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If a stent is good enough for a President….

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This is to acknowledge that Emmanouil S. Brilakis, MD, PhD has disclosed that he does have financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Brilakis will be discussing off-label uses in his presentation.

Biographical information:

Emmanouil Brilakis, MD, PhD received his medical degree from the National Kapodistrian University of Athens, Greece. He trained in Internal Medicine, Cardiovascular Diseases and Interventional Cardiology at the Mayo Clinic. He completed a Masters in Clinical Research at the Mayo Clinic and a PhD in Clinical Research at the National Kapodistrian University of Athens, Greece. Since 2004 he is an interventional cardiologist at VA North Texas Healthcare System where he leads a dynamic clinical trial research group. His research interests include the prevention and treatment of saphenous vein graft disease, percutaneous treatment of coronary chronic total occlusions, intracoronary imaging with special emphasis on near-infrared spectroscopy and optical coherence tomography, and medical treatment optimization after coronary stenting.
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Purpose and overview

The goal of this presentation is to review the currently available coronary revascularization modalities, discuss how to select the optimal revascularization modality for each patient, and review the medical management of patients after coronary stent implantation.

Educational objectives.

1. Discuss the various types of coronary revascularization
2. Evaluate the indications for coronary revascularization, especially for percutaneous coronary intervention
3. Review the different types of coronary stents and the medical management after coronary stent implantation

Introduction

Part 1. The President's stent

On August 6, 2013, former President George W. Bush was found to have a positive stress test and successfully underwent percutaneous coronary intervention (PCI) with stent placement. This event received extensive media attention and stirred intense controversy: some argued that stenting was unnecessary, whereas others argued that it was both appropriate and useful. While the full details of former President's case are not available, the goal of this review is to discuss the risks, benefits, goals and alternatives of PCI, as well as the care of patients post PCI.

Part 2. Types of coronary revascularization.

Coronary artery disease (CAD) is the leading cause of morbidity and mortality in developed countries. Patients with CAD may have no symptoms or may present with stable angina, acute coronary syndromes or sudden cardiac death. There are 3 major treatment strategies for CAD patients: lifestyle modification, medical therapy, and coronary revascularization. Lifestyle modification and medical therapy is administered to all patients with CAD, but there is currently controversy about when and how coronary revascularization is needed.

Coronary revascularization can be achieved with surgery (coronary artery bypass grafting – CABG) or with PCI. Some patients may undergo "hybrid" revascularization with both CABG and PCI, although there is limited data supporting this approach.

CABG is achieved by inserting autologous grafts into the coronary artery segment distal to the occlusion. The internal mammary artery is used in most cases, as it has excellent long-term patency and its use has been associated with improved survival during long-term follow-up. Saphenous vein grafts have high failure rates with approximately 50% occluding by 10 years post CABG.

PCI is performed by inflating a balloon within the coronary lesion to open up the blockage, usually followed by implantation of a coronary stent. Coronary stents are metallic scaffolds that prevent vessel recoil and reduce the risk for restenosis. Stents are currently used in >90% of patients undergoing PCI,[1] as they significantly improve procedural success and subsequent clinical outcomes.[2] Two types of coronary stents are currently available in the United States: bare metal (BMS) and drug-eluting (DES). DES elute an antiproliferative drug and are commonly classified into first generation (sirolimus-eluting and paclitaxel-eluting) and second generation (everolimus-eluting and zotarolimus-eluting). First generation DES have stainless-steel platforms, whereas second generation DES have cobalt–chromium or platinum–chromium platforms with thinner strut thickness and more biocompatible, durable polymer coatings.

Part 3. Indications for revascularization

The goals of any treatment strategy is to (a) prolong life or (b) improve the quality of life (or both). In patients with acute coronary syndromes, coronary revascularization achieves both goals. In contrast, in patients with stable coronary artery disease the benefits of coronary revascularization have been more controversial. Coronary revascularization may prolong survival in patients with severe CAD, including those with

left main coronary artery disease, however, in patients with less extensive CAD no survival benefit has been observed. However, revascularization (by either PCI or CABG) significantly improves symptoms and therefore quality of life compared to medical therapy.

