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Pharmacotherapy During Percutaneous Coronary Interventions

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1. Introduction

Percutaneous arterial catheterization and transluminal dilatation of stenotic vessels were first described by Charles T. Dotter and Melvin P. Judkins in their seminal paper published in 1964 (1). With the advent of contemporary coronary angioplasty and stenting techniques for patients with coronary artery disease (CAD) and acute coronary syndromes (ACS), the procedure has now been termed percutaneous coronary intervention (PCI). While PCI has done much in the modern era to improve patient outcomes in the face of acute myocardial infarction as well as in disabling cardiac angina, its benefits can still be limited by peri-procedural complications such as acute vessel closure and stent thrombosis as well as conditions occurring after 30 days post-PCI, such as in-stent restenosis or late stent thrombosis. Additionally, catheter and wire associated thrombus formation can occur during PCI in the absence of adequate anticoagulation. Excess anticoagulation on the other hand carries a risk of major gastrointestinal or intracranial bleeding as well as vascular access bleeding complications. Stent thrombosis is a rare, but serious complication of PCI and usually presents as death or ST-elevation myocardial infarction. Coronary stents are generally made of stainless steel or cobalt chromium alloys rendering them thrombogenic until they are completely covered by endothelial tissue. The timing of complete endothelialization is variable and depends on whether the implanted stent is bare metal or drug-eluting, as well as which type of anti-proliferative drug the stent is coated with. Stent thrombosis can be described based on its timing relative to stent placement and is associated with a number of different risk factors (Table 1). Acute stent thrombosis occurs within 24 hours of PCI and in one pooled analysis, approximately 80 percent of all bare metal stent (BMS) thromboses occurred within this acute period (2). Subacute stent thrombosis occurs up to 30 days after PCI and this time period encompasses the majority of all thrombotic events observed in both BMS and drug-eluting stents (DES) (3). Stent thrombosis after 30 days and up to one year post-PCI is referred to as late stent thrombosis and seems to occur with equal frequency in BMS and DES, particularly in the absence or cessation of dual anti-platelet therapy with aspirin or clopidogrel (4-5). Occurring even less commonly at greater than one year post-PCI, very late stent thrombosis appears to be associated with DES more than BMS and is thought to be related to delayed neo-intimal coverage as well as ongoing vessel inflammation (6). Current ACC/AHA guidelines make a number of recommendations regarding the concurrent use of antiplatelet, antithrombotic, and

thrombolytic pharmacotherapy during PCI to prevent such complications. The goal of this chapter will be to describe different therapeutic agents available to clinicians during PCI and to summarize the most current guidelines regarding their use.

2. Anti-platelet agents

2.1 Aspirin

Aspirin causes an irreversible inactivation of the cyclooxygenase-1 enzyme required for prostaglandin and thromboxane synthesis, which in turn diminishes platelet aggregation. The use of aspirin for secondary prevention has been shown to decrease overall mortality in patients with established CAD or a CAD equivalent such as diabetes (7-10). Meanwhile, the net benefit for its use in primary prevention is less certain and needs to be weighed against individual risk for major gastrointestinal or extra-cranial bleeding (11). Extensive studies have also shown significant reductions in mortality and morbidity with the use of aspirin in unstable angina (UA) as well as in both non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). In one of the earliest trials from the Results of a Veterans Administration Cooperative Study, Lewis et al. reported a 51% reduction in incidence of death or acute MI as well as a 50% reduction in rates of nonfatal MI in patients with UA who received aspirin (12). These findings were reproduced in subsequent studies and helped to solidify the role for the use of aspirin in UA (13-14). The RISC trial evaluated the role of aspirin in both NSTEMI and UA patients and again demonstrated that aspirin was associated with a significant reduction in the combined endpoint of death and MI with differences persisting beyond one-year providing evidence for the long-term benefit of aspirin in NSTE-ACS (15). The landmark trial ISIS-2 then expanded the role of aspirin use to standard therapy in STEMI (16). ISIS-2 randomized 17,187 patients presenting with acute STEMI to streptokinase, aspirin, both therapies, or neither, and demonstrated an additive effect of aspirin to thrombolytic therapy. Currently, the ACC/AHA guidelines for the management of UA, NSTEMI and STEMI recommend immediate treatment with aspirin for all patients for indefinite duration (17). The recommendations for the use of aspirin in PCI with stenting are derived from several early clinical trials in which treatment with high dose aspirin (650 mg to 990 mg/day) along with dipyridamole or ticlopidine in percutaneous transluminal coronary angioplasty (PTCA) was compared to placebo. Patients who were treated with aspirin-based regimens uniformly had better outcomes with significant reductions in peri-procedural complications including abrupt vessel closure, dissection or MI (18-19). Pre-treatment with aspirin monotherapy was tested against aspirin plus dipyridamole and shown to have an independent beneficial effect (20). Subsequent studies comparing high-dose versus low-dose aspirin (1500 mg vs. 80 mg/day) prior to PTCA showed no difference in the incidence of MI or in the rate of major complications and restenosis (21). The most current ACC/AHA recommendations for the use of aspirin in PCI are that higher dose aspirin (300 mg to 325 mg) be given at least 2 hours before PCI as well as for at least 1 month after BMS implantation, 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation (17).

2.2 Ticlopidine

Thienopyridines block the adenosine diphosphate (ADP) receptor P2Y12 on platelet surfaces thereby decreasing platelet activation and aggregation (see section on platelet function

testing below). Ticlopidine was the first widely used thienopyridine that began to have an antiplatelet effect within 24 to 48 hours after its administration. The STAIG trial was one of the first multicenter trials to evaluate the role of thienopyridines, particularly ticlopidine, in ACS (22). 652 patients with UA were randomized within 48 hours of presentation to conventional medical therapy alone versus ticlopidine in addition to conventional treatment. Ticlopidine use was associated with a reduction in vascular mortality by 46.8% (4.8% vs. 8.9%) and MI by 53.2% (5.1% vs. 10.9%). Further randomized trials such as STARS, MATTIS, ISAR, and FANTASTIC compared antiplatelet therapy with ticlopidine and aspirin to conventional anticoagulant therapy with heparin or warfarin in PCI with bare metal stenting and demonstrated a clear reduction in stent thrombosis, death, MI, or emergent CABG (23-26). Ticlopidine use, however, has been associated with significant side effects including thrombocytopenia, neutropenia and thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS); thus it is crucial that biweekly monitoring of blood counts be performed for four months after initiation of ticlopidine (27-28).

2.3 Clopidogrel

Due to the unfavorable side effect profile of ticlopidine, interest began to develop in clopidogrel as a potential thienopyridine alternative. The efficacy of clopidogrel in the treatment of CAD had already been demonstrated in the CAPRIE trial in which clopidogrel use significantly reduced the combined endpoint of ischemic stroke, MI and vascular death in patients with atherosclerotic disease (29). Clopidogrel's overall safety benefit as compared to ticlopidine was then convincingly demonstrated in the CLASSICS trial and a meta-analysis later found that clopidogrel use was at least as efficacious as ticlopidine with fewer major adverse cardiac events (MACE) as well as a lower incidence of mortality (30-31). Based on these findings, clopidogrel replaced ticlopidine as the thienopyridine of choice in combination with aspirin as standard therapy after PCI. Several landmark trials then fully expanded the application of clopidogrel therapy to ACS and PCI. Investigators in the CURE trial found a 20% reduction in the primary combined endpoint of cardiovascular death, MI, or stroke (9.3% vs. 11.4%) in 12,562 patients with NSTE-ACS when treated with combined aspirin and clopidogrel as compared to aspirin alone (32). When the subset of patients undergoing PCI was analyzed separately in the PCI-CURE substudy, pre-treatment with clopidogrel plus aspirin prior to PCI led to both immediate and long-term benefits in reducing ischemic vascular events and death (33-34). The CREDO trial later confirmed the benefit of upstream clopidogrel therapy in more than 2,100 patients who were randomized to receive either clopidogrel at a 300 mg loading dose or placebo 3 to 24 hours before elective PCI, followed by 75 mg/day for 28 days in both groups and then either clopidogrel or placebo out to one year according to the original randomization (35). The results from CREDO also proved the benefits of long-term clopidogrel therapy by finding a 26.9% relative risk reduction in the combined end point of death, MI, or stroke at one year (8.5% vs. 11.5%, 95% CI 3.9-44.4). Two additional randomized trials, CLARITY-TIMI 28 and COMMIT/CCS-2, then demonstrated that clopidogrel therapy when added to aspirin also improved outcomes in patients with STEMI being treated with fibrinolytics and heparin (36-37).

