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Cost Effectiveness of Antiplatelet and Antithrombotic Therapy in The Setting of Acute Coronary Syndrome: Current Perspective and Literature Review

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Abstract

Acute Coronary Syndromes are associated with high rates of morbidity and mortality. The advances of antiplatelet and anticoagulation therapy over several years time have result in improved in cardiac outcomes, but with increased health care costs. Multiple cost effectiveness studies have been performed to evaluate the use of available antiplatelet agents and anticoagulation in the setting of both ST Elevation myocardial infarction (STEMI) and Non-ST Elevation Acute Coronary Syndrome (NSTEMI-ACS). Early on the use of GPI prove to be economically attractive in the management of ACS, however the introduction of P2Y₁₂ receptor antagonist limited their use to a bail out agents in complex interventions. Generic clopidogrel is probably still an economically attractive P2Y₁₂ receptor antagonist choice especially in low risk ACS, while both ticagrelor and prasugrel present an economically attractive alternative option especially in high risk ACS and patients at risk for stent thrombosis. While enoxaparin presents an economically dominant alternative to heparin in NSTEMI-ACS, its role in STEMI in the contemporary era is unclear. During PCI, bivalirudin monotherapy was shown to be an economically dominant alternative to the combination of heparin and GPI in ACS. However, new studies may suggest that using heparin monotherapy may offer an attractive alternative. The comparative and cost effectiveness of different combinations of antiplatelet and antithrombotic therapy will be the focus of future expected clinical and economic assessments.

1. Introduction

Acute coronary syndromes (ACS) refer to a spectrum of clinical presentations that results from decreased blood flow in the coronary arteries; the decrease in blood flow may range from a total or subtotal occlusion causing ST segment elevation myocardial infarction (STEMI) to a significant, but incomplete compromise of blood flow presenting as a Non-ST Segment Elevation Acute Coronary Syndrome (NSTEMI-ACS) which include Non-ST Elevation Myocardial Infarction (NSTEMI) and Unstable Angina (UA). (1) ACS is one of

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the most common and costly hospital admissions in the United States (US) with a yearly estimate of 1.365 million hospitalizations associated with an approximate cost of \$US 150 billion. (2, 3) Similarly, ACS is associated with very high cost in Europe; this cost varies from around 1.9 billion Euros in the United Kingdom, 1.3 billion Euros in France, 3.3 billion Euros in Germany, 3.1 billion Euros in Italy and 1.0 billion Euros in Spain. (4)

The management of ACS has undergone major changes after the introduction of percutaneous coronary intervention (PCI). While thrombolytic therapy used to be the primary choice of emergent reperfusion in STEMI, primary PCI within 120 minutes of presentation became the standard of care for reperfusion in STEMI. Similarly the management of NSTEMI-ACS changed dramatically from an era where only 30% of these patients were revascularized to a new standard of care where early invasive strategy with PCI done in the first 48 hours when feasible (80-85%). (5) This shift was associated with major changes in the pharmacology used in this setting. The choice of antiplatelet agent used in addition to aspirin moved from the use of the platelet glycoprotein IIb/IIIa receptor inhibitors (GPI) exclusively during the 1990's to the adoption of P2Y₁₂ receptor antagonists use with the introduction of clopidogrel (1997), followed by prasugrel (2009) and ticagrelor (2011). Similarly, the choice of antithrombotic agent has changed from exclusive use of heparin to include the use of low molecular weight heparin (LMWH) and bivalirudin. The choice of antithrombotic, antiplatelet or combination during the PCI varies from the combination of heparin and GPI at the beginning to the debate of using bivalirudin or heparin alone recently.

The availability of many antiplatelet and antithrombotic agents as well as the countless possibilities for combination of these agents with the potential benefits and risks of each in the setting of ACS make it challenging for physicians to choose wisely. In this paper we review the cost-effectiveness of anti-platelet and anti-thrombotic agents. To better understand this literature, we first a brief perspective on cost effectiveness and decision-making.