Two key studies have examined whether PCI improves outcomes compared to medical therapy: the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE)[3] and the Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME-2)[4] trial. The COURAGE trial did not show any difference in survival with PCI compared to medical therapy, although quality of life was better with PCI. A major criticism of the COURAGE trial was that it enrolled very few of the screened patients (selection bias), and included several patients with mild/moderate ischemia, who were not necessarily symptomatic. Moreover, 1/3 of patients in the medical therapy arm opted to cross over to PCI, demonstrating that even if mortality was not improved, patients opted for the therapy to improve symptoms.

The FAME trial demonstrated that PCI guiding by fractional flow reserve (FFR) measurement had superior outcomes compared to standard, angiography-driven PCI.[5] FFR is an invasive method for determining whether a coronary stenosis causes ischemia. In the FAME 2 trial FFR-guided PCI improved symptoms and reduced the need of urgent re-admission for coronary angiography compared to optimal medical therapy alone.[4]

These studies along with reports of inappropriate PCI cases by some physicians and increasing healthcare costs have stirred extensive controversy of the appropriateness of PCI and on whether PCI overutilization exists. An analysis from the National Cardiovascular Data Registry (NCDR) suggested that PCIs were “inappropriate” in 1.1% of patients with ACS vs. 11.6% of patients with stable CAD.[6] Since 2009 appropriateness criteria for PCI have been published and are increasingly being utilized for assessing the outcomes of PCI programs in the US. These criteria were based on consensus from a panel with 14-16 members who voted on several clinical scenarios.[7] For patients without symptoms and single vessel CAD there are 18 clinical scenarios (Figure 1); PCI is appropriate in 3, uncertain in 9, and inappropriate in 6 scenarios).

Asymptomatic					
Stress Test Med. Rx					
High Risk Max Rx	U	A	A	A	A
High Risk No/min Rx	U	U	A	A	A
Int. Risk Max Rx	U	U	U	U	A
Int. Risk No/min Rx	I	I	U	U	A
Low Risk Max Rx	I	I	U	U	U
Low Risk No/min Rx	I	I	U	U	U
Coronary Anatomy	CTO of 1-vz.; no other disease	1-2-vz. disease; no prox. LAD	1-vz. disease of prox. LAD	2-vz. disease with prox. LAD	3-vz. disease; no left main

Figure 1. Appropriateness criteria for coronary revascularization among asymptomatic patients with single vessel coronary artery disease.[7]

Part 4. PCI vs. CABG

Selecting the optimal coronary revascularization strategy (PCI vs. CABG) remains the focus of intense study, however two recent studies have provided important information that can assist with revascularization strategy selection.

The Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) trial, randomized 1800 patients with previously untreated three-vessel or left main coronary artery disease to PCI using paclitaxel-eluting stents or CABG.[8] The trial developed a summary metric of the angiographic severity of coronary artery disease, called the SYNTAX score. During 5 years of follow-up patients with three-vessel disease and low Syntax score as well as patients with left main disease and low or intermediate Syntax score had similar similar outcomes with PCI and CABG. In contrast, patients with high SYNTAX score or 3-vessel disease and intermediate Syntax score had better outcomes with CABG.

The Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial randomized 1900 patients with diabetes mellitus to PCI with first generation drug-eluting stents or CABG.[9] During a median follow-up of 3.8 years patients undergoing CABG had lower incidence of myocardial infarction and all-cause mortality but higher incidence of stroke.[9]

Because of the constant evolution of both PCI and CABG comparisons of the modalities are always limited, however, based on the SYNTAX and FREEDOM trial CABG is usually recommended for patients with complex coronary artery disease and patients with diabetes mellitus and multivessel coronary artery disease, whereas PCI is recommended for patients with less extensive coronary artery disease.