With the role of clopidogrel now clearly defined in all forms of ACS as well as PCI, the timing and dose of clopidogrel pre-treatment for PCI came under question. In a pre-

specified sub-group analysis, the PCI-CLARITY trial found that early treatment with clopidogrel (300 mg) led to significantly better outcomes in all time groups ranging from within 6 hours before PCI to as far as 96 hours ahead of PCI (38). A substudy from CREDO, however, found that the benefit was only seen if clopidogrel (300 mg) was given 10 to 12 hours before PCI and did not become significant unless given >15 hours prior to PCI, with a maximum effect seen at 24 hours (39).

Since pre-treatment with clopidogrel for >15 hours prior to PCI is not always practical in situations of ACS or ad hoc decisions to stent at the time of diagnostic angiography, the issue was raised as to whether higher loading doses of clopidogrel could be beneficial by increasing the level of platelet inhibition or by decreasing the time required until its maximum antiplatelet effects were achieved. In an unselected cohort of over 1,000 patients, who were given a 600 mg dose of clopidogrel, in vitro studies found that maximum platelet inhibition was seen by two hours and additional testing showed that clopidogrel 600 mg dosing seemed to achieve more intense levels of peak platelet inhibition when compared with the conventional 300 mg dose (40-41). Several large studies then sought to evaluate whether these pharmacodynamic differences could translate into improved patient outcomes. The ARMYDA-2 trial randomized 255 patients with stable angina or NSTE-ACS to either 600 mg or 300 mg of clopidogrel given four to eight hours prior to PCI (42). By 30 days, the composite endpoint of death, MI, or target vessel revascularization (TVR) occurred in only 4% of the 600 mg group as compared to 12% in the 300-mg group, a difference that was entirely driven by rates of peri-procedural MI ($p < 0.05$). No differences were reported in the rates of major bleeding between the two groups. The benefit of a clopidogrel 600 mg loading dose was seen again in a subgroup analysis from the HORIZONS-AMI trial in which 3,602 patients with STEMI undergoing primary PCI were randomized to either bivalirudin or unfractionated heparin (UFH) plus a glycoprotein (GP) IIb/IIIa inhibitor (43). Clopidogrel loading doses of either 300 mg (1,153 patients) or 600 mg (2,158 patients) were chosen at the clinician's discretion and after multivariable analysis, the 600 mg dose was found to be an independent predictor of lower rates of 30-day MACE without higher bleeding. The CURRENT-OASIS 7 trial then randomized over 25,000 patients with ACS (29.2% STEMI) who were referred for an invasive strategy and compared the regimen of double dose clopidogrel (600 mg loading dose followed by 150 mg daily for six days and then 75 mg daily thereafter) versus standard dose clopidogrel (300 mg loading dose followed by 75 mg daily) (44). The investigators found that while there was no significant difference in the primary outcome of cardiovascular death, MI or stroke at 30 days (4.2% in the double dose group vs. 4.4% in the standard dose group; HR 0.94; 95% CI 0.83-1.06; $p = 0.30$), double dose clopidogrel was associated with a significant reduction in the secondary outcome of stent thrombosis in the greater than 17,000 patients who underwent PCI (1.6% vs. 2.3%; HR 0.68; 95% CI 0.55-0.85; $p=0.001$). Notably, major bleeding occurred significantly more in the double dose group (2.5% vs. 2.0%; HR 1.24; 95% CI 1.05-1.46; $p=0.01$). Several subsequent smaller studies including ISAR-CHOICE, ALBION, and PREPAIR have attempted to look at whether even higher loading doses of clopidogrel (900 mg and 1200 mg) might carry additional benefit when compared to the 600 mg and 300 mg doses (45-47). These studies found that while treatment with increasing doses of clopidogrel did in fact result in greater levels of platelet inhibition, clinical endpoints such as MACE and troponin release were not statistically different. At this point, larger prospective trials evaluating clinical outcomes are needed before clopidogrel loading doses above 600 mg can be justified.

With regards to timing of double-dose clopidogrel pre-treatment, the ISAR-REACT trial showed that among 2,159 patients undergoing PCI, a clopidogrel 600 mg loading dose could be given as early as as 2 hours prior to PCI without detrimental effects when compared to longer durations of pre-treatment (2 to 3 hours, 3 to 6 hours, 6 to 12 hours, > 12 hours) (48). Similarly, the PRAGUE-8 and ARMYDA-5 PRELOAD trials reported no differences in outcomes when clopidogrel 600 mg was given to patients with stable angina or NSTE-ACS either before (mean of 19 and 6 hours respectively) or immediately after diagnostic coronary angiography, but prior to PCI (49-50).

The RELOAD and ARMYDA-4 RELOAD trials attempted to address the question of whether an additional loading dose of clopidogrel was required prior to PCI in stable and ACS patients who were already receiving chronic clopidogrel therapy (51-52). The trials found that although clopidogrel reloading produced significantly greater levels of platelet inhibition, there was no difference in the primary endpoint of MACE. A subgroup analysis, however, showed that when reloaded with clopidogrel 600 mg, there was a significant benefit in patients with ACS who underwent PCI. While there is not enough evidence to make definitive recommendations regarding this issue, it may be reasonable to reload patients receiving chronic clopidogrel therapy with clopidogrel 600 mg prior to PCI for ACS or if their risk for stent thrombosis is high.

2.4 Prasugrel

Despite the increasing use of higher doses of clopidogrel, there are still many cases of breakthrough thrombotic events in patients receiving standard dual antiplatelet therapy (32). Limitations of clopidogrel therapy are thought to be due to its delayed onset of action, modest platelet inhibition effects, and a wide range of inter-individual variability with regards to platelet responsiveness. Prasugrel is a third-generation thienopyridine and like clopidogrel, also requires biotransformation to its active metabolite before binding to P2Y12 receptors and inhibiting platelet aggregation. In contrast to clopidogrel however, prasugrel has been shown to achieve greater levels of platelet inhibition more rapidly and more consistently among healthy individuals as well as in patients with CAD and those who are undergoing PCI (53-55). The JUMBO-TIMI 26 trial was a phase 2 randomized study of 904 patients designed to assess the safety of prasugrel when administered at the time of PCI and the results of this trial showed no difference in the rates of clinically significant bleeding events (56). In PRINCIPLE-TIMI 44, 201 subjects were randomized to either prasugrel 60 mg or clopidogrel 600 mg as a loading dose one half hour prior to elective PCI, and then to either prasugrel 10 mg or clopidogrel 150 mg as a maintenance dose (57). The prasugrel groups were found to achieve significantly greater levels of platelet inhibition in both the loading and maintenance phases. To assess prasugrel's clinical efficacy, the landmark TRITON-TIMI 38 trial enrolled 13,608 patients with moderate- to high-risk ACS (including both NSTE-ACS and STEMI) undergoing PCI and randomly assigned patients to either prasugrel (60 mg loading dose followed by 10 mg maintenance dose) or clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) (58). At 15 month follow-up, prasugrel reduced the composite endpoint of death, nonfatal MI or nonfatal stroke by 20% in comparison to clopidogrel (9.9% vs. 12.1%; HR 0.81; 95% CI 0.73-0.90; $p<0.001$) with the majority of the difference driven by lower rates of nonfatal MI (7.4% vs. 9.7%). Stent thrombosis was also significantly reduced with prasugrel (1.1% vs. 2.4%; $p<0.001$), however,

the risk for bleeding in all categories was significantly increased including major bleeding (2.4% vs. 1.8%; p=0.03), life-threatening bleeding (1.4% vs. 0.9%; p=0.01), and fatal hemorrhage (0.4% vs. 0.1%; p=0.002). Risk factors for bleeding included age ≥75 years, history of stroke or TIA, and body weight <60 kg. Overall mortality did not differ significantly between the treatment groups.

