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Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention: Economic Considerations

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Abstract

Percutaneous coronary intervention (PCI) is one of the most common medical procedures performed for treatment of coronary artery disease. Antiplatelet medications as adjunctive therapy for PCI are used routinely, with indications for specific agents or their combinations varying depending on the clinical scenario. While the cost-effectiveness of well-established agents has been extensively studied, newer drugs have not been evaluated as thoroughly. In addition, the clinical application of some antiplatelet drugs has recently changed, thus making older studies of cost effectiveness less applicable to the current landscape of clinical practice. This article reviews cost-effectiveness considerations of antiplatelet therapies in treatment of coronary artery disease in patients undergoing PCI. Aspirin, P2Y12 inhibitors including clopidogrel and the newer agents prasugrel and ticagrelor, as well as GP IIb/IIIa inhibitors are discussed. Overall, the use of dual antiplatelet therapy (DAPT) with aspirin and P2Y12 inhibitor in patients undergoing PCI improves ischemic outcomes and appears to be cost-effective. The few available studies suggest that recently approved medications prasugrel and ticagrelor are cost-effective alternatives to clopidogrel. However, no direct comparison between these two newer agents is available. The indications for GP IIb/IIIa inhibitors have changed in the current PCI era, and there is a paucity of cost-effectiveness data for their use in contemporary care.

Introduction

Coronary artery disease is exceedingly common and expensive.¹ In addition to medical therapy, percutaneous coronary intervention (PCI), including balloon angioplasty, stent placement, and adjunctive procedures such as thrombectomy and atherectomy, is frequently utilized in the treatment of symptomatic coronary artery disease. PCI is the treatment of choice for two major subsets of coronary artery disease: high risk acute coronary syndromes (ACS), including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA), and in conjunction with optimized guideline-directed medical therapy for stable, symptomatic ischemic heart disease^{2, 3}

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Coronary angioplasty is achieved by inflating specially designed balloons at super-atmospheric pressures to relieve the stenosis at the site of the lesion. This results in obligatory injury to the vessel wall structures, which exposes thrombogenic subendothelial matrix and collagen to platelets, which may initiate platelet adhesion and activation, which in turn promotes thrombus formation.⁴ Bare metal stent (BMS) implantation reduces the natural tendency for vessel recoil after balloon angioplasty, thus promoting long-standing vessel patency. However, tissue healing after said injury leads to scar tissue formation and stent restenosis. Drug-eluting stents (DES) reduce this reaction and thus limit scar tissue formation and restenosis, but increases the time for re-epithelization of the stent struts, thus prolonging the existence of and exposure to a potentially thrombogenic milieu.⁵ This prolonged exposure can lead to both early and delayed (>1 year) stent thrombosis, manifesting as acute coronary syndromes and myocardial infarction.

Several pharmacological strategies have been utilized to decrease the risk of thrombotic events. First, periprocedural anticoagulation with either unfractionated or low-molecular-weight heparin or bivalirudin is routinely used. In addition, as platelets are central to the initiation, propagation and maintenance of PCI-related thrombus, several antiplatelet regimens have been employed. The anti-platelet agents can be categorized into aspirin, thienopyridine (clopidogrel and prasugrel) and non-thienopyridine (ticagrelor) ADP P2Y₁₂ receptor inhibitors, and glycoprotein (GP) IIb/IIIa inhibitors. As a group, these agents have been shown to decrease ischemic events in patients undergoing PCI, but their use varies based on the clinical setting.⁶⁻⁸

Current recommendations for antiplatelet therapy in patients undergoing PCI differ somewhat based on the indication for PCI, as well as type of stent implanted (BMS vs. DES). The indications can be generalized to ACS (STEMI and NSTEMI/UA), in which PCI generally portends a survival benefit, and non-ACS (stable angina), where PCI is a symptomatic treatment.² Aspirin is recommended for all manifest coronary disease and should be initiated before PCI and indefinitely thereafter. A P2Y₁₂ inhibitor loading dose is recommended at the time of or prior to ACS-PCI, while clopidogrel alone is recommended for non-ACS PCI. The recommended duration of dual antiplatelet therapy (DAPT) varies: in the setting of PCI for ACS the current recommendation is for 12 months of DAPT regardless of the type of stent implanted, while for PCI in the non-ACS setting at least 12 months of DAPT is recommended for patients receiving DES and at least 1 month and up to 12 months for patients receiving BMS. Earlier discontinuation of DAPT in patients at high risk of bleeding is reasonable if this risk exceeds the perceived benefit.