Part 5. Life after stents

The main complications after stent implantation are in-stent restenosis and stent thrombosis. Stent thrombosis usually presents as ST-segment elevation acute myocardial infarction (MI) and is associated with high mortality. Compared to BMS, DES decrease the risk of restenosis, but may be associated with slightly increased risk of very late stent thrombosis (0.6% per year for first generation DES), due to delayed vessel healing.[10]

The goal of medical treatment after coronary stenting is (a) to prevent stent thrombosis and (b) to slow the progression of coronary artery disease and prevent major adverse cardiac events. The risk for stent thrombosis is highest within the first 30 days after stenting, but continues at a lower rate for at least 3 years in patients receiving DES. Several clinical factors are associated with increased stent thrombosis risk, such as presentation with an acute coronary syndrome (ACS), depressed left ventricular ejection fraction, diabetes, renal failure, treatment of bifurcation lesions, and stent type.[10] Dual antiplatelet therapy (DAPT) is currently recommended in all patients receiving coronary stents to reduce the risk of stent thrombosis.

5.1. Antiplatelet therapy after stent implantation

DAPT with aspirin and an oral $P2Y_{12}$ adenosine-diphosphate (ADP) receptor inhibitor is the standard treatment after coronary stenting. Compared to warfarin, DAPT reduces cardiac events (such as stent thrombosis, MI, and cardiac death), major bleeding and vascular access complications after coronary stenting. However, approximately 1 in 7 patients may discontinue ADP $P2Y_{12}$ inhibitor within 30 days post PCI, which is associated with higher mortality over the ensuing 11 months, emphasizing the importance of careful patient selection and counseling after coronary stent implantation (especially DES).[11]

5.1.1 Aspirin dose

Aspirin should be administered indefinitely post PCI. Due to similar efficacy and higher bleeding risk with higher doses, low dose aspirin (usually 81mg daily) is preferred and carries a class IIA recommendation after PCI. The Clopidogrel and Aspirin Optimal Dose Usage to Reduce Recurrent Events-Seventh Organization to Assess Strategies in Ischemic Syndromes (CURRENT-OASIS 7) trial prospectively compared low dose (75-100mg daily) vs. high dose (300-325mg daily) aspirin in patients with ACS and found similar 30 day incidence of cardiovascular death, MI, or stroke with both aspirin doses.[12]

5.1.2 Types, mechanisms of action, and clinical efficacy of $P2Y_{12}$ receptor inhibitors

The $P2Y_{12}$ receptor is the main platelet receptor responsible for ADP-induced platelet aggregation. Four $P2Y_{12}$ inhibitors are currently available for clinical use in the US: ticlopidine, clopidogrel, prasugrel and ticagrelor (**Table 1**).[10]

Ticlopidine, clopidogrel, and prasugrel are thienopyridine prodrugs that require conversion to an active metabolite that irreversibly binds to the $P2Y_{12}$ receptor. Conversion of clopidogrel to its active metabolite requires at least two cytochrome (CYP) dependent steps and mutations of enzymes involved in this pathway (especially CYP2C19 and CYP3A4) are largely responsible for significant interindividual variability in clopidogrel responsiveness. In contrast, prasugrel is more rapidly and reliably converted to its active metabolite with little interindividual variability resulting in a faster and more potent inhibition of platelet activity compared to clopidogrel. Ticagrelor belongs to a new family of antiplatelet agents, cyclopentyl-triazolo-pyrimidines, which directly and reversibly binds to the $P2Y_{12}$ receptor, also resulting in more rapid and potent inhibition of platelet activity compared to clopidogrel. A few key trials have examined the efficacy of clopidogrel along with the new $P2Y_{12}$ receptor inhibitors, prasugrel and ticagrelor.

Table 1. $P2Y_{12}$ inhibitors currently in clinical use after percutaneous coronary intervention.

	Ticlopidine	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Thienopyridine	Cyclopentyl-triazolo-pyrimidine
Pharmacology	Highly CYP dependent conversion to prodrug	Highly CYP dependent conversion to prodrug	Requires conversion to prodrug (less CYP dependent)	Directly acting inhibitor
Potency of Platelet Inhibition	**+**	**+**	**++**	**++**
Time to Peak Platelet Inhibition[13]	**3-4 days**	**4-5 hours (300mg) 2-3 hours (600mg)**	**2-4 hours**	**2-4 hours**
Dosing	**Twice daily**	**Once daily**	**Once daily**	**Twice daily**
Time required for antiplatelet effect to dissipate	**5 days**	**5 days**	**7 days**	**5 days**
Cost for 1 month	~$45.00[a]	$14.50 (generic)[a] $218.87 (Plavix)[b]	$218.52[b]	$260.78[b]

[a] Estimate from Costco Pharmacy, 1701 Dallas Parkway, Plano, TX 75039-4520
[b] Medical Letter 53(1372) Sep. 5, 2011

Ticlopidine

Ticlopidine is currently used very infrequently due to increased risk of hematological complications (neutropenia and thrombotic thrombocytopenic purpura), allergic exanthema, and diarrhea compared to clopidogrel.