The 2009 ACC/AHA Joint STEMI/PCI updated guidelines recommend that in patients with ACS in whom PCI is planned, a loading dose of either clopidogrel of at least 300 to 600 mg (Class I, Level of Evidence C) or prasugrel 60 mg (provided there are no contraindications) (Class I, Level of Evidence B) be given as soon as possible. For STEMI patients who have received fibrinolytic therapy, clopidogrel at a loading dose of either 300 or 600 mg should be given followed by clopidogrel as the thienopyridine of choice for maintenance therapy (Class I, Level of Evidence C). The choice and duration of maintenance therapy for ACS patients receiving a BMS or DES should be either clopidogrel 75 mg daily (Class I, Level of Evidence B) or prasugrel 10 mg daily (provided there are no contraindications) (Class I, Level of Evidence B) for at least 12 months unless the risk of morbidity due to bleeding outweighs the anticipated benefit of thienopyridine therapy, at which point earlier discontinuation should be considered (Class I, Level of Evidence C). In patients in whom coronary artery bypass grafting (CABG) is planned and can be delayed, it is recommended that clopidogrel be withdrawn for at least 5 days (Class I, Level of Evidence B) and prasugrel for at least 7 days (Class I, Level of Evidence C) unless the need for revascularization and/or the net benefit of the thienopyridine outweighs the risks of bleeding (Class I, Level of Evidence C). Age ≥ 75 years, history of TIA or stroke, and active major bleeding are contraindications to prasugrel therapy. Body weight < 60 kg is a relative contraindication to prasugrel therapy and consideration of lowering the maintenance dose from 10 mg to 5 mg daily should be given, though the safety and efficacy of the 5 mg dose have not been established (17).

2.5 Ticragrelor

Ticragrelor is an oral antiplatelet agent from the cyclopentyltriazolopyrimidine class that reversibly binds the ADP-P2Y12 platelet receptor. Like prasugrel, it is known to produce a more rapid and intense reduction in platelet function when compared to clopidogrel. In the PLATO trial, 18,624 patients with ACS (38% STEMI) were randomized to either ticragrelor (180 mg loading dose followed by 90 mg twice daily) or clopidogrel (300 to 600 mg loading dose followed by 75 mg daily) in addition to chronic aspirin therapy (59). At 12 months, ticragrelor therapy was associated with a significant reduction in the primary efficacy endpoint of cardiovascular death, MI or stroke (9.8% vs. 11.7%; HR 0.84; 95% CI 0.77-0.92; p<0.001). Importantly, the rate of death from any cause was reduced in the ticagrelor group (4.5% vs. 5.9% with clopidogrel, p<0.001). Furthermore, there were no significant differences in the rates of major bleeding, although ticagrelor was associated with a higher rate of bleeding not related to CABG. The STEMI patients in PLATO, when analyzed separately, also showed a benefit of ticagrelor over clopidogrel with trends consistent with the overall PLATO trial. In addition, ticagrelor reduced rates of MI alone, total mortality, and stent thrombosis. The reductions in stent thrombosis (ST) for ticagrelor versus clopidogrel were 1.6% vs. 2.4% (definite ST, p=0.03), 2.6% vs. 3.4% (definite or probable ST), and 3.3% vs. 4.3% (definite, probable, or possible ST). A subgroup analysis of patients with chronic kidney

disease found that ticragrelor produced a more pronounced reduction in the primary endpoint when compared to patients with normal renal function as well as an overall decrease in total mortality (60).

3. Anti-thrombotic agents

3.1 Unfractionated heparin

Unfractionated heparin (UFH) inhibits platelet aggregation and fibrin formation by accelerating the action of antithrombin, which in turn inactivates factors IIa, IXa, and Xa. The evidence for UFH therapy in UA and NSTE-ACS has been well defined in early trials such as RISC and ATACS (61-65), however, the benefits in acute STEMI are less clear. Current ACC/AHA guidelines on the management of acute STEMI recommend intravenous UFH therapy for all patients treated with a fibrin-specific fibrinolytic agent (alteplase, tenecteplase, reteplase) or a non-fibrin-specific agent (streptokinase, urokinase, anistreplase) if the risk for systemic embolization is high (large or anterior MI, atrial fibrillation, prior embolus, or known left ventricular thrombus). The goal for activated partial thromboplastin time (aPTT) should be 1.5 to 2.0 times control or between 50-70 seconds. The benefit of adjunctive UFH with fibrinolytic therapy is thought to be due to its effect on maintaining infarct vessel patency as there is limited data regarding any improvements in either mortality or reinfarction (66-69). In patients being referred for PCI, current guidelines recommend intravenous treatment with UFH (17). UFH use during PCI is believed to reduce the risk for acute vessel closure as well as catheter or wire thrombosis and has been extrapolated from data obtained from PTCA prior to the era of coronary stenting and dual anti-platelet therapy (70). The 2005 ACC/AHA/SCAI guidelines for PCI recommend that in patients not receiving a glycoprotein (GP) IIb/IIIa inhibitor, UFH should be given using a bolus of 70 to 100 IU/kg to target an activated clotting time (ACT) between 250 to 350 seconds. For patients who are receiving a GP IIb/IIIa inhibitor, heparin bolus should be lowered to 50 to 70 IU/kg to achieve an ACT of 200 to 250 seconds (71). Heparin monitoring during PCI is generally done with ACT instead of aPTT as the anticoagulation levels required during the procedure are frequently too high for aPTT to track. An alternative strategy endorsed by the 2005 European Society of Cardiology guidelines for PCI was a single bolus of 100 IU/kg without ACT monitoring (72). The routine use of UFH after uncomplicated procedures has not been shown to reduce stent thrombosis and is not recommended given its association with increased rates of bleeding and vascular access complications. UFH use can cause autoimmune heparin-induced thrombocytopenia, a rare but potentially lethal complication associated with thrombosis. Treatment includes prompt withdrawal of UFH or low molecular weight heparin (LMWH) and initiation of alternative anticoagulation therapy (argatroban, lepirudin, bivalirudin).

3.2 Low-Molecular-Weight Heparin

Low-molecular-weight heparin (LMWH), like UFH, prevents clot propagation, but possesses several advantages over UFH due to different mechanisms of action. The ratio of anti-Xa/anti-IIa activity is significantly higher in LMWH compared to UFH, thereby inhibiting thrombin generation more effectively with potentially less bleeding. Suppression of the release of von Willebrand factor also augments LMWH's anticoagulant effect.

Increased bioavailability leads to a longer duration of systemic anticoagulation and less binding to plasma proteins and produces a more consistent anticoagulant effect. Several trials including FRISC, FRIC, FRAXIS, TIMI 11-B, and ESSENCE have found that treatment with LMWH is at least as effective as UFH across a spectrum of ACS patients while maintaining a comparable safety profile (73-79). The efficacy and safety of LMWH in PCI as compared to UFH was studied in over 10,000 patients with NSTE-ACS being referred for early invasive strategy in the SYNERGY trial (80). While enoxaparin use was shown to be non-inferior to UFH, it was associated with a significantly higher rate of major bleeding (9.1% vs. 7.6%). STEEPLE, a trial designed to assess the safety of enoxaparin (a single intravenous bolus of either 0.50 or 0.75 mg/kg prior to PCI) compared to UFH in over 2,500 patients undergoing elective PCI was terminated early due to an excess mortality rate among the patients receiving lower dose enoxaparin (81). As such, the 2005 ACC/AHA/SCAI guideline update for PCI recommends UFH as first line antithrombotic therapy in patients undergoing PCI except in patients with heparin-induced thrombocytopenia (Class I, Level of Evidence C). LMWH is a reasonable alternative in patients with UA/NSTEMI (Class IIa, Level of Evidence B) and in patients with STEMI (Class IIb, Level of Evidence B) (71).