The recommendations for use of GP IIb/IIIa inhibitors have been updated recently.^{2, 9} The benefit of these intravenous platelet inhibitors in the setting of PCI has been demonstrated in multiple studies. However, current management strategies, in particular adoption of early intervention, treatment of patients with P2Y₁₂ inhibitors, and increasing use of bivalirudin as an anticoagulant have diminished their applicability to contemporary practice, largely owing to the excess bleeding that accompanies their use when paired with aspirin and a P2Y₁₂ inhibitor.^{10, 11} Nonetheless, GP IIb/IIIa inhibitors are considered reasonable at the time of PCI for patients not pretreated with P2Y₁₂ inhibitor in both ACS (class IIa) and non-ACS (class IIa & IIb) settings.^{2, 9} Furthermore, in patients exhibiting high-risk features, such

as diabetics with elevated biomarkers and dynamic EKG changes, administration of GP IIb/IIIa inhibitors prior to or at the time of PCI has a class I indication as part of DAPT in UA/NSTEMI.¹⁰ It is noteworthy that routine administration of GP IIb/IIIa inhibitors prior to primary PCI for STEMI (i.e. facilitated PCI) is not beneficial, and may be harmful.² The intravenous P2Y12 blocker cangrelor, which like GP IIb/IIIa inhibitors has been used intra-procedurally, has recently been approved by the FDA, and is likely to be incorporated into practice, especially in patients with acute coronary syndromes (ACS).¹²

Cost-Effectiveness based on Models and Clinical Trials

Cost-effectiveness analysis (CEA) always involves comparison of a new therapy to a previous standard or control.¹³ Effectiveness is most commonly measured in life years or quality adjusted life years, which permits comparison of CEA across wide disciplines in medicine. The fundamental measure is the incremental cost effectiveness ratio (ICER), which is the ratio of the incremental cost of a new therapy compared to control divided by the incremental cost. There are always assumptions involved in the calculation of both the measure of effectiveness and cost, and associated error. CEA may be developed entirely from models or from patient level data alongside clinical trials.¹⁴ CEA from trials offers patient level data, permitting assessment of stochastic error. However, virtually all CEA involve some element of modeling. The time horizon of CEA poses analytic challenges; it may be confined to a clinical trial period, a limited number of years or lifetime. Lifetime assessment theoretically offers the best approach to making CEA comparable across disciplines. However, both CEA from models and alongside clinical trials require assumptions about life expectancy, which may be difficult to evaluate. There will generally be uncertainty concerning life expectancy of the control group, and if there is a difference in survival at the end of observed clinical trial data, the survival curves could continue to move apart, move in parallel or converge, offering varying results. The various sources of uncertainty can be assessed to some extent by sensitivity analysis, which is generally available in most published CEA.

Aspirin

There is a paucity of studies illuminating the cost-effectiveness of aspirin in the setting of PCI, either for the ACS or non-ACS indication. However, the clinical effectiveness of aspirin has been evaluated as a primary, as well as secondary prevention agent. The effectiveness of aspirin in primary prevention depends upon the patient risk profile, with higher risk population deriving most benefit. Additionally there are gender specific differences, with aspirin appearing effective in reducing the rate of myocardial infarction in high risk men and stroke in high risk women.¹⁵ The role of aspirin in secondary prevention is well established in both men and women.¹⁶ However, aspirin increases the risk of gastrointestinal bleeding and hemorrhagic stroke.¹⁷

Several cost-effectiveness studies have been performed with aspirin (table 1). One study, using Markov state-transition model with a base-case of 45 year old man with 10 year risk for coronary heart disease of 7.5% demonstrated aspirin as being dominant for primary prevention in this population.¹⁸ The study was conducted from a third-party payer

perspective, and included only men. Duration of treatment was 10 years with a lifetime event-horizon. Aspirin increased mean quality adjusted life years (QALYs) from 17.16 to 17.20 at a lower cost (\$6090 vs. \$6694). Another Markov model-based European study examined the cost effectiveness of aspirin separately in men and women across ages and levels of risk.¹⁹ Event rates were extrapolated from the Dutch population data and a gender-specific meta-analysis was used to estimate clinical effectiveness of aspirin in both genders. The ICER ranged from €34 for 65 year old men with 5 times baseline risk for cardiovascular disease (CVD), to €141,160 for 45 year old men with twice the baseline risk. Similar risk related variability was noted for women. The authors concluded that, using a threshold of €20,000, aspirin in primary prevention is cost effective for men with a 10 year CVD risk of 10% and women with 10 year CVD risk of 15%. Similarly, Earnshaw *et al* showed that treatment with aspirin for primary prevention was less costly and more effective than no treatment in men older than 45 years of age with 10 year risk of CHD greater than 10%.²⁰ For secondary prevention, Gaspoz *et al.* in a Coronary Heart Disease Policy model-based study found that increasing the use of aspirin from current levels to all eligible patients for 25 years would have an ICER of \$11,000 per QALY gained.²¹

The majority of patients undergoing PCI have a significant burden of coronary disease, and in many cases the PCI is performed as treatment of an index or recurrent myocardial infarction. Therefore, these patients fall into either the secondary prevention category, or are in the high-risk primary prevention group of patients. Indeed, in a recently published observational comparative effectiveness study of coronary revascularization strategies, the 4 year unadjusted mortality in the PCI cohort was 20.9%.²² Thus, despite the absence of direct evidence, it is probably reasonable to extrapolate the results of the primary and secondary prevention cost-effectiveness analyses of aspirin to patients undergoing PCI.