Clopidogrel

While early studies demonstrated a benefit for short-term (2 to 4 weeks) thienopyridine in addition to aspirin after stenting primarily to prevent stent thrombosis, two key trials suggested that longer duration of clopidogrel after PCI may be beneficial (**Table 2**).

Among the 2,658 ACS patients in the CURE trial who underwent PCI with BMS, continuing clopidogrel after the first 4 weeks post PCI for a mean of 8 months was associated with 31% reduction (from 12.6% to 8.8%, relative risk 0.69, 95% CI 0.54 to 0.87, p=0.002) in the incidence of cardiovascular death, MI, or revascularization without

an increase in major bleeding.[14] The Clopidogrel for the Reduction of Events During Observation (CREDO) trial evaluated prolonged clopidogrel administration after PCI in a lower risk population with approximately 1/3 undergoing PCI for non-ACS indications.[15] In CREDO, compared to clopidogrel for 28 days after PCI, continuing clopidogrel for 1 year resulted in a 26.9% relative reduction in the 12-month incidence of death, MI, and stroke.[15] However only patients who received clopidogrel pre-treatment were included in the long-term clopidogrel arm, making it impossible to separate the benefit of clopidogrel loading from that of prolonged clopidogrel administration.

The PCI-CURE and CREDO trials did not examine the optimal clopidogrel dose. The CURRENT-OASIS 7 trial randomized 25,086 ACS patients to high dose (600 mg loading followed by 150 mg daily for 6 days, followed by 75 mg daily thereafter) vs. low dose (300 mg loading followed by 75 mg daily) clopidogrel.[12] The 30-day incidence of the primary ischemic endpoint (cardiovascular death, MI, or stroke) was similar in both groups, whereas major bleeding was higher in the high dose clopidogrel group.[12] In the subgroup of 17,263 patients undergoing PCI, high-dose clopidogrel was associated with a 15% reduction in the incidence of the primary ischemic endpoint, however this analysis did not meet the prespecified threshold of significance for a test of interaction.[12] As a result, after the initial loading dose most patients currently receive 75 mg of clopidogrel daily.

Prasugrel

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 study randomized 13,608 patients with moderate to high risk ACS (scheduled to undergo PCI to prasugrel or clopidogrel before or up to 1 hour after PCI.[16] During a median follow-up of 14.5 months, compared to clopidogrel (with a loading dose of 300 mg) prasugrel reduced the incidence of cardiovascular death, MI, or stroke (9.9% vs. 12.1%, $P<0.001$) and stent thrombosis[17] but also increased the risk for TIMI major and fatal bleeding.[16] Patients with ST-segment elevation MI and diabetes had greater reduction in the primary ischemic endpoint without an increase with non-CABG related TIMI major bleeding. Prasugrel was associated with harm among patients with prior transient ischemic attack or stroke [hazard ratio 1.54 (95% CI: 1.02 to 2.32) for the composite of death, nonfatal MI, nonfatal stroke, or non–CABG-related nonfatal TIMI major bleeding] and provided no benefit among patients ≥75 years-old or <60 kg body weight.[16]

Table 2. Pivotal $P2Y_{12}$ inhibitor trials post coronary stent implantation[10]