3.3 Fondaparinux

Fondaparinux, a selective inhibitor of factor Xa, was tested against UFH in 350 patients undergoing urgent or elective PCI in the ASPIRE pilot trial and was found to have similar efficacy and safety outcomes (82). This issue was further examined in the much larger OASIS-6 trial, which included over 12,000 STEMI patients split into two strata based on whether UFH was indicated or not (83). Stratum 1 in which UFH was not indicated consisted of 5,658 patients most of whom had received fibrinolytic therapy with streptokinase and in whom adequate reperfusion was achieved and PCI was not planned. Stratum 2 consisted of 6,434 patients in whom UFH was indicated (those who received a fibrin-specific fibrinolytic agent, those in whom adequate reperfusion was not achieved, or those in whom primary PCI was planned). Patients in each stratum were then randomized to receive either fondaparinux or placebo. Although there was an overall decrease in the primary endpoint of death or reinfarction with fondaparinux (9.7% vs. 11.2%), investigators found that this effect was driven mainly by a significant reduction in events in the stratum that did not receive heparin or primary PCI and that there was actually a trend towards worse outcomes with fondaparinux in the stratum of patients who received heparin and were treated with primary PCI. Fondaparinux use was also associated with a higher rate of catheter related thrombosis as well as coronary complications during PCI such as acute vessel closure, no reflow phenomenon, and dissection. Therefore, the 2007 focused update of the ACC/AHA/SCAI guidelines for PCI do not recommend fondaparinux use as the sole anticoagulant to support PCI and when used should be supplemented with another agent that has anti-IIa activity such as UFH or bivalirudin (84).

3.4 Direct thrombin inhibitors

Direct thrombin inhibitors (e.g., hirudin, bivalirudin, lepirudin) inactivate thrombin by binding directly to its catalytic site and hold several advantages over UFH in that antithrombin is not required as a cofactor allowing clot-bound thrombin to be inactivated

(85). Additionally, there is no thrombin-mediated activation of platelets. Hirudin, a naturally occurring peptide derived from the saliva of the medicinal leech has been studied in patients with ACS undergoing reperfusion therapy with fibrinolytics or PCI (TIMI-9B, GUSTO-IIB, HELVETICA) and found to have no benefit when compared to UFH with comparable rates of major bleeding (86-88). The pilot trial HERO reproduced a similar finding with bivalirudin, a synthetic peptide that directly inhibits free and clot-bound thrombin (89). When given concurrently with streptokinase, bivalirudin was more effective than UFH in producing early infarct-related artery patency (TIMI grade 3 flow) without increasing the risk of major bleeding. The follow up HERO-2 mortality trial found that bivalirudin had similar rates of mortality at 30 days (10.5% vs. 10.9% with UFH, OR 0.99) with a small reduction in reinfarction at 96 hours (1.6% vs. 2.3%) and a nonsignificant trend toward more severe bleeding (0.6% vs. 0.4%) (90). The 2004 AHA/ACC guidelines on the management of STEMI state that it is reasonable to consider bivalirudin as an alternative to UFH in patients with heparin-induced thrombocytopenia and who are treated with streptokinase.

The role of bivalirudin in primary PCI was evaluated in the HORIZONS-AMI trial in which 3,602 patients with STEMI undergoing primary PCI were randomized to receive treatment with either UFH plus a GP IIb/IIIa inhibitor or to treatment with bivalirudin alone with provisional GP IIb/IIIa inhibitor (91). The investigators found that anticoagulation with bivalirudin alone resulted in lower rates of MACE at 30 days (9.2% vs. 12.1%; RR 0.76; 95% CI 0.63-0.92; p=0.005), major bleeding (4.9% vs. 8.3%; RR 0.60; 95% CI 0.46-0.77; p<0.001), 30-day death from cardiac causes (1.8% vs. 2.9%; RR 0.62; 95% CI 0.40-0.95; p=0.03), and 30-day overall mortality (2.1% vs. 3.1%; RR 0.66; 95% CI 0.44-1.00; p=0.047). There was a concern about a significant 1% increase in acute stent thrombosis seen within 24 hours, however, the rates for stent thrombosis at 30 days were similar in both groups. Bivalirudin was further examined in the REPLACE-2, ISAR-REACT 3, and ACUITY randomized trials evaluating patients across a broad spectrum of disease (stable CAD to high-risk ACS) undergoing PCI (92-94). The results of these trials solidified bivalirudin's favorable safety and efficacy profile when compared to UFH plus a GP IIb/IIIa inhibitor by demonstrating the non-inferiority of bivalirudin in preventing ischemic complications after PCI along with a reduction in rates of major bleeding. Additionally, a meta-analysis of randomized trials revealed that bivalirudin use provided greater absolute benefits in the prevention of ischemic and bleeding complications in patients with renal insufficiency (95). In the 2009 Focused Update of the ACC/AHA guidelines for the management of patients with STEMI/PCI, bivalirudin was added as an acceptable anticoagulant for primary PCI (Class I, Level of Evidence B) as well as in STEMI patients undergoing PCI who are at high risk of bleeding (Class IIa, Level of Evidence B) (17).

3.5 Glycoprotein IIb/IIIa inhibitors

Glycoprotein (GP) IIb/IIIa is an integrin receptor expressed on the surface membrane of platelets that undergoes a conformational change following platelet activation allowing it to bind to fibrinogen and cross-link with other platelets. This forms the basis for platelet aggregation and the pathologic vascular thrombosis seen in ACS. Three GP IIb/IIIa inhibitors are currently approved for use in ACS and PCI although much of the evidence supporting their use was established in the era prior to dual oral antiplatelet therapy.

Abciximab is the Fab fragment of a human-murine monoclonal antibody directed at the GP IIb/IIIa receptor. A number of clinical trials have attempted to evaluate its use in patients undergoing PCI for stable angina or ACS. These include EPIC, EPILOG, CAPTURE, RAPPORT, ADMIRAL, ISAR-2, ISAR-REACT, ISAR-SWEET, CADILLAC, ACE, EPISTENT, and ERASER (96-107). Pooled analyses of several of these trials have found that abciximab significantly reduced the incidence of 30-day death and MI when compared to placebo (HR 0.55; 95% CI 0.43-0.69; p<0.001) (108). This benefit was found regardless of the type of coronary intervention used including balloon angioplasty, elective stenting, bail-out stenting, and directional atherectomy, without an increase in significant bleeding complications. Protection from major adverse outcomes with abciximab continued out to six months and was independent of gender and a significant mortality benefit persisted at three years (6.4% vs. 5.0%; HR 0.78; 95% CI 0.63-0.98; p=0.03) (109-110). In the BRAVE-3 study, 800 patients presenting within 24 hours of STEMI were treated with aspirin, clopidogrel 600 mg, and randomized to either abciximab or placebo given prior to primary PCI. There were no significant differences between the two groups with respect to the primary endpoint of infarct size as measured by single-photon emission computed tomography (SPECT) or in 30 day MACE (111).