ADP P2Y12 Receptor Inhibitors

Clopidogrel

The addition of P2Y12 inhibitors to aspirin has been shown to be beneficial in patients undergoing PCI and has formed the basis of DAPT.²³ Until recently, thienopyridines clopidogrel and ticlopidine have been the two agents available for this purpose, with clopidogrel used predominantly due to hematological adverse reactions associated with the use of ticlopidine.²⁴ In 2010 prasugrel became available for patients with ACS undergoing PCI, followed more recently by approval of non-thienopyridine ticagrelor for the same indication.^{7, 8} Of the four currently available P2Y12 inhibitors, clopidogrel has been the most extensively studied clinically, as well as from the cost-effectiveness perspective.

Several trials evaluated the benefits of clopidogrel in varied clinical settings, most involving high-risk patient populations or patients presenting with ACS: CAPRIE,²⁵ CURE,⁶ CREDO,²⁶ CLARITY TIMI-28,²⁷ CHARISMA,²⁸ COMMIT.²⁹ These trials inform clinical decisions in patients with coronary artery disease in the acute setting as well as for secondary prevention. However, some but not all of these trials included and separately evaluated patients undergoing PCI. Economic considerations of clopidogrel as a secondary prevention agent have been reviewed previously.^{30, 31}

The CURE trial showed beneficial effects of DAPT with aspirin plus clopidogrel compared to aspirin alone in the setting ACS without ST elevation when initiated at the time of the index event and continued for an average duration of up to 1 year.⁶ The trial's primary outcome - a composite of death from cardiovascular causes, nonfatal myocardial infarction, or stroke occurred in 9.3% of the patients in the clopidogrel group and 11.4% of the patients in the placebo group (relative risk with clopidogrel as compared with placebo, 0.80; 95% CI 0.72 to 0.90; $P < 0.001$).⁶ Additionally, PCI-CURE evaluated the effectiveness and cost-effectiveness of clopidogrel plus aspirin versus aspirin alone in 2658 patients with non-ST-elevation acute coronary syndrome undergoing PCI in the CURE trial.³² Rates of the composite primary endpoint were 4.5% and 6.4% for the clopidogrel and placebo groups, respectively (relative risk 0.70; 95% CI 0.50–0.97, $p = 0.03$). Multiple authors have used based CEA on CURE and PCI-CURE. (Table 1).^{33–42}

In all studies in Table 1 based on CURE and PCI CURE, DAPT with aspirin and clopidogrel compared to aspirin alone was found to be well within the commonly quoted threshold for cost effectiveness ($< \$50,000$). However, while studies based on the CURE trial elucidate the economic implications of DAPT in the setting of ACS, only the two studies based on PCI CURE trial are specifically relevant to the patient population undergoing PCI in this setting. Furthermore, because CURE and PCI-CURE included only patients with ACS without ST elevation, cost effectiveness analyses based on these trials are not directly relevant to the PCI population in other clinical settings, i.e. ST elevation MI and stable coronary disease on DAPT.

Clinical benefit of adding clopidogrel to the background of fibrinolysis and aspirin in patients with STEMI was demonstrated in the CLARITY TIMI 28 trial.²⁷ In this trial 3491 patients within 12 hours of onset of STEMI were randomly assigned to clopidogrel or placebo in addition to fibrinolytic agent and aspirin. The primary efficacy end point was a composite of an occluded infarct-related artery on angiography or death or recurrent myocardial infarction before angiography. Primary end-point was reached in 21.7% in the placebo arm and 15.0 percent in the clopidogrel arm, representing a 6.7% absolute and 36% relative risk reduction (95% CI, 24 to 47%; $P < 0.001$).²⁷ A planned prospective analysis of patients who underwent PCI was reported in the PCI-CLARITY study.⁴³ During the 30 day study period, the incidence of cardiovascular death, MI, or stroke was decreased in the clopidogrel arm compared to placebo (70 [7.5%] versus 112 [12.0%]; adjusted OR, 0.59 [95% CI, 0.43–0.81]; $P = .001$). The number needed to treat was 23. However, patients undergoing PCI received prior fibrinolysis, and PCI was performed with a delay of 2 to 8 days after the index event, which is not representative of current practice. Gibler *et al.* evaluated the cost-effectiveness of DAPT in the setting of STEMI treated with fibrinolysis in CLARITY TIMI 28, and found clopidogrel therapy to be dominant in 35% of bootstrap simulations and cost less than \$50,000 per life year gained in 67% of simulations (Table 1).⁴⁴ However, no analysis is available for the PCI-CLARITY study specifically, and therefore Gibler's study only tangentially elucidates the cost-effectiveness of clopidogrel for PCI in this setting.

