration of Dual Antiplatelet Therapy After Coronary Stenting

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INTRODUCTION

- Coronary artery stents are used in the majority of patients who undergo percutaneous coronary intervention to improve symptoms in patients with obstructive coronary artery disease. They function both to prevent abrupt closure of the stented artery soon after the procedure as well as to lower the need for repeat revascularization compared to balloon angioplasty alone.

- Stent thrombosis is an uncommon but serious complication of coronary artery stenting that often presents as death and is almost always accompanied by myocardial infarction.
DEFINITIONS OF STENT THROMBOSIS AND RESTENOSIS

- After a successful procedure, coronary stents can fail to maintain vessel patency due to stent thrombosis or stent restenosis. Stent thrombosis is an abrupt thrombotic occlusion of a previously patent stent. It is a serious complication that presents as sudden death or myocardial infarction (MI) in most patients. Despite successful repeat revascularization, the six-month mortality is high.
DEFINITIONS OF STENT THROMBOSIS AND RESTENOSIS

- Events occurring within the first 30 days were considered to represent acute or sub acute stent thrombosis.

- Events occurring after 30 days were considered to represent late stent thrombosis.
WHY DUAL ANTI PLATELET THERAPY vs ASPIRIN MONOTHERAPY

- The rationale for the use of DAPT is derived from the known tendency of circulating blood to clot in the presence of metal. This period of risk decreases after the metal portion of the stent is endothelialized. More intense antiplatelet therapy (DAPT) lowers the risk of stent thrombosis compared to aspirin alone.

- In early studies of patients who received bare metal stents (BMS), the rate of stent thrombosis was significantly lower with aspirin plus ticlopidine than with aspirin alone (or aspirin plus warfarin).

  STARS trial - 1653 patients were randomly assigned to aspirin alone or in combination with warfarin or ticlopidine. The primary end point included all clinical events reflecting stent thrombosis within 30 days: death, revascularization of the target lesion, angiographically documented thrombosis, or MI. The rate of the primary end point was significantly lower with aspirin plus ticlopidine than with aspirin plus warfarin or aspirin alone (0.5 versus 2.7 or 3.6 percent, respectively).

- Subsequent studies demonstrated similar efficacy between ticlopidine and clopidogrel but a better side effect profile with Clopidogrel.
LONG-TERM DUAL ANTIPLATELET THERAPY

- All patients who undergo percutaneous coronary intervention (PCI), receive dual antiplatelet therapy (DAPT), which is the combination of aspirin and a P2Y12 receptor blocker to reduce the risk of myocardial infarction (MI) or death from stent thrombosis.
For stable patients and for acute coronary syndrome patients treated with either DES or BMS in whom surgery is not planned and the bleeding risk is not excessive prescribe **DAPT for 12 months**
DURATION OF DUAL ANTI PLATELET THERAPY

- The minimum duration of uninterrupted DAPT therapy is
  - 30 days for patients who receive BMS
  - 6 months for patients who receive DES
DUAL ANTI PLATELET THERAPY WITH DRUG ELUTING STENTS

- For patients who have received DES
  - recommend at least 12 months of DAPT.

- For patients who remain free of bleeding events
  - continue DAPT for at least an additional 18 months.
AMERICAN COLLEGE OF CARDIOLOGY (ACC)

- Class IIb ACC RECOMMENDATION
- 1. Continuation of DAPT beyond 12 months may be considered in patients undergoing stent implantation.
- (Level of Evidence: C)
DAPT Study

- The DAPT study randomly assigned 9961 patients, who had been successfully treated with 12 months of aspirin and a P2Y12 receptor blocker (either clopidogrel or prasugrel), to continue receiving the P2Y12 receptor blocker or placebo for another 18 months in addition to aspirin.

- Enrolled patients had either stable (38 percent) or unstable disease.

- Exclusion criteria included a major adverse cardiovascular or cerebrovascular event, repeat revascularization, or moderate or severe bleeding within the first 12 months after the index procedure. In addition, patients not compliant with P2Y12 therapy were excluded. The following findings were reported:
The rates for each of the co-primary end points of stent thrombosis and major adverse cardiovascular and cerebrovascular events (a composite of death from any cause, MI, or stroke) were lower with continued P2Y12 therapy. The reduction in events with continued DAPT was mostly attributable to a lower rate of MI (2.1 versus 4.1 percent; HR 0.47, p<0.001).

The rate of the primary safety end point of moderate or severe bleeding was increased with continued DAPT (2.5 versus 1.6 percent, p = 0.001).

The rate of death from any cause was higher in the DAPT group. This increase was due to an increase in non-cardiac deaths (1.0 versus 0.5 percent, p = 0.002).
The optimal duration of DAPT therapy in patients treated with DES is not well established. However, aspirin is continued indefinitely in all patients managed with a bare-metal stent or DES, and DAPT is an option for >12 months in patients who have received a DES. This determination should balance the risks of stent thrombosis and ischemic complications versus bleeding and should be jointly made by the clinician and the patient.
There have been no randomized trials of differing aspirin doses in stable patients who undergo PCI in the stent era.