2. Cost Effectiveness Analysis and Decision Making

The primary goal of cost-effectiveness analysis is to evaluate different health care intervention options in common terms so that policy and other decision makers can be informed of the most efficient method of producing extra health benefits from among the alternative ways that health care dollars can be distributed. The metric used to assess incremental cost effectiveness is the Incremental Cost-effectiveness Ratio (ICER). An ICER is defined as the ratio of incremental costs to incremental health benefits of treatment 1 compared to treatment 2, or $ICER = (C1 - C2)/(HB1 - HB2)$; where C1 and C2 are cost for treatment 1 and 2, respectively and HB is the health benefit of treatment 1 and 2, respectively. (6)

The ICER defines the cost that should be assumed for gaining one unit of output. In other words, if one of the alternatives is the usual practice, then it will tell us how much it will cost to gain a unit of outcome when moving from the usual practice to a new alternative. The health benefit may be measured in any sensible unit, such number of MIs averted, but

most studies use the conventional option of measuring clinical benefits as either the number of added life-years (LYs) or quality-adjusted life years (QALYs). (6, 7) Both of these approaches require estimation of life expectancy with and without the intervention being considered.

When assessing whether a treatment is cost effective, a requirement for threshold can arise when policy makers seek a benchmark to compare different treatments and judge different studies. In general, wealthier countries may be willing to pay more (i.e. accept higher threshold) for a given treatment than poorer countries. (6, 8) In the United States, a cost-effectiveness ratio $< \$50,000$ per LY or QALY is frequently regarded as economically attractive, in part because it approximates the cost of providing chronic hemodialysis to patients with renal failure, at a cost that meets willingness-to-pay through Medicare. (6)

Conversely, a cost-effectiveness ratio of $> \$100,000$ per added LY or QALY is frequently regarded as economically unattractive. The range between these two benchmarks is the gray zone in which there is no consensus on whether a treatment is economically acceptable. (6) However, these benchmarks in the US are really outdated, furthermore, assigning the same ICER threshold for different treatment in wide range of diseases and different burden of this disease may not be reasonable. Some countries may assign a general threshold for most cases, but allow for a higher threshold for treatment that relieves considerable burden of illness, i.e. “the rule of rescue”. For example in Netherlands, the average acceptable ICER is around $\text{€}20,000$, but an ICER of $\text{€}80,000$ per QALY will be acceptable for illnesses associated with a considerable disease burden. (9) Similarly in Great Britain the limit of acceptable ICER varies between $\text{£}20,000$ and $\text{£}30,000$ depending on the burden of the disease. (10)

3. Literature Search Methodology

Relevant studies were identified through electronic searches of MEDLINE and the Cochrane Central Register of Controlled Trials databases. The search strategy used the terms “Cost Effectiveness” “Antiplatelet” “Antithrombotic” “Anticoagulation” paired with “Acute Coronary Syndrome” “Non ST Elevation MI”, and “ST Elevation MI”. In addition, we searched bibliographies of relevant studies, reviews and editorial letters for articles that are written in English. Among 3026 articles, 88 were reviewed for the purpose of the review and 49 were used in the final version. Our choice for cost effectiveness studies included both cost-effectiveness simulations using Markov models, and cost effectiveness performed with randomized controlled trials (RCTs). While our original intention was to include cost effectiveness that were derived from observational studies, we ended up excluding these as they were very few and did not add to the content of our review.

4. Cost Effectiveness of Reperfusion in ST Segment Elevation Myocardial Infarction (STEMI)

The management of STEMI witnessed major changes after the introduction of PCI. While thrombolysis was considered the mainstay therapy early on, primary PCI has become the standard of care currently based on multiple trials that compared the two strategies. A meta-

analysis of 22 pooled randomized controlled trials (RCTs) comparing PCI with thrombolysis showed that primary PCI was associated with a significant reduction in 30-day mortality in both patients who presented early and in those who presented longer than 4 hours after symptom onset. (11) PCI was associated with a higher early reperfusion rate and a higher proportion of patients achieving TIMI grade 3 flow.(12)

Of the many trials comparing both strategies, economic assessment was available from two RCTs. The first of these is the Comparison of Angioplasty and Pre-hospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) trial that compared primary coronary angiography (PCA) to pre-hospital thrombolysis (PHT) in patients with STEMI. The thrombolysis strategy in this trial included the use of rescue PCI, as needed. The one-year primary end point event-rate (death, MI, and stroke) was not different after PCA or PHT (14% vs. 16.4%, $p = \text{NS}$). Costs were lower in the PCA group either during the in-hospital period (8,287 vs. 9,170 \$, $p = 0.0001$) and after one-year follow-up, in relation to a higher rate of subsequent revascularizations in the PHT group (49% vs. 23%, $p < 0.01$) and longer hospital stay (10 vs. 9.1 days, $p = 0.03$). (13) It should be noticed that these data are derived from a trial performed between 1997 and 2000 with a very long hospital stay that is not pertinent to the current PCI care.