Similarly, the COMMIT trial demonstrated efficacy of DAPT with aspirin and clopidogrel in treatment of STEMI.²⁹ Among 45,852 patients who were randomized, addition of

clopidogrel decreased the combined primary end-point of death, reinfarction or stroke to 9.2% from 10.1% in the placebo arm ($p=0.002$). A significant reduction of rates of death from 8.1% to 7.5% ($p=0.03$) was also noted, representing a 7% relative risk reduction. Cost-effectiveness analysis by Berg *et al.* based on the CLARITY and COMMIT trials found that 1 year of DAPT was a dominant strategy in Sweden and France with cost savings of €11 and €67, respectively for patients similar to the CLARITY population.⁴⁵ (table 1) In Germany, the ICER for clopidogrel was €2 per life year gained. For patients with the profile and event rates similar to those in the COMMIT study, the incremental cost of treatment with clopidogrel was €38 in Sweden, €798 in Germany, and €45 in France, with ICERS €2772, €1144, and €2786 per life year gained, respectively. The authors concluded the treatment to be cost-effective in the setting of STEMI. Zhang *et al.* evaluated the short and long term cost-effectiveness of clopidogrel plus aspirin versus aspirin alone in medically managed STEMI patients. Short term findings using patient level trial data from COMMIT, clopidogrel is a dominate strategy. The lifetime ICER, extrapolating results from CURE, for clopidogrel was \$7806/LYG.⁴⁶ However, the COMMIT trial did not have a significant population of patients undergoing PCI, and therefore these findings are only marginal at best in informing us about the cost effectiveness of clopidogrel in the setting of PCI for STEMI indication.

As discussed above, another major indication for PCI is stable angina despite guideline-directed medical therapy. In this stable setting, PCI is an elective procedure. The benefits of DAPT with addition of P2Y12 inhibitors ticlopidine or clopidogrel to aspirin in this group of patients are well documented.^{47, 48} The CREDO trial established the currently recommended regimen of long-term treatment with aspirin and clopidogrel combination for 12 months after elective PCI.²⁶ The trial demonstrated a 26.9% relative reduction in ischemic events at one year (95%CI 3.9–44.4%, $p=0.02$).

Subsequently, several cost-effectiveness analyses were published based on the CREDO data. Beinart *et al.* evaluated long-term cost-effectiveness of DAPT compared to aspirin for 1 year.⁴⁹ The Framingham Heart Study and the Saskatchewan Health database were used to derive estimates of lost life expectancy due to in-trial events, and in-trial estimates of event rates and costs were used. Using Framingham-based estimates, not including costs beyond the trial period, the ICERs ranged from \$3,684 to \$4,353. Using Saskatchewan-based estimates, ICERs ranged from \$2,929 to \$3,460. Over 97% and 98% of the bootstrap estimates were below \$50,000 per LYG, respectively. The authors concluded the treatment was highly cost effective. In another analysis, Cowper *et al.* evaluated the effects of prolonging clopidogrel treatment from 1 month to 1 year.⁵⁰ Event rate was based on patients who underwent PCI at Duke Medical Center, with the effect of extended treatment based on the CREDO trial data. For the total sample, the ICER was \$15,696/LYG, ranging from \$10,333/LYG in high-risk patients to \$26, 568/LYG in low-risk patients. In a Swedish analysis, Ringborg *et al.* found ICER to be €3,022/LYG, and concluded that the three cost-effectiveness analyses indicate that long term treatment with 1 year of clopidogrel after elective PCI is a cost-effective strategy.⁵¹

Based on a meta-analysis of combining all 3 PCI related trials of DAPT (PCI-CLARITY, PCI-CURE and CREDO trials), Berg *et al.* performed a Markov model-based cost-

effectiveness analysis.⁵² The ICER range for Sweden, Germany and France ranged from €4,225 to €7,871 for treatment duration of 1 year. The authors concluded that this treatment strategy is cost-effective in a wide range of treatment groups.

Prasugrel

Prasugrel is a thienopyridine P2Y₁₂ ADP receptor blocker. Although a pro-drug like clopidogrel, it requires fewer steps for conversion to active form and is a more potent receptor blocker than clopidogrel.⁵³ In TRITON TIMI-38, prasugrel in combination with aspirin was shown to significantly reduce rates of ischemic events in patients undergoing PCI for ACS when compared to the combination of aspirin plus clopidogrel.^{7, 53} For ACS patients, the hazard ratio of primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke was 0.81 (95%CI, 0.73 to 0.90; P<0.001) for prasugrel vs. clopidogrel. Prasugrel was noted to decrease rates of MI from 9.7% to 7.4% (p=0.001) and stent thrombosis from 2.1% to 1.1% (p=0.001) compared with clopidogrel, albeit at the expense of increased bleeding rates.