Tirofiban is a non-peptide molecule that exhibits dose dependent inhibition of the GP IIb/IIIa receptor. The RESTORE trial randomized 2,139 patients with ACS undergoing PTCA with balloon angioplasty or directional atherectomy to either placebo or tirofiban (10 μg/kg/3 min intravenous bolus followed by continuous infusion of 0.15 μg/kg/min for 36 hours) (112). The composite end point (death from any cause, MI, bypass surgery for angioplasty failure or recurrent ischemia necessitating repeat PCI) was reduced by tirofiban at two days (RR 38%; p<0.005) and at seven days (RR 27%; p=0.022) post-PTCA however this reduction was no longer statistically significant at 30 days (10.3% vs. 12.2%; p=0.16) and at 6 month follow up (113). The ADVANCE trial then evaluated whether higher doses of tirofiban would confer a benefit in 202 patients with ACS undergoing primary PCI (114). Patients were randomly assigned to either placebo or tirofiban (25 μg/kg/3 min bolus plus 0.15 μg/kg/min continuous infusion for 24 to 48 hours). The results of this study showed that treatment with high dose tirofiban produced a significant reduction in the primary endpoint of death, MI, target vessel revascularization, or bailout use of a GP IIb/IIIa inhibitor (35% vs. 20%; HR 0.51; 95% CI 0.29-0.88; p=0.01). The difference was driven by a reduction in MI and bailout use of GP IIb/IIIa inhibitors with no significant effect on mortality. Bleeding rates were comparable between tirofiban and placebo. Subgroup analyses found that while patients with ACS benefited from tirofiban use, those with stable angina did not. Diabetics also appeared to gain a benefit with tirofiban while nondiabetics did not. Upstream use of tirofiban prior to PCI in patients with STEMI was evaluated in three trials: TIGER-PA, ON-TIME, and ON-TIME 2 (115-117). These trials demonstrated that tirofiban use was generally associated with improved electrocardiographic endpoints such as resolution of ST-segment elevations with no increase in the risk of major or minor bleeding. In the ON-TIME 2 trial, approximately 1,000 patients with STEMI were randomized to pre-treatment with either high dose tirofiban or placebo prior to PCI and while there was an improvement in ST-segment resolution in the tirofiban group, there was no significant difference between the two groups in angiographic variables such as Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow or blush grade. Later results from ON-TIME 2 however reported a significant reduction in 30 day MACE in the tirofiban

group (5.8% vs. 8.6%; p=0.043) that was maintained at 1-year follow up (3.7% vs. 5.8%; p=0.08) (118).

Eptifibatide is a synthetic, nonimmunogenic cyclic heptapeptide inhibitor of GP IIb/IIIa with an active pharmacophore which is derived from the structure of barbourin, a GP IIb/IIIa inhibitor isolated from the venom of the Southeastern pigmy rattlesnake (119). It has a rapid onset of action with a plasma half-life of 10-15 minutes making its antiplatelet effect rapidly reversible. Its use in ACS and PCI has been evaluated in several clinical trials. In the PURSUIT trial, 10,948 patients were randomized to eptifibatide or placebo in conjunction with UFH and aspirin (120). By four days, the combined endpoint of death and nonfatal MI were reduced by 1.5% in the eptifibatide group (14.2% vs. 15.7%; p=0.04). More remarkably, this benefit was apparent as early as 96 hours and persisted through 30 days with a greater benefit observed in patients undergoing early angioplasty (121). In the IMPACT-II trial of 4,010 patients undergoing elective, urgent or emergent PCI, treatment with eptifibatide during PCI reduced the rates of early abrupt vessel closure and ischemic events by 30 days (122). The benefits of eptifibatide have also been shown in patients undergoing elective PCI, as seen in the ESPRIT trial that randomized 2,064 patients to pre-treatment with placebo or ebtifibatide prior to PCI (123). The trial was terminated early for efficacy as pre-treatment with ebtifibatide led to a significant reduction in the primary end point of death, MI, urgent revascularization, or need for bail-out GP IIb/IIIa inhibitor at 48 hours (6.6% vs. 10.5%; p=0.0015) as well as at 30 days (6.8% vs. 10.5%; p=0.0034). With regards to safety endpoints, bleeding rates with eptifibatide were equivalent to placebo in IMPACT-II (4.8% vs. 5.1%), although severe bleeding without hemorrhagic stroke was increased in PURSUIT (11.6% vs. 9.2%) (104, 106). Additionally, a pooled analysis of eight randomized control trials showed that eptifibatide did not significantly increase the rate of thrombocytopenia compared to placebo (124).

The general benefits of intravenous GP IIb/IIIa inhibitors have been evaluated in a meta-analysis pooling data from 21 trials involving patients with a broad range of CAD (125). The study reported that GP IIb/IIIa inhibitor use produced significant reductions in the combined end point of 30-day death, MI, or urgent revascularization in patients undergoing PCI (7.8% vs. 11.6%), patients with NSTE-ACS (11.4% vs. 12.8%), and patients with acute STEMI who underwent angioplasty (3.9% vs. 7.8%). The benefits of adjunctive GP IIb/IIIa inhibitors in acute STEMI remain uncertain however. As discussed in the section on bivalirudin, the HORIZONS-AMI trial randomized 3,602 patients with STEMI undergoing primary PCI to UFH with a GP IIb/IIIa inhibitor (either abciximab or eptifibatide) or to bivalirudin alone with provisional GP IIb/IIIa (91). All patients were treated with aspirin and a thienopyridine prior to PCI. Of the 1,661 patients who were randomized to treatment with UFH, 757 received a double bolus of eptifibatide and 863 received abciximab. In the bivalirudin alone plus provisional GP IIb/IIIa arm, only 53 of 1,674 patients received eptifibatide and 72 received abciximab. At 30 days, the primary endpoint of MACE as well as major bleeding was higher in the group that received UFH and a GP IIb/IIIa inhibitor as compared to bivalirudin alone. A subgroup analysis of the UFH plus GP IIb/IIIa group compared those treated with eptifibatide and abciximab and found that there was no significant difference in the incidence of stent thrombosis at one year (126).

With regards to the timing of adjunctive GP IIb/IIIa use in patients undergoing PCI for acute STEMI, a meta-analysis of six randomized trials including TIGER-PA and ON-TIME

found that early administration (prior to transfer to catheterization laboratory) as compared to late (at the time of PCI) improved measures of coronary patency as well as clinical outcomes (127). The FINESSE trial also addressed the issue of timing of GP IIb/IIIa inhibitor therapy. In the trial, 2,453 patients with STEMI were randomized to pre-PCI treatment with a half-dose fibrinolytic agent plust abciximab, pre-PCI abciximab alone, or abciximab at the time of PCI (128). The primary endpoint was composite death, ventricular fibrillation occurring over 48 hours after randomization, cardiogenic shock and congestive heart failure during the first 90 days after randomization. The results of this trial showed no benefit and perhaps a trend towards more bleeding with abciximab pre-treatment as compared to abciximab given at the time of PCI.

With regards to its safety profile, there does appear to be an increased risk of bleeding with the use of intravenous GP IIb/IIIa inhibitors, however a pooled analysis of 14 randomized trials including approximately 28,000 patients found no difference in the incidence of intracerebral hemorrhage when comparing heparin plus any GP IIb/IIIa inhibitor to heparin plus placebo (0.12% vs. 0.09%, OR 1.3), or when comparing a GP IIb/IIIa inhibitor alone with heparin alone (129).