The Swedish Early Decision reperfusion Study (SWEDES) trial, reported in 2010, randomized 205 STEMI patients to be managed either with primary PCI with adjunctive enoxaparin and abciximab or with enoxaparin followed by reteplase. The clinical outcome did not differ significantly between the groups. Compared to reteplase arm, PCI use was associated with higher cost of interventions (\$4,602 vs. \$3,807; $P = .047$) and cost of drugs (\$1,309 vs. \$1,202; $P = .001$), but with lower of hospitalization (\$7,344 vs. \$9,278; $P = .025$). At 1 year there was a trend towards lower total cost and better quality-adjusted survival with PCI (\$25,315 and 0.759 added LY PCI vs. \$27,819 and 0.728 added LY reteplase; $P = \text{NS}$). (14)

These studies led to a shift in the primary reperfusion strategy in the US. It is estimated that primary PCI is used in 85% of all STEMI cases that undergo reperfusion, with thrombolytic agents used in only 9% and the combination of thrombolytic agents with PCI in 6%. (15) This shift was associated with changes in the antiplatelet and anticoagulation agents used.

5. Cost Effectiveness of Early Invasive versus Early Conservative Strategies in Patients with Non-ST Segment Elevation ACS (NSTEMI-ACS)

The expansion of PCI use led to a gradual shift in the management of NSTEMI-ACS as well. While initially many patients were treated only medically with intervention reserved for those with recurrent ischemia, a more aggressive approach with early revascularization started to emerge as an alternative choice. The timing of the procedure also shifted over time as well. This time shift can be seen with the change in the definition of an early invasive strategy in different trials comparing early invasive and conservative approaches from 7 days in FRISC II to 2 days in TACTICS-TIMI 18

The Fragmin and Revascularization during Instability in Coronary Artery Disease II (FRISC II) trial compared an early invasive with an early non-invasive strategy in 2457 patients with NSTEMI-ACS. The results showed that the early invasive strategy was associated with a significant reduction in the composite of death or MI (10.4% vs. 14.1%; $p=0.005$). There were also reductions in readmission (37% vs. 57%; $P < 0.001$) and revascularization after the initial admission with the early invasive strategy (7.5% vs. 31%; $P < 0.01$). (16)

The economic analysis of FRISC II that was published in 2002 showed that at the end of 1 year, the early invasive strategy was associated with a \$3511 [23,876 Swedish Koruna (SEK)] higher cost compared to the non-invasive arm. The ICER for choosing the invasive instead of the non-invasive strategy was substantially high with \$206,470 per avoided death and \$94,852 per avoided death or MI. (17) However, it should be noted that what was called an early invasive approach in this trial was not associated with an early intervention. In contrast, the intervention was done within one week and was associated with longer hospital stay (12 days vs. 8 day). This trial does not represent the current early invasive strategy where PCI is performed within 48 hours.

Reflecting more contemporary practice, the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy (TACTICS-TIMI 18) trial randomized 2220 patients with UA/NSTEMI to either an early invasive strategy with routine catheterization and revascularization as appropriate within 48 hours, or to a conservative, or “selective invasive” strategy, with catheterization performed only if the patient had objective evidence of recurrent ischemia or a positive stress test. All patients were provided with appropriate medical therapy. The early strategy was associated with a significant reduction in the composite of death and MI (7.3 % vs. 9.5 %; $P < 0.05$). (18)

The economic analysis of the trial published in 2002 showed that the early invasive arm had higher initial costs (\$15,714 vs. \$14,047) but lower follow-up costs out to 6 months (\$6098 vs. \$7180) with similar cumulative 6-month costs (\$19,780 vs. \$19,111). Therefore, the early invasive strategy was shown to be cost effective with estimated ICER of \$13,000 per LY gained. (19) This data showed that adapting an early invasive approach with the intervention specifically done in the first 48 hours was an economically attractive option.

Similarly to the shift seen in the management of STEMI. Primary PCI shifted as well from being used only for residual or recurrent ischemia to a standard of care where PCI is done in the first 48 hours in approximately 80%-85% of the cases. (5) This shift was associated also with significant changes in the choice and sometimes in the duration of both antiplatelet and anticoagulation.