Two published reports evaluated the cost-effectiveness of prasugrel in the setting of PCI based on TRITON TIMI 38. In the first study, which used the Saskatchewan Health Database for life expectancy estimates beyond the 14.7 months of trial follow up, and patient-level outcomes from the trial to derive clinical effect, treatment with prasugrel compared to clopidogrel was projected to decrease cost by \$221 and to increase life expectancy by 0.102 years, rendering it an economically dominant strategy.⁵⁴ By bootstrap analysis prasugrel was confirmed as the dominant treatment 79.7% of the time, while a cost-effective ICER of <\$50,000 was noted in 99.8% of repetitions. Prasugrel remained a dominant therapy despite widely varying assumptions during sensitivity analyses. Furthermore, prasugrel remained economically attractive compared to hypothetical generic clopidogrel at a presumed cost of \$1 per day, which yielded an ICER of \$9,727. The ICER for prasugrel crossed \$50,000 when the price difference with clopidogrel reached \$7.67.

The second report evaluated cost effectiveness of prasugrel compared to clopidogrel from the US managed care organization perspective.⁵⁵ In this disease-progression model-based study the current daily costs of \$6.08 for clopidogrel and \$6.07 for prasugrel were used. Due to proximity of availability of generic clopidogrel, price difference of \$3–\$4 was evaluated in sensitivity analyses. Even at the \$3 cost difference cost savings of \$175 per 100 patients were noted with prasugrel. However, at a threshold of \$4 cost difference, prasugrel became the more expensive therapy. Nonetheless, even at that price differential, the cost per life year gained was \$13,906. The above analyses suggest that prasugrel may be a cost-effective alternative to clopidogrel as part of DAPT in patients undergoing PCI for ACS.

Ticagrelor

Ticagrelor is an oral non-thienopyridine inhibitor of P2Y₁₂ ADP receptor. It provides more rapid and efficacious platelet inhibition than clopidogrel.⁵⁶ In the PLATO trial, carried out in the setting of ACS, ticagrelor was shown to reduce the composite primary end-point of death from vascular causes, MI or stroke from 11.7% to 9.8% when compared with clopidogrel (HR, 0.84; 95% CI, 0.77 to 0.92; P<0.001).⁸ Moreover, ticagrelor reduced the risk of death

from vascular cause from 5.1% to 4.0% ($p=0.001$), corresponding to an absolute risk reduction of 1.1%. This was achieved with no significant difference in rate of major bleeding, albeit with an increase in non-CABG related bleeding from 3.8% with clopidogrel to 4.5% ($p=0.03$). Ticagrelor is now approved for use in patients with ACS undergoing PCI.

The cost-effectiveness of ticagrelor based on data from the PLATO study was published by Nikolic *et al.*⁵⁷ Over a lifetime, the ICER was €753/QALY gained. A 2011 evaluation of ticagrelor by the National Institute of Health and Clinical Excellence (NICE) of the British National Health Service, the committee noted that all ICERs for ticagrelor were below £5,400 in the manufacturer's submission, but that due to some inherent flaws in the model used for the calculation, more plausible ICERs were £7897/QALY gained for all ACS, £8872/QALY gained for STEMI, £7215/QALY gained for NSTEMI and £9131/QALY gained for unstable angina based on their Evidence Review Group's sensitivity analyses.⁵⁸ Ticagrelor, therefore, gained NICE approval and was deemed cost-effective. Thus, it appears that although robust peer-reviewed evidence is still lacking for ticagrelor, it is likely to be a cost effective approach to treatment for patients undergoing PCI in the setting of acute coronary syndrome.

GP IIb/IIIa inhibitors

GP IIb/IIIa inhibitors interfere with the final common pathway in platelet aggregation. There are three agents currently available in the U.S. Abciximab is a monoclonal chimeric antibody that binds the GP IIb/IIIa receptor non-competitively but irreversibly, while small-molecule agents eptifibatid and tirofiban are competitive GP IIb/IIIa inhibitors with reversible binding. The biologic half-life of abciximab is approximately 12 to 24 hours, while eptifibatid and tirofiban show recovery of platelet aggregation after 4 hours.⁴ As previously discussed, these agents have shown efficacy in the setting of PCI for stable CAD and ACS, but most pivotal trials evaluating their clinical effectiveness were carried out in the era before routine stenting during PCI and routine DAPT, and with heparin as predominant anticoagulation therapy.^{59–65} In more recent trials, addition of GP IIb/IIIa inhibitors to anticoagulation therapy (e.g. bivalirudin) on background of pretreatment with clopidogrel showed no benefit, with possible exception of high risk ACS.^{10, 66–69} For example, in a 2009 meta-analysis of 16 trials of GP IIb/IIIa inhibitors including 10,085 patients with STEMI, De Luca found they did not reduce 30 day mortality (2.8 vs. 2.9%, $p=0.75$) or reinfarction (1.5 vs. 1.9%, $p=0.22$), but significantly increased major bleeding complications (4.1 vs. 2.7%, $p=0.0004$).⁷⁰ A significant relationship between increased patient risk profile and potential mortality benefit was observed.