When deciding between agents for use in PCI, it is unclear whether one GP IIb/IIIa inhibitor holds any significant advantage in clinical efficacy over another. It is likely that the level of platelet inhibition achieved at two hours is similar between all three agents although there is some suggestion that the current recommended dosing regimen for tirofiban produces relatively less platelet inhibition in the first 15 to 60 minutes after coronary intervention (130). One of the few clinical trials to compare the clinical efficacy of two GP IIb/IIIa inhibitors head to head was the TARGET trial in which 4,809 patients undergoing elective PCI were randomly assigned to either abciximab or tirofiban (131). The study showed that abciximab (0.25 mg/kg bolus followed by 0.125 μg/kg [maximum 10 μg/min] for 12 hours) was significantly superior to tirofiban (10 μg/kg bolus followed by 0.15 μg/kg for 18 to 24 hours) in reducing the composite end point of death, MI, or urgent revascularization at 30 days (6% vs. 7.6%; HR 0.79). The difference appeared to be driven mainly by less procedure related MIs in the abciximab group (5.4% vs. 6.9%). A subgroup analysis found that this benefit was limited to patients who had ACS or were non-diabetic. At six months however, there was no longer any difference in the primary composite endpoint between the two drugs and by one year, the benefit of abciximab in the subgroup of patients with ACS had disappeared (132-133). A higher tirofiban bolus dose regimen (25 μg/kg bolus over three minutes followed by 0.15 μg/kg/min for 18 hours) given prior to PCI is being compared with pre-treatment with abciximab in the ongoing TENACITY trial. MULTISTRATEGY was an open-label, multi-center European trial which randomized 745 patients with STEMI undergoing primary PCI in a 2-by-2 factorial design to pre-treatment with either high dose tirofiban or abciximab and sirolimus-eluting stent versus bare-metal stent (134). All patients received dual oral anti-platelet therapy with aspirin and clopidogrel as well as with UFH. There was no significant difference between the GP IIb/IIIa groups in the primary end points of ST-segment resolution at 90 minutes after PCI (RR 1.020; 97.5% CI 0.958-1.086; p=0.001 for non-inferiority) and the rate of MACE at 8 months. Rates of major and minor bleeding complications were similar, however the incidence of moderate or severe thrombocytopenia was increased with abciximab (4.0% vs. 0.8%; p=0.004). To date abciximab has not been directly compared to ebtifibatide to evaluate relative clinical efficacy, although one study showed that compared to tirofiban, ebtifibatide was as effective

as abciximab in achieving a greater proportion of patients in whom there was greater than 80% inhibition of platelet activation at 15 minutes (135). A retrospective analysis of 452 patients with STEMI undergoing primary PCI who received adjunctive therapy with either abciximab or eptifibatide found no significant differences in clinical outcomes including reinfarction (2% vs. 3% for eptifibatide and abciximab respectively), repeat revascularization (3% vs. 4%), bleeding complications (8% vs. 12%), congestive heart failure (5% vs. 3%), cerebrovascular accidents (0% vs. 2%), renal failure (2% vs. 3%), and all-cause mortality at discharge (5% vs. 4%) as well as at 6 months (6.5% vs. 6.4%; HR 0.976; 95% CI 0.43-2.23; log-rank, p=0.95) (136).

Given the above evidence, the 2009 ACC/AHA Focused Updates of the STEMI and PCI guidelines concluded that in the setting of dual antiplatelet therapy with aspirin and a thienopyridine plus either UFH or bivalirudin as the anticoagulant, GP IIb/IIIa inhibitors can be useful at the time of primary PCI but cannot be recommended as routine therapy. In select cases such as for the patient with a large thrombus burden or for patients who have not received adequate thienopyridine loading, adjunctive treatment with a GP IIb/IIIa inhibitor (abciximab [Level of Evidence A], tirofiban [Level of Evidence B], or eptifibatide [Level of Evidence B]) may be of more benefit (Class IIa) (17).

3.6 Fibrinolytic therapy

Fibrinolytic therapy restores blood flow in the infarct-related artery and has been shown to improve mortality in STEMI patients who are not able to receive timely PCI, though not in patients with NSTE-ACS. The mortality benefit of fibrinolytic therapy was first demonstrated with streptokinase in the GISSI-2 and ISIS-2 landmark trials (137-141). Streptokinase is a single chain polypeptide derived from beta-hemolytic streptococcus that binds to and cleaves peptide bonds on plasminogen causing an indirect conformational change that then activates plasmin. Streptokinase is antigenic and can infrequently cause an immunologic sensitization and allergic reaction with repeated use exposure. Increased doses are required to neutralize the body's anti-streptococcal antibodies.

Alteplase (recombinant tissue-type plasminogen activator, t-PA) is a serine protease that is naturally produced by endothelial cells and possesses no antigenic features. In contrast to streptokinase (nonfibrin-specific), t-PA is one of several fibrin-specific agents whose ability to convert plasminogen to plasmin is greatly enhanced after binding preferentially to fibrin in a thrombus with resultant local fibrinolysis. The results of the clinical trial GUSTO-I comparing streptokinase and t-PA in 41,000 patients with STEMI demonstrated an absolute survival benefit of 1% with t-PA at 30 days (6.3% vs. 7.3%) that persisted at one year (9.1% vs. 10.1%) with the most benefit seen in patients less than 75 years old and in those with anterior wall infarctions (142-143). Streptokinase however remains the most widely used fibrinolytic agent worldwide. Although it is less efficacious than alteplase, it maintains a reasonable efficacy to safety ratio with a lower risk of intra-cranial hemorrhage and is significantly less expensive.

Two other genetically engineered fibrin-specific agents currently approved in the US for use in the treatment of acute STEMI include reteplase (r-PA) and tenecteplase (TNK). Like t-PA, these agents are not antigenic and have no associated risk of allergic reaction. r-PA is a recombinant nonglycosylated form of human tissue plasminogen activator. In comparison

to t-PA, r-PA has a longer half-life and binds fibrin with lower affinity improving its ability to penetrate into clots, though clinical trials (RAPID I and II, GUSTO III, INJECT) have generally demonstrated similar outcomes with r-PA and t-PA (144-148). The newest of these, tenecteplase (TNK) is a recombinant plasminogen activator derived from the native t-PA. It possesses 14 times more specificity to fibrin and is 80 times more resistant to inhibition by plasminogen activator inhibitor 1 (PAI-1) (149). It has a longer plasma half-life, allowing for easier and faster treatment with a single intravenous bolus injection and has been shown in several clinical trials including TIMI 10A and 10B, ASSENT-1 and ASSENT-2 to be as effective as t-PA with a significant reduction in non-cerebral bleeding (150-153).

Lanoteplase (n-PA) is another genetically engineered mutant of wild-type t-PA, however, it is not currently approved for use due to an increase in hemorrhagic stroke (154-155). Anistreplase (APSAC) is another fibrinolytic agent that has a significantly longer half-life compared to streptokinase (90 to 100 minutes versus 18-23 minutes). Like streptokinase and staphylokinase, it is antigenic leading to restrictions in repeated use. Though its efficacy and safety profiles were similar to streptokinase, anistreplase is no longer available. Urokinase is a non-fibrin specific fibrinolytic and is a nonselective activator of plasminogen. Urokinase is currently used only in the treatment of pulmonary embolism.

Absolute contraindications to fibrinolytic therapy include any history of intracranial hemorrhage, history of ischemic stroke within the preceding three months, presence of a cerebral vascular malformation or a primary or metastatic intracranial malignancy, symptoms or signs suggestive of an aortic dissection, a bleeding diathesis or active bleeding with the exception of menses, and a significant closed-head trauma within the preceding three months (156). Furthermore, combination therapy with fibrinolytic agents and GP IIb/IIIa inhibitors is not recommended owing to a lack of mortality benefit with significantly higher rates of bleeding seen in the GUSTO V and ASSENT-3 trials (157-162).

In patients with acute STEMI, PCI has been shown to be more effective than fibrinolytic therapy in preventing death, reinfarction, and stroke (163). However, many patients are unable to receive prompt PCI, particularly those who first present to a hospital without PCI capabilities. In such cases, it is recommended that patients who are eligible receive early fibrinolytic therapy. The issue of whether and when to perform coronary angiography and PCI in patients who have received fibrinolytic therapy is complex and has been examined extensively in clinical trials. Evidence suggests that patients who are able to attain normalization of blood flow (TIMI grade 3) in the infarct-related artery after fibrinolysis tend to have the most favorable outcomes (164-165). Although fibrinolytic therapy restores patency (TIMI grade 2 or 3) in 80% of infarct-related arteries, it only restores normalization of flow (TIMI grade 3) in 50-60% of arteries. This provides the rationale for performing PCI following the administration of fibrinolytic therapy. Two trials, GRACIA-2 and FAST-MI, have demonstrated equivalency in efficacy and safety when comparing fibrinolytic therapy followed by PCI to primary PCI (166-167). Previously used terms describing specific reperfusion strategies with PCI after fibrinolytic therapy have included *facilitated PCI* and *rescue PCI*, however, the 2009 STEMI/PCI Focused Update considered these labels potentially misleading. Though these terms are no longer used in the recommendations, many of the previous supporting trials refer to these strategies so a brief review will be necessary.