	PCI-CURE[14]	**CREDO[15]**	**TRITON-TIMI 38[16]**	**PLATO[18]**
N	2,658	2,116	13,608	18,624
Population	Non-ST segment elevation ACS patients	ACS (excluding STEMI) and stable angina patients	Moderate to high-risk ACS patients with planned PCI	ACS patients treated with early invasive or conservative approach
Follow-up (months)	8	12	14.5	12
Therapy	Clopidogrel vs. Placebo	Clopidogrel vs. Placebo	Prasugrel vs. Clopidogrel	Ticagrelor vs. Clopidogrel
Ischemic Endpoint	CV death, MI	Death, MI, stroke	CV death, MI, stroke	Vascular death, MI, stroke
Event Rate (%)	4.5 vs. 6.4	8.5 vs. 11.5	9.9 vs. 12.1	9.8 vs. 11.7
HR	RR 0.70 (95% CI 0.50 to 0.97) P=0.03	RRR 26.9% (95% CI 3.9 to 44.4%) P=0.02	0.81 (95% CI 0.73 to 0.90) P<0.001	0.84 (95% CI 0.77 to 0.92) P<0.001
NNT	53	33	45	53
Bleeding Endpoint	Disabling bleeding, intraocular bleeding, bleeding requiring ≥2 units of blood	TIMI Major	Non-CABG related TIMI Major	Non-CABG related TIMI Major
Event Rate (%)	2.7 vs. 2.5	8.8 vs. 6.7	2.4 vs. 1.8	2.8 vs. 2.2
HR	RR 1.12 (95% CI 0.70 to 1.78) P=0.64	NR P=0.07	1.32 (95% CI, 1.03 to 1.68) P=0.03	1.19 (95% CI 1.02 to 1.38) P=0.03
NNH	-	-	167	167

PCI-CURE, PCI Clopidogrel in Unstable angina to prevent Recurrent Events
CREDO, Clopidogrel for the Reduction of Events During Observation
TRITON-TIMI 38, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38
PLATO, Study of Platelet Inhibition and Patient Outcomes

HR, hazard ratio; CI, confidence intervals; RRR, relative risk reduction; RR, relative risk; NR, not reported; ACS, acute coronary syndrome; STEMI, ST-segment elevation acute myocardial infarction; CV, cardiovascular; MI, myocardial infarction; TIMI, thrombolysis in myocardial infarction; CABG, coronary artery bypass graft surgery; NNT, number needed to treat; NNH, number needed to harm

Ticagrelor

The Study of Platelet Inhibition and Patient Outcomes (PLATO) trial randomized 18,624 patients with ACS to ticagrelor or clopidogrel and followed them for a median duration of 277 days.[18] PCI was performed in 61% of patients. Ticagrelor reduced the 12-month incidence of vascular death, MI or stroke compared to clopidogrel (9.8% versus 11.7%; p<0.001) as well as all-cause mortality (4.5% vs. 5.9%, P<0.001)[18] and stent thrombosis.[19] Patients with decreased renal function derived greater absolute (4.7% vs. 1.0%) and relative (23% vs. 10%) risk reduction.[20] Ticagrelor was associated with a higher rate of non-CABG -related major bleeding, dyspnea (13.8% vs. 7.8%) and ventricular pauses lasting ≥3 seconds (but not requiring specific treatment). Significant geographic differences in the effect of ticagrelor were observed (no benefit in North American patients vs. benefit in the rest of the world) and were attributed to co-administration of >100 mg daily aspirin dose, which was more common in North America. Hence, patients receiving ticagrelor should receive low dose (75-100 mg daily) aspirin.

P2Y12 inhibitor selection: summary

Selection of $P2Y_{12}$ inhibitor depends on the patient's clinical presentation and comorbidities: non-ACS patients receive clopidogrel, whereas ACS patients may also be treated with ticagrelor or prasugrel, which provide superior efficacy compared to clopidogrel, but are also associated with increased risk of bleeding.

5. 1.3 Optimal Duration of $P2Y_{12}$ Inhibitor Administration

The recommended duration of DAPT administration is currently 12 months for ACS patients and for non-ACS patients receiving DES, if the patients do not have increased risk for bleeding. Non-ACS patients receiving BMS should be treated with a minimum of 1 month of DAPT, although the American PCI guidelines recommend 12 month DAPT administration to those patients as well, unless they are considered to have high bleeding risk. At present, published data do not support routine continuation of DAPT beyond 12 months, except possibly for patients at high risk of stent thrombosis.