The current ACC/AHA Guidelines for PCI, therefore, reflect the paucity of clearly demonstrated benefit of GP IIb/IIIa inhibitors in the current PCI era.² Recommendations vary based on the clinical setting, level of patient risk and anticoagulant used: in the setting of STEMI administration of these agents is a class IIa indication (albeit with evidence level C (consensus) in patients pretreated with clopidogrel); in high-risk troponin-positive non-ST elevation ACS patients who are not adequately pretreated with clopidogrel and not treated with bivalirudin, GP IIb/IIIa inhibitors have a class I indication; in patients undergoing elective PCI these agents have a class IIa or IIb indication without and with pretreatment

with clopidogrel, respectively. There are no explicit recommendations for use of these agents in patients treated with bivalirudin as an anticoagulant. However, they are used provisionally in this setting.

Although multiple evaluations of cost effectiveness of abciximab, eptifibatide and tirofiban have been published, these analyses are based on the older studies of clinical effectiveness.^{71–76} From the positive results of these studies, it appears that in aggregate, use of GP IIb/IIIa inhibitors in addition to heparin alone without routine background DAPT is cost effective. However, it is unclear whether the use of these agents would be cost-effective in the current era of PCI with routine stenting, DAPT and frequent use of bivalirudin as an anticoagulant. For example, when comparing strategies for patients undergoing PCI with stenting based on REPLACE 2, Cohen *et al*⁷⁷ and Summer *et al*⁷⁸ found bivalirudin with provisional GP IIb/IIIa inhibitor to dominate heparin with routine GP IIb/IIIa inhibitor.⁷⁹ Also, in the setting of STEMI, Schwenkglens evaluated cost effectiveness of bivalirudin with provisional use of GP IIb/IIIa inhibitors compared to heparin with routine GP IIb/IIIa on background of aspirin and clopidogrel pretreatment.⁸⁰ The analysis, based on results of the HORIZONS AMI trial, found that in 99.2% of simulation bivalirudin with provisional GP IIb/IIIa had ICERs below £20,000/QALY gained. Similarly, evaluation of this strategy in patients with non-ST elevation ACS based on results of the ACUITY trial found ICER to be £9,906/QALY gained, with 71.2% of simulations the ICER remained under £20,000.⁸¹ The results of these analyses suggest that use of GP IIb/IIIa inhibitors as provisional agents adjunctively with bivalirudin is a more cost-effective strategy than routine use with heparin.

Platelet Function Testing and Genetics

Clinical evaluation of still controversial strategies including on-treatment platelet reactivity guided and genetic testing guided DAPT is currently ongoing. While there has been a preliminary CEA of genotype driven therapy, more definitive analyses of such strategies will need to be conducted if therapeutic benefit of platelet reactivity testing or genotype guided DAPT is shown.⁸²

Conclusions

Overall, the use of DAPT with aspirin and P2Y12 inhibitor in patients undergoing PCI improves ischemic outcomes and appears to be cost-effective. Available studies suggest that newer agents such as prasugrel and ticagrelor are cost-effective alternatives to clopidogrel in the setting of ACS. However, no direct comparison between prasugrel and ticagrelor is available. The use of GP IIb/IIIa inhibitors is changing in the current PCI era, but they appear cost effective as provisional agents used with bivalirudin or when used with heparin in patients not treated with up-front DAPT. There is paucity of evidence for cost-effectiveness of routine use GP IIb/IIIa inhibitors with heparin on background of P2Y12 inhibitor loading, especially in patients undergoing PCI for stable CAD or low risk ACS.

The cost effectiveness of platelet function and genetic testing guided DAPT will need to be evaluated if therapeutic benefit of such strategies is demonstrated. Additionally, optimal duration of DAPT has not yet been definitively established and studies are ongoing to

evaluate regimens as short as 6 months. Should such approaches prove to be clinically acceptable, the cost effective attractiveness of such strategies would strengthen the argument for its implementation. In the era of acute societal awareness of the limited healthcare resources available to treat an unlimited number of ailments, cost-effectiveness analyses continue to be of utmost importance in evaluation of novel therapies, especially in a rapidly evolving field of interventional cardiology.

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Key Points For Decision Makers

- Antiplatelet therapy for PCI appears cost-effective
- A critical component of cost-effectiveness analysis is choosing the most clinically relevant comparator. By its nature, cost-effectiveness analysis offers incremental comparison to a new therapy or service compared to a previous standard. If an inappropriate standard is chosen, a new therapy may incorrectly seem to offer good value.
- With evolution of clinical practice, new studies are required to adequately evaluate new therapies and confirm relevance of older studies

Table 1

Cost effectiveness studies based on CURE and PCI-CURE trials for efficacy estimates.