Facilitated PCI involves initial treatment with full or half dose fibrinolytic agent or a combination of fibrinolytic and GP IIb/IIIa agents followed by immediate PCI. Two large, randomized clinical trials have addressed this issue. The trial ASSENT-4-PCI was intended to randomize 4,000 patients with STEMI who presented within 6 hours of symptom onset to full-dose tenecteplase or placebo prior to primary PCI (168). The trial was terminated early due to a significant increase in the primary endpoint of death, heart failure, or shock within 90 days in the tenecteplase group (19% vs. 13%, RR 1.39, 95% CI 1.11-1.74), along with increased mortality (6% vs. 3%), in-hospital stroke (1.8% vs. 0%; mostly intra-cranial hemorrhage), as well as reinfarction (6% vs. 4%) and target vessel revascularization (7% vs. 3%) at 90 days. The FINESSE trial, described in more detail in the GP IIb/IIIa section, showed that there was no benefit in the treatment of acute STEMI with half-dose reteplase and abciximab prior to PCI with trends toward an increase in intra-cranial hemorrhage as well as major and minor bleeding (128). One possible explanation for the poor outcomes seen with facilitated PCI is the immediate nature of planned PCI after fibrionlytic therapy (median time period of 104 minutes between tenecteplase and PCI in the ASSENT-4- PCI trial). Recanalization of the infarct artery occurs 30-45 minutes after tenecteplase injection, so the relatively short time gain from the point of recanalization until PCI likely exposes the patient to more bleeding risk associated with full-dose fibrinolytic and antithrombotic therapy relative to any potential smaller benefit of PCI. A subgroup analysis showing a trend toward better outcomes when tenecteplase was given in the ambulance compared to much worse outcomes when given at a PCI center is consistent with this theory. The results of these and various smaller trials, as well as a 2006 meta-analysis have led most major society guidelines to recommend against facilitated PCI with full dose fibrinolytic therapy, though the 2007 PCI Focused Update makes a weak recommendation for the consideration of facilitated PCI using regimens other than full-dose fibrinolytic therapy in patients with high-risk STEMI in whom bleeding risk is low and PCI is not immediately available within 90 minutes (Class IIb, Level of Evidence: C) (84).

Rescue PCI refers to the strategy of performing PCI only if there are clinical or electrocardiographic signs of failed reperfusion of the infarct artery after treatment with fibrinolytics. The 2007 PCI Focused Update makes a Class I recommendation for rescue PCI or emergency CABG for cardiogenic shock in patients less than 75 years of age (Level of Evidence: B), severe congestive heart failure and/or pulmonary edema (Killip class III) (Level of Evidence: B), or hemodynamically compromising ventricular arrhythmias (Level of Evidence: C). Rescue PCI is also reasonable for cardiogenic shock in patients 75 years of age or older if they are suitable candidates for revascularization (Level of Evidence: B), hemodynamic or electrical instability (Level of Evidence: C), persistent ischemic symptoms (Level of Evidence: C), or for <50% ST-segment resolution in the lead that showed the greatest degree of ST elevation at presentation at 90 minutes after initiation of fibrinolytic therapy and a moderate or large area of myocardium at risk (anterior MI, inferior MI with right ventricular involvement or precordial ST-segment depression) (Level of Evidence: B) (Class IIa). These recommendations were based largely on results from the REACT trial as well as a subsequent meta-analysis of 8 rescue PCI trials demonstrating a clear benefit of rescue PCI over repeated doses of fibrinolytic therapy or medical management for failed fibrinolysis (169-172).

As stated above, the 2009 STEMI/PCI Focused Update has abandoned the potentially confusing terms facilitated PCI (immediate planned PCI usually performed within 2 hours of fibrinolytic or fibrinolytic plus GP IIb/IIIa therapy) and rescue PCI (PCI reserved for only those who fail fibrinolysis) in favor of a *pharmacoinvasive strategy* (17). Several trials have provided valuable evidence informing the 2009 STEMI/PCI Focused Update on this matter. In the CARESS-in-AMI trial, 600 STEMI patients 75 years of age or younger with one or more high-risk features (extensive ST-segment elevation, new left bundle branch block, previous MI, Killip class >2, or left ventricular ejection fraction ≥35%) were treated with half-dose reteplase, abciximab, heparin, and aspirin, and randomly assigned to immediate transfer for PCI or to standard medical management at the local hospital with transfer only for rescue PCI (173). The primary outcome was a composite of death, reinfarction, or refractory ischemia at 30 days. PCI was performed in 85.6% of the patients assigned to immediate transfer for PCI and rescue PCI was performed in 30.3% of the standard care/rescue PCI group. The primary outcome occurred significantly less in the immediate PCI group compared to standard care/rescue PCI (4.4% vs. 10.7%; HR 0.40; 95% CI 0.21-0.76; log rank p=0.004). There was no difference in major bleeding or strokes between the two groups. In the TRANSFER-AMI trial, 1,059 high-risk STEMI patients who were treated with tenecteplase within two hours of symptom onset were then randomized to either immediate transfer for cardiac catheterization (PCI within 6 hours) or to standard medical care (174). High-risk STEMI was defined as ST segment elevation ≥2 mm in two anterior leads or ST-segment elevation ≥1 mm in two inferior leads plus one or more of the following: systolic blood pressure <100 mmHg, heart rate >100 beats/min, Killip class II or III, ST-segment depression ≥2 mm in the anterior leads, or ST-segment ≥1 mm in right sided lead (V4R). Standard care included rescue PCI if required, or delayed angiography >24 hours after STEMI. All patients received aspirin, tenecteplase, and heparin or enoxaparin with a recommendation for clopidogrel. The primary endpoint was the composite of death, reinfarction, recurrent ischemia, new or worsening congestive heart failure, or cardiogenic shock within 30 days. Cardiac catheterization PCI were performed in 98.5% and 84.9% of the patients assigned to early PCI at a median of 2.8 hours after randomization and in 88.7% and 67.4% of the patients assigned to standard treatment at a median of 32.5 hours after randomization. At 30 days, the primary endpoint was significantly reduced in the early PCI group (11.0% vs. 17.2%; RR 0.64; 95% CI 0.47-0.87; p=0.004) with no significant differences between the groups in the incidence of major bleeding. Several other trials have evaluated the timing of PCI after fibrinolysis with an early pharmacoinvasive therapy compared to standard care including GRACIA-1, NORDISTEMI, and SIAM III (175-177). Each had a different study design and thus examined slightly different patient populations but all have confirmed the observations seen in CARESS-in-AMI and TRANSFER-AMI that a pharmacoinvasive strategy with immediate or early PCI after fibrinolytic therapy (within 3 to 24 hours) produces better outcomes than standard medical care with rescue PCI or routine late PCI (over 24 hours).