Compared to BMS, patients receiving DES may be at increased risk for very late (>1 year post PCI) stent thrombosis, raising the question of whether prolonged DAPT beyond 1 year could be beneficial. A meta-analysis of 4 randomized-controlled trials testing a variety of DAPT durations after DES confirmed that extended DAPT did not provide clinical benefit in non-ACS patients, yet increased the risk for TIMI major bleeding (odds ratio 2.64, 95% CI 1.31 to 5.30).[21] These studies challenge the traditional paradigm of 12 months of DAPT after DES and highlight the paucity of data behind the current recommendation. Shorter or longer than 12-month DAPT duration is currently being examined in two large ongoing clinical trials. Shorter duration of DAPT may be beneficial for patients receiving second generation DES who are at lower risk of stent thrombosis compared to other DES.

5.1.4. Special scenarios

Non-cardiac surgery after stent implantation

Approximately 4-7% of patients who receive coronary stents require non-cardiac surgery each year after stent implantation.[10] Non-cardiac surgery post stenting may lead to perioperative stent thrombosis, due to a combination of surgery-induced prothrombotic state and antiplatelet therapy discontinuation. This risk is highest early after stenting for up to 6 weeks after BMS and at least up to 6 months after DES implantation. If possible, non-cardiac surgery after DES should be postponed until after a 6 month course of DAPT with aspirin and clopidogrel is completed (Figure 2). If, however, surgery needs to be performed earlier, continuation of dual (or at least single) oral antiplatelet therapy may help minimize the stent thrombosis risk.[10] In patients who require surgery early after stenting and in whom all antiplatelet therapy needs to be discontinued (for example in patients undergoing intracranial or spine surgery) preoperative administration of a short-acting intravenous agent (such as glycoprotein IIb/IIIa inhibitor, heparin, or cangrelor) has been proposed, however the efficacy and safety of such a treatment has been poorly studied. Moreover, the highest risk period for stent thrombosis is immediately after surgery, not before.[22] Given these risks, noncardiac surgery should be performed at centers with primary PCI capacity to enable rapid treatment if stent thrombosis occurs. In addition, communication and collaboration between the surgeon, cardiologist and anesthesiologist are important to help optimize the management of such patients.

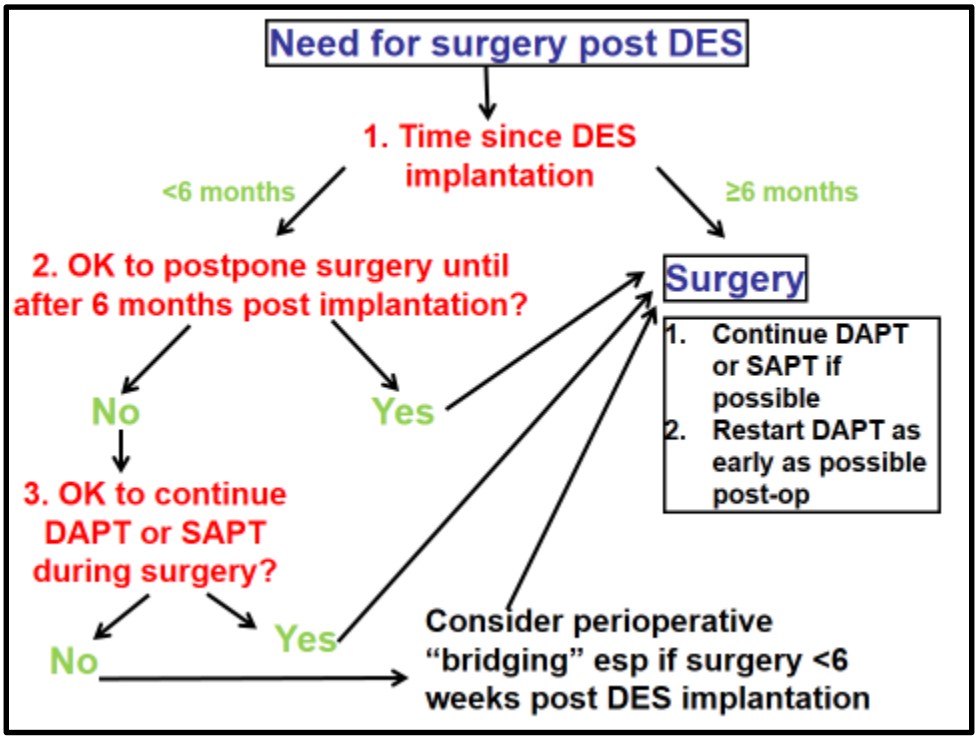

Figure 2. Algorithm for approaching patients who need noncardiac surgery after DES implantation.