Author	Study	Comparators	Funding	Health Care System	Year	Description	Findings
Pignone et al ¹⁸	Published literature	Aspirin vs no aspirin for primary prevention	Bayer and CDC	US	2003	Markov model in men, lifetime time horizon	Aspirin is a dominant strategy compared to no aspirin
Greving et al ¹⁹	Published literature	Aspirin vs no aspirin for primary prevention	Netherlands Organization for Health Research and Development	Holland	2005	Markov model, 10 year time horizon	ICER depended on age and gender and overall risk profile, with lower ICER in higher risk populations
Eamshaw et al ²⁰	Published literature	Aspirin vs no aspirin for primary prevention	Bayer and NCI	US	2009	Markov model in men, lifetime time horizon	Aspirin dominates no treatment in men older than 45 years with 10 year CHD risk >10%
Gaspoz et al ²¹	Published literature	Aspirin +/- Clopidogrel vs no therapy for secondary prevention	AHRQ and NHLBI	US	2000	Coronary Heart Disease Policy Model, 25 year time horizon	The ICER for aspirin from current use to all eligible patients is \$11,000/QALY gained. The ICER for clopidogrel in aspirin intolerant is \$31,000/QALY gained. Routine clopidogrel is not favorable, although the ICER is sensitive to the cost of clopidogrel.
Latour-Pérez et al ³³	CURE	Clopidogrel + Aspirin vs Aspirin in ACS	Sanofi	Spain	1999	Markov model; treated for 1 year; societal perspective; lifetime event horizon	ICER €2,000/QALY gained Range €5,000 to €0,000 based on risk
Badia et al ³⁴	CURE	Clopidogrel + Aspirin vs Aspirin in ACS	Sanofi-Aventis + Bristol-Myers Squibb	Spain	2003	Patient-level outcomes and Markov model; treated 1 year; short and long term analyses	ICER €7190 per event avoided short term ICER €8132/LYG long term
Lindgren et al ³⁵	CURE	Clopidogrel + Aspirin vs Aspirin in ACS	Sanofi	Sweden	2000	Markov model; treated x 1 year; payer perspective; lifetime time horizon	ICER €1365/LYG (study patients) ICER €1009/LYG (registry patients)
Lindgren et al ³⁶	PCI-CURE + literature	Clopidogrel for up to 1 year + Aspirin vs Clopidogrel up 4 weeks + Aspirin in ACS	Sanofi-Aventis	Sweden	2004	Markov model; treated x 1 year; societal perspective; lifetime event-horizon	ICER €10,993LYG (direct cost only) ICER €8,127/LYG (with indirect cost)
Weintraub et al ³⁷	CURE	Clopidogrel + Aspirin vs Aspirin in ACS	Sanofi-Aventis	US	2001	Patient-level outcomes; life expectancy estimates; event horizon 1 year;	ICER \$6,318/LYG (Framingham estimate) ICER \$6,475/LYG (Saskatchewan estimate)
Mahoney et al ³⁸	PCI CURE	Clopidogrel for up to 1 year + Aspirin vs Clopidogrel up 4 weeks + Aspirin in ACS	Sanofi-Aventis	US	2001	Patient-level outcomes; US based; life expectancy estimates; event horizon 1 year;	ICER \$2856-\$4775LYG (Overall) ICER dominant-\$935/LYG (Early PCI)
Lamy et al ³⁹	CURE	Clopidogrel + Aspirin vs Aspirin in ACS	Sanofi-Aventis	UK, US, Sweden, France, Canada	2001	Patient-level outcomes; societal perspective; treated for 9 months; event horizon 9 months;	ICER per primary event: £10,366 UK, \$22,484 USA, SKr 127,951 Sweden, €16,186 France, and C\$7973 Canada
Schleinitz et al ⁴⁰	CURE	Clopidogrel + Aspirin vs Aspirin in ACS	NIH + VA	US	2002	Markov model; US based; treated for 1 year; societal perspective; lifetime event horizon	ICER \$15,400/QALY gained
Bruggenjung ⁴¹	CURE	Clopidogrel + Aspirin vs Aspirin in ACS	Sanofi-Aventis	Germany	2005	Markov model; German based; treated x 1 year; payer perspective;	ICER €8,113/LYG