The issue of the optimal dose of aspirin was evaluated by subgroup analysis of the 17,263 acute coronary syndrome patients who underwent early PCI in the CURRENT-OASIS 7 trial. There was no significant difference in the primary outcome (cardiovascular death, MI, or stroke at 30 days) between those who were randomly assigned for 30 days to a dose of 300 to 325 mg compared to those given 75 to 100 mg. While there was no significant difference in the rate of major bleeding, the rate of minor bleeding was significantly higher in those who received the higher dose of aspirin.
DOSE OF ASPIRIN

- CLASS I ACC RECOMMENDATION

- Aspirin should be continued indefinitely. The maintenance dose should be 81 mg daily in patients treated with ticagrelor and 81 mg to 325 mg daily in all other patients. (Level of Evidence: A)
DOSES OF DAPT

- Clopidogrel (PLAVIX) – 75 mg once daily

- Prasugrel (EFFIENT) – 10 mg once daily; for patients who weigh less than 60 kg, 5 mg once daily is the recommended dose

- Ticagrelor (BRILINTA) – 90 mg twice daily
ORAL P2Y12 INHIBITORS

- Clopidogrel 75 mg daily
  Prodrug, activity limited by metabolization

- Prasugrel 10 mg daily
  Prodrug, not limited by metabolization
  More rapidly and to a greater degree than clopidogrel

- Ticagrelor 90 mg twice daily
  Active drug
P2Y12 NEW AGENTS

- Prasugrel and Ticagrelor have been studied in patients with UA/NSTEMI and STEMI patients
- Prasugrel only used in patients undergoing invasive strategy
Combined Oral Anticoagulant Therapy and Antiplatelet Therapy

- Some preference toward use of BMS to DES in patients who require long-term anticoagulation in an attempt to reduce the exposure period to DAPT.
Combined Oral Anticoagulant Therapy and Antiplatelet Therapy

**CLASS I ACC RECOMMENDATION**
- The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a P2Y12 receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding. (Level of Evidence: C)

**CLASS IIB**
- Targeting an INR 2-2.5 might be reasonable in patients also on aspirin and a P2Y12 inhibitor
Combined Oral Anticoagulant Therapy and Antiplatelet Therapy

- WOEST TRIAL – What is Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting
  - Group 1 – warfarin plus clopidogrel 75 mg daily
  - Group 2 – warfarin plus clopidogrel 75 mg daily plus aspirin 81 mg daily

- Primary endpoint of TIMI Bleeding events was lower in double vs triple therapy group
TEMPORARY D/C OF DAPT

- Temporary discontinuation of DAPT before 30 days is associated with high risk.
- The risk is uncertain between one and six months.
- Temporary discontinuation of the P2Y12 receptor blocker after six months may be safe as long as aspirin is continued.
At least four studies have attempted to quantify this risk:

In the PARIS the hazard ratio for major adverse cardiovascular events was non-significantly higher for patients with interruption.

The ACDC study evaluated 1,622 individuals who received a DES and were placed on aspirin and clopidogrel and followed for one year. During this time, 111 patients temporarily discontinued at least one antiplatelet agent: clopidogrel was stopped in 31, aspirin in 27, and both drugs in 53. The median duration of cessation was seven days. The rate of acute coronary syndrome was not significantly different between those who discontinued and those who did not.

In a pooled analysis of data from 4,896 individuals in studies of the Resolute zotarolimus-eluting stent (table 1), 1,069 had interruption of DAPT: 166 in the first month and 903 between 1 and 12 months. Among those with interruption in the first month, there were six definite/probable stent thrombosis events (3.61 percent). There was one episode of stent thrombosis between 1 and 12 months, a rate that was comparable to those without interruption.
CLASS I ACC RECOMMENDATIONS

In patients receiving a stent (bare-metal stent or drug-eluting stent [DES]) P2Y12 inhibitor therapy should be given for at least 12 months. Options include:

- Clopidogrel: 75 mg daily (Level of Evidence: B) or
- Prasugrel
  - Patients should receive a loading dose of prasugrel, provided that they were not pretreated with another P2Y12 receptor inhibitor.
  - 10 mg daily (Level of Evidence: B) or
- Ticagrelor
  - The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.
  - 90 mg twice daily (Level of Evidence: B)
DAPT RECOMMENDATIONS FOR NON COMPLIANT PATIENTS

- Patients who are not likely to comply with a recommendation for one year of dual antiplatelet therapy (DAPT) or who have a planned procedure that requires early cessation of antiplatelet therapy may be better candidates for a bare metal stent (BMS) than a drug-eluting stent (DES).
SUMMARY OF RECOMMENDATIONS

- At the time of percutaneous coronary intervention, the choice between bare metal and drug-eluting stents (BMS and DES) should be made after taking into account the patient’s ability to comply with recommendations for the minimum uninterrupted duration of DAPT.

- For patients treated with either DES or BMS who are not at high bleeding risk and who do not have planned noncardiac surgery within one year, DAPT is recommended for at least 12 months rather than a shorter treatment duration.

- Practitioners should evaluate patients after the first 12 months of DAPT to be certain that there has not been major bleeding or other difficulty related to DAPT. For patients who have had a complication of DAPT, continuation after 12 months may not be appropriate.
SUMMARY OF RECOMMENDATIONS

- For patients who have not had a significant complication with DAPT during the first 12 months, consider continuing such therapy for an additional 18 months (CLASS IIB) after discussion with the patient.

- For patients treated with BMS at high bleeding risk or who have planned non-cardiac surgery within one year, recommend a minimum of one month of uninterrupted DAPT.

- For such patients treated with DES, recommend uninterrupted DAPT for a minimum of six months.
In patients undergoing **elective stenting**, clopidogrel is the preferred P2Y12 receptor blocker.

Prasugrel and ticagrelor have been studied only in patients with **acute coronary syndromes**.

Aspirin should be continued indefinitely in all stented patients.
SUMMARY OF RECOMMENDATIONS

- Daily dose of aspirin of 81 to 325 mg

- The dose of clopidogrel is 75 mg daily.

- The dose of prasugrel is 10 mg once daily. For patients who weigh less than 60 kg, 5 mg once daily is the recommended dose.

- The dose of ticagrelor is 90 mg twice daily.