6. Cost Effectiveness of Antiplatelet Therapy in ACS

The benefit of antiplatelet therapy in the setting of acute coronary syndrome was established first with aspirin in the ISIS-2 trial (Second International Study of Infarct Survival-2 Trial). Aspirin, an inhibitor of platelet aggregation via inhibition of thromboxane A_2 , was found to be as effective as streptokinase in reducing mortality when used alone, and with better outcomes while using both in combination in the setting of STEMI. (20) This trial demonstrated the importance of platelet aggregation in the setting of acute coronary

syndrome and the potential benefit of using even more potent platelets activation inhibitors in this setting. This led first to the introduction of intravenous GPI in the management of ACS followed later on by the introduction of oral P2Y₁₂ receptor antagonists. Table-1 shows the comparative and cost effectiveness of each of the currently available agents.

6.1 Cost Effectiveness of Platelet Glycoprotein IIb/IIIa Receptor Inhibitors

Many trials evaluated the clinical and economic impact of using GPIs in the setting of ACS as well as after coronary interventions. One of the earliest of these trials is The Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis (RESTORE) trial. In this trial 2197 patients presenting with acute coronary syndrome and undergoing coronary intervention (balloon angioplasty or directional atherectomy) within 72 hours of presentation were randomized to either tirofiban or placebo. The results showed that the use of tirofiban was associated with a significant reduction in the composite of death, MI and target vessel revascularization (TVR) at two days (8% vs. 12%, $p = 0.002$). This difference was not statistically significant at 30 days (10.3 % vs. 12.2%; $P=0.16$). There was no significant difference in major bleeding rate between the two groups (5.3% vs. 3.7%; $P=0.096$). (21) The economic evaluation of RESTORE published in 1998 showed that the cost of tirofiban use was not significantly higher than placebo either as in-hospital cost (\$12,230 $\pm$ 5,527 t vs. \$12,145 $\pm$ 5,882; $P = 0.75$) or at 30 days (\$12,446 $\pm$ 5,814 vs. \$12,402 $\pm$ 6,147; $P = 0.87$). (22)

Another trial evaluating the efficacy of GPI is The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy [PURSUIT] trial. In this trial 10,948 patients with ischemic chest pain were randomized to receive a bolus and infusion of either eptifibatide or placebo. For patients undergoing percutaneous revascularization within 72 hours after randomization, eptifibatide use was associated with a significant reduction in the incidence of the composite of death or MI at 30 days (11.6 % vs. 15,6%; $P=0.01$). (23) Bleeding requiring transfusion was more common among patients treated with eptifibatide [11.6 % vs. 9.2 %; $P<0.001$]. (23) An economic evaluation of the 3522 US patients enrolled in PURSUIT, published in 2000, showed that the use of eptifibatide was associated with a non-statistically significant \$372 cost advantage. The ICER for eptifibatide therapy was \$16,491 per LY (Life-Years) gained and \$19,693 per QALY (quality adjusted life years) gained. (24)

In summary, the use of GPI inhibitors was shown in the early days to be an economically attractive option in the setting of ACS, when no other options were available in addition to aspirin in this patient population with highly aggregated platelets activity. However, It should be noticed that the data from both RESTORE and PUSUIT trials are irrelevant to the contemporary era after the introduction of P2Y₁₂ receptor antagonists and bivalirudin. The use of GPI is confined now to high-risk patients as a bail out agent in addition to all other agents.

6.2 Cost Effectiveness of P2Y₁₂ Receptor Antagonists

The benefit of dual antiplatelet therapy (DAPT) was established with data showing that the combination of aspirin and ticlopidine was associated with higher platelets inhibition than

aspirin alone in patients with CAD treated with PCI. (25) However, ticlopidine use was associated with severe side effects. Subsequently, clopidogrel, a P2Y₁₂ receptor antagonist, was studied in multiple clinical trials and proved to be an effective option for DAPT with fewer side effects than ticlopidine. However, the use of clopidogrel was still associated with substantial interpatient variability and a delayed onset of action. The reduced pharmacologic response in some patients to clopidogrel was associated with increased risk for adverse clinical events, including MI and stent thrombosis. This limitation of clopidogrel led to the introduction of the more potent antiplatelet agents such as prasugrel and ticagrelor.