Based on the above evidence, a pharmacoinvasive approach to the management of STEMI patients who present to a hospital without PCI capabilities has been developed, which includes routine use of a pharmacologic agent (either fibrinolytic therapy or a GP IIb/IIIa inhibitor) prior to transfer to a PCI-capable hospital for diagnostic angiogram and consideration of PCI (17). Patients with STEMI who present to a PCI capable hospital are

not recommended to receive fibrinolytic therapy and should undergo prompt PCI no later than 90 minutes after presentation. STEMI patients who present to a hospital without PCI capability should be triaged to either immediate transfer for PCI or to receive fibrinolytic therapy if deemed an appropriate candidate. Those with high-risk STEMI features (congestive heart failure, cardiogenic shock, electrical instability, etc.), elevated bleeding risk with fibrinolytic therapy, or presenting more than 4 hours after symptom onset may be better suited for immediate transfer for PCI without delay for fibrinolytic therapy if the time required for transport to the receiving hospital is not prolonged. STEMI patients who present early after symptom onset with low bleeding risk are the most suitable candidates for fibrinolytic therapy. If after receiving the fibrinolytic agent the patient is deemed to have high-risk features, the patient should then be immediately transferred for PCI with the intention to perform diagnostic catheterization with possible PCI within 3 to 24 hours of presentation. Patients who are not judged to be high-risk may be transferred to a PCI-capable hospital after receiving antithrombotic therapy or may be observed in the initial facility.

3.7 Platelet function testing (P2Y12 testing)

Several studies have shown that patients with high platelet reactivity despite being treated with clopidogrel have a higher incidence of cardiovascular events after PCI (178). This has led to a departure from the "one size fits all" paradigm in clopidogrel use during PCI as well as investigations into the different genetic and clinical factors that affect individual response in platelet reactivity. Clopidogrel is a prodrug which requires biotransformation to its active thiol metabolite via the hepatic cytochrome P450 system (179). It exerts its antiplatelet effect by irreversibly binding the adenosine diphosphate receptor P2Y12, a G-protein coupled receptor found on the platelet surface, which mediates inhibition of adenylyl cyclase resulting in the final activation of the GPIIb/IIIa receptor (180). Blockade of this pathway with clopidogrel inhibits platelet aggregation and along with the co-administration of aspirin has contributed to a substantial reduction in thrombotic complications peri-PCI (181). Pharmacokinetic and pharmacodynamic data have revealed significant inter-individual variability in platelet response to clopidogrel, with reports of clopidogrel "non-responsiveness" in up to 30% of Caucasian patients (182-183). There are many potential causes of clopidogrel response variability with recent studies focusing on genetic variations in hepatic CYP isoenzymes, in particular single-nucleotide polymorphisms of CYP2C19. In a genetic substudy from the TRITON-TIMI 38 trial, patients with a reduced function CYP2C19 allele who were treated with clopidogrel had lower serum levels of active clopidogrel metabolite as well as diminished platelet inhibition leading to higher rates of major adverse cardiovascular events including stent thrombosis when compared to noncarriers of the CYP2C19 allele (12.1% vs. 8.0%; HR 1.53; 95% CI 1.07 to 2.19; p = 0.01) (184). Additionally, variants in ABCB1, a gene encoding for efflux pump P-glycoprotein expressed on intestinal epithelial cells, have been reported to affect clopidogrel absorption and efficacy. Carriers of the specific ABCB1 polymorphism 3435C→T, particularly those who are TT homozygotes have lower serum levels of active metabolite when treated with clopidogrel as well as higher rates of a combined endpoint of cardiovascular death, myocardial infarction, or stroke (12.9% vs. 7.8%; HR 1.72; 95% CI 1.22–2.44; p=0.002) (185). Further studies are needed to determine how much a role

ABCB1 variants play in clopidogrel response variability. Genome-wide association studies have shown that the heritability of platelet response to clopidogrel may be as high as 70%, with the reduced function CYP2C19*2 polymorphism accounting for only 12% of the clopidogrel response variability (186). As such, much of the inter-individual variability cannot be explained by genotype differences alone. Given the complexity of testing for multiple genetic polymorphisms along with its as yet uncertain yield, there has been increasing interest recently in the direct assessment of platelet reactivity peri-procedurally.

A number of different methods exist for the laboratory quantification of platelet inhibition. Light transmittance aggregometry (LTA) analyzes percent inhibition by measuring the amount of transmitted light through a vial of platelet plasma before and after the addition of ADP, which induces platelet aggregation. LTA is considered the "gold standard" for measurement of platelet aggregation but the test is very labor intensive and thus limits its routine use for guiding clinical care. Other tests for platelet inhibition include flow cytometry, platelet function analyzer (PFA-100), vasodilator-stimulated phosphoprotein (VASP) phosphorylation assay, and the bedside VerifyNow P2Y12 assay, which measures the aggregation of platelets to fibrinogen-coated beads. A study by Price et al. reported that the optimal cut-off value for post-PCI platelet reactivity as measured by the VerifyNow P2Y12 assay is 235 PRU (P2Y12 reactivity units) (187). Patients with increased residual platelet reactivity (measured at ≥235 PRU) after PCI had significantly higher rates of cardiovascular death (2.8% vs 0%, p=0.04), stent thrombosis (4.6% vs 0%, p=0.004), and the combined ischemic endpoints (6.5% vs 1.0%, p=0.008) at 6 months. Due to its high predictive value for post-PCI outcomes and its ease of use as a point-of-care platelet function assay, the use of VerifyNow P2Y12 assay as a clinical guide for intensified platelet inhibition therapy was recently evaluated in the large multi-center trial, GRAVITAS (188). Investigators in the GRAVITAS trial randomized patients with stable CAD or NSTE-ACS and high on-treatment platelet reactivity as defined by a PRU value of ≥230 after PCI to treatment with either high-dose clopidogrel (first-day loading dose of 600mg, followed by 150mg daily for 6 months) or standard-dose clopidogrel (required to have received either 300mg loading dose at the time of PCI or at least 75mg daily for seven days preceding PCI and standard maintanence 75mg dose for 6 months). The results of the trial failed to demonstrate a reduction in the incidence of cardiovascular death, non-fatal MI, or stent thrombosis with the use of high-dose clopidogrel (2.3% vs 2.3%; HR 1.01; 95% CI 0.58-1.76; p=0.97) (11). A second trial, TRIGGER—PCI, intended to compare the use of clopidogrel versus prasugrel in patients undergoing stenting for stable CAD with high post-PCI residual platelet reactivity (defined as a PRU>208 utilizing the VerifyNow P2Y12 assay). Unfortunately, the trial was terminated early due to an unexpected low rate of primary endpoint events in both groups, reported to be even less than the low event rates seen in the GRAVITAS trial. It has been hypothesized that these two trials were negative mainly because the patient population studied was at low risk for cardiovascular complications – patients with stable CAD undergoing successful uncomplicated PCI with contemporary drug-eluting stents. Based on the results of these two trials, it may be argued that platelet function testing in these low-risk situations has limited value as there is little to be gained from more potent platelet inhibition. Whether a personalized approach to intensified platelet inhibition therapy can be beneficial in higher risk groups such as patients with acute coronary syndromes, patients

with diabetes, patients with complex coronary anatomy and complex interventions as well as clopidogrel "hypo-responsiveness" remains to be determined and requires further prospective investigation.

Absence or termination of dual anti-platelet therapy
Stent under-expansion
Inflow or outflow obstruction (CAD >50%)
Greater stent length
Small vessel diameter
Emergent PCI or ACS
Residual thrombus or stent edge dissection
Subtherapeutic peri-procedural anticoagulation
Severe left ventricular dysfunction
History of brachytherapy
Cocaine use
Post-procedure TIMI flow grade <3
Bifurcation lesions
Malignancy
Genetic polymorphisms in hepatic enzymes involved in clopidogrel metabolism
High on-treatment platelet reactivity (with clopidogrel)

Table 1. Factors associated with increased risk of stent thrombosis

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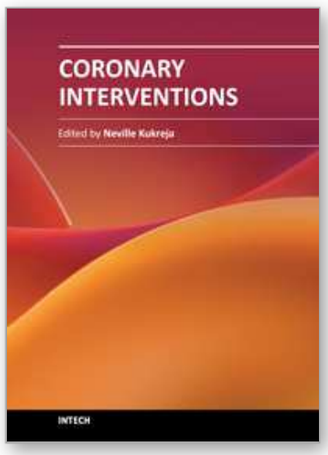

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