Author	Study	Comparators	Funding	Health Care System	Year	Description	Findings
Kolm et al ⁴²	CURE & PCI CURE	Clopidogrel + Aspirin vs Aspirin in ACS	Sanofi-Aventis	Canada	2003	Patient-level outcomes; treated for 1 year; event horizon 1 year;	ICER <\$10,000 per event prevented ICER <\$4,000/LYG
Gibler et al ⁴⁴	CLARITY	Clopidogrel vs Placebo load in STEMI	NA	US	NA	Patient-level data alongside clinical trial for short term. Simulation lifetime	Short term clopidogrel is dominant. Lifetime <\$6000/LYG
Berg et al ⁴⁵	CLARITY and COMMIT	Clopidogrel vs Placebo in STEMI	NA	Sweden, Germany, France	2005	Markov model.	CLARITY: clopidogrel for up to 1 year dominant in Sweden and France. ICER of €92/LYG in Germany. COMMIT: ICERs were €2772, 4144, and 2786/LYG in Sweden Germany and France
Zhang ⁴⁶	COMMIT	Clopidogrel + aspirin vs Placebo + aspirin in medically managed STEMI	Sanofi-Aventis + Bristol-Myers Squibb	US	2002	Patient level data alongside clinical trial short term. Lifetime model	Short term clopidogrel is a dominate strategy. Lifetime ICER clopidogrel is \$7806/LYG
Beinart ⁴⁹	CREDO	Clopidogrel loading plus 1 year vs clopidogrel for 28 days in PCI	Sanofi-Aventis	US	NA	Patient level data alongside clinical trial, lifetime time horizon	Clopidogrel loading is dominant short term. ICER 3000–5000/LYG over a lifetime.
Cowper ⁵⁰	CREDO + Duke database	Extending clopidogrel for 1 year after PCI vs not extending clopidogrel	AHRQ	US	2000	Simulation	The ICER for extending clopidogrel from one month to one year after PCI was \$15,696/LYG.
Ringborg et al ⁵¹	CREDO	Clopidogrel loading plus 1 year vs clopidogrel for 28 days in PCI	Sanofi-Aventis	Sweden	2004	Markov model	The ICER was €3022/LYG for clopidogrel loading plus 1 year of therapy.
Berg et al ⁵²	PCI-CURE, CREDO, CLARITY, Swedish registries	Prolonged treatment with clopidogrel after PCI vs no prolonged treatment	NA	Sweden, Germany, France	2006	Meta-analysis, Markov model	Pre-treatment with clopidogrel compared with aspirin alone is dominant. Long-term clopidogrel compared with 1-month treatment years ICERs of €4225/QALY to 7871/QALY.
Mahoney et al ⁵⁴	TRITON	Prasugrel vs Clopidogrel in ACS	Eli Lilly	US	2005	Patient level data alongside clinical trial, lifetime time horizon	The ICER was \$9727/LYG for prasugrel compared to clopidogrel.
Mauskopf et al ⁵⁵	TRITON/administrative database	Prasugrel vs Clopidogrel in ACS	Eli Lilly	US managed care	2009	Simulation	Prasugrel is dominant in ACS patients, results sensitive to drug prices.
Nikolic et al ⁵⁷	PLATO	Ticagrelor vs Clopidogrel in ACS	AstraZeneca	Sweden	2010	Markov model, lifetime time horizon	Over a lifetime, the ICER was €2753/QALY gained for ticagrelor compared to clopidogrel.
Cohen et al ⁷⁷	REPLACE-2	Bivalirudin with provisional GP IIb/IIIa inhibitor vs UFH GP IIb/IIIa in non-emergent PCI	NA	US	2002	Patient level data alongside clinical trial, 30 day time horizon	Bivalirudin with provisional GP IIb/IIIa inhibitor costs less with no difference in clinical outcome compared to UFH GP IIb/IIIa
Summers et al ⁷⁸	REPLACE-2 plus literature	Bivalirudin with provisional GP IIb/IIIa inhibitor vs UFH GP IIb/IIIa in non-emergent PCI	NA	US	NA	Simulation	Bivalirudin with provisional GP IIb/IIIa inhibitor dominates UFH GP IIb/IIIa inhibitor. The results are sensitive to how much bivalirudin is given
Schwenkelenks et al ⁸⁰	HORIZONS-AMI	Bivalirudin vs heparin and GP IIb/IIIa inhibitor in primary PCI for STEMI	The Medicines Company	United Kingdom	2009–2010	Markov model, lifetime time horizon.	Bivalirudin dominated UFH with GP IIb-IIIa inhibitor

Author	Study	Comparators	Funding	Health Care System	Year	Description	Findings
Schwenckenks et al ⁸¹	ACUTY and GRACE UK dataset	Bivalirudin vs heparin and GP IIb/IIIa inhibitor for invasive management of non-STEMI ACS	The Medicines Company	United Kingdom	2008	Markov model, lifetime time horizon.	The ICER for Bivalirudin vs UFH with GP IIb-IIIa inhibitor was £9,906/QALY gained
Crespin et al ⁸²	PLATO plus claims database	Ticagrelor vs Genotype-Driven Antiplatelet Therapy for Secondary Prevention after ACS	NIA and NIGMS	US	2009	Markov model, 5 year time horizon	The ICER for ticagrelor compared to genotype-driven treatment was \$10,059/QALY gained, and was sensitive to the price of ticagrelor

Abbreviations: ACS: acute coronary syndrome, AHRQ: Agency for Health Research and Quality, CDC: Centers for Disease Control and Prevention, ICER: incremental cost effectiveness ratio, LYG: Life year gained, NA: not available, NCI: National Cancer Institute, NHLBI: National Heart Lung and Blood Institute, NIA: National Institute of Aging, NIGMS: National Institute of General Medical Sciences, PCI: percutaneous coronary intervention, QALY: quality adjusted life year, STEMI: ST elevation myocardial infarction, UFH: unfractionated heparin