Patients who need oral anticoagulation

Patients requiring oral anticoagulation (for example for atrial fibrillation or mechanical heart valve) who undergo coronary stenting present a challenging clinical

dilemma. As discussed earlier, DAPT therapy significantly reduces cardiac events after coronary stenting compared to oral anticoagulation.[10] However, coadministration of DAPT and oral anticoagulation ("triple therapy") is associated with high bleeding risk.[10]

An alternative strategy was tested in the What is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting (WOEST) trial that randomized 573 patients to dual therapy with oral anticoagulation and clopidogrel (75 mg daily) or to triple therapy with oral anticoagulation, clopidogrel, and aspirin 80 mg daily.[23] Treatment was continued for one month after BMS (35% of patients) and one year after DES (65% of patients). At one year follow-up, bleeding was significantly reduced in the dual therapy group without an increase in MI, target vessel revascularization, stroke, or stent thrombosis.[23] There was also a statistically significant reduction in mortality in the dual therapy group compared to triple therapy. Based on the WOEST trial omitting aspirin may be an attractive option in patients requiring oral anticoagulation, although more clinical trials are needed to confirm those findings.

Use of genetic and functional platelet testing to determine the intensity of antiplatelet therapy

Genetic polymoprhims such as the CYP2C19 loss of function allele result in decreased response to clopidogrel, and have been associated with increased risk of cardiovascular events in some but not all studies. Given the significant interindividual variability in the degree of platelet inhibition achieved with clopidogrel, tailoring of antiplatelet therapy based on functional platelet activity is theoretically an appealing strategy. In 2010 the FDA issued a Black Box warning for clopidogrel suggesting that CYP2C19 genetic testing may identify individuals who are poor metabolizers of clopidogrel, which can be used to adjust the dosing of clopidogrel or consider alternative antiplatelet agents. However, tailoring antiplatelet therapy based on platelet function testing did not improve clinical outcomes in two large clinical trials (Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety – GRAVITAS and Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting - ARCTIC).[24,25]

DAPT and proton pump inhibitors

Although omeprazole, a proton pump inhibitor may decrease the effectiveness of clopidogrel in pharmacodynamic observational studies, the COGENT (Clopidogrel and the Optimization of Gastrointestinal Events) trial found no difference in the incidence of cardiovascular events between patients on clopidogrel receiving omeprazole or placebo, in spite of a significant reduction in gastrointestinal bleeding with omeprazole.[26] Use of proton pump inhibitors other than omeprazole may be preferred in patients who receive clopidogrel after PCI, as there is no clear evidence that other proton pump inhibitors interfere with metabolism of clopidogrel.

5.2. Other therapies

Patients who receive coronary stents are at increased risk for recurrent cardiovascular events, emphasizing the need for secondary prevention measures, such as treating diabetes, dyslipidemia and hypertension through lifestyle modification,

medications and complete smoking cessation. There are several medications of proven benefit to patients with cardiovascular disease, such as statins, beta-blockers, and angiotensin converting enzyme inhibitors. Finally, participation in a cardiac rehabilitation program can be highly beneficial.

Conclusions

Percutaneous coronary interventions have revolutionized the treatment of coronary artery disease and can provide significant clinical benefits. Coronary stents are used in nearly all PCIs and second generation drug-eluting stents are currently the standard of care. Dual antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor significantly improves the outcomes of patients undergoing coronary stenting. Aspirin should be administered indefinitely, whereas the $P2Y_{12}$ inhibitor is usually administered for 12 months after stenting. Several ongoing studies will allow further optimization of the medical management of patients who receive coronary stents.

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