Several trials have evaluated the economics of using oral P2Y₁₂ receptor antagonist after PCI. The PCI-CURE substudy of the Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE) trial showed that the use of clopidogrel was associated with a significant reduction of the composite of cardiovascular death, MI, or urgent TVR at 30 days (4.5% vs. 6.4%; P=0.03). Long-term administration of clopidogrel after PCI was associated with a lower rate of cardiovascular death, MI, or any revascularisation (p=0.03) and with 31% reduction cardiovascular death or MI (p=0.002). There was no significant difference in major bleeding between the groups (p=0.64). (26)

The cost effectiveness analysis of CURE-PCI, published in 2006, showed that clopidogrel was associated with a higher average cost at 1 year of \$253 - \$423. For patients who underwent PCI during the initial hospitalization, the difference was less substantial and ranged from \$155 lower to \$90 higher with clopidogrel. Clopidogrel proved to be a very attractive option with ICER of \$2856 to \$4775 per LY without PCI and a dominant strategy in the early PCI subgroup. (27) Currently with generic clopidogrel and the adoption of early PCI strategy, the use of DAPT with clopidogrel will remain dominant when compared to ASA alone.

After clopidogrel was established as both a clinically effective and cost-effective strategy for PCI, the role of the novel ADP receptor antagonists remained in question. The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI-38) randomized 13,608 patients with moderate-to-high-risk ACS to receive either prasugrel or clopidogrel at the time of PCI. The study showed that prasugrel was associated with a significant reduction in the combined endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke (9.9% vs. 12.1%; P < 0.001), as well as a significant reduction in urgent TVR (2.5% vs. 3.7%; P<0.001) and stent thrombosis (1.1% vs. 2.4%; P<0.001). Patients receiving prasugrel, however, had significantly higher rates of major bleeding (2.4% prasugrel vs. 1.8% clopidogrel, P < 0.03). (28)

The cost-effectiveness analysis of the TRITON-TIMI-38 trial published in 2010, showed that over 14.7 months follow-up, prasugrel was associated with a net savings of \$221 per patient when compared to clopidogrel (\$ 26,067 vs. \$26,28). This saving was attributed to the lower rate of rehospitalizations involving PCI. Prasugrel was associated with life expectancy gains of 0.102 years (95% CI [0.030-0.180]), primarily because of the decreased rate of nonfatal MI. Prasugrel was shown to be a dominant strategy. (29) This impact was more prominent in males, diabetic patients, ST-elevation MI and in patients with Age <75 y,

body weight ≥ 60 kg, and no history of stroke/TIA. The impact was less prominent in females, non-diabetic patients and those presenting with NSTEMI or have a history of stroke/TIA. In patients with Age ≥ 75 y, body weight < 60 kg, and history of stroke/TIA, prasugrel was not associated with improvement in the clinical outcomes and was associated with similar costs. Figure-1 summarizes the cost assessment of TRITON-TIMI-38 Trial. However, this comparison was done between prasugrel and “branded” rather than lower cost “generic” clopidogrel. Thus, it is unclear whether prasugrel will remain an economically attractive alternative in comparison to “generic” clopidogrel.

The Study of Platelet Inhibition and Patient Outcomes (PLATO) randomized 18,624 patients with moderate-to-high-risk ACS to receive either ticagrelor or clopidogrel upstream or at the time of PCI. The study showed that the use of ticagrelor was associated with a significant reduction in the composite of death from vascular causes, MI, or stroke (9.8% vs. 11.7%; $P<0.001$). This reduction was significant as well in cardiovascular death (4.0% vs. 5.1%; $P=0.001$) and MI (5.8% vs. 6.9%; $P=0.005$), but not with stroke (1.5% vs. 1.3%; $P=0.22$). The use of Ticagrelor was not associated with an increase risk of major bleeding (11.6% Ticagrelor vs. 11.2% clopidogrel; $P=0.43$). (30)

Economic evaluation of PLATO, reported in 2013, comparing ticagrelor to generic clopidogrel showed that even though ticagrelor use was associated with higher costs of €362, that was balanced by a QALY gain of 0.13 compared with generic clopidogrel at 1 year. Therefore the use of ticagrelor was an economically attractive option with an ICER of €2753 per QALY gained and €372 per LY gained. (31) The attractiveness of ticagrelor is more prominent in patients with STEMI, NSTEMI, diabetic patients and to lesser degree in those presenting with unstable angina. Nonetheless, the ICER for both QALY and LY was still economically attractive in all the ACS patients enrolled in PLATO. Figure-2 summarizes the cost effectiveness of PLATO trial.

In summary, the use of DAPT including oral P2Y₁₂ receptor antagonists is the standard of care as it represents the most reasonable option both clinically and economically. Deciding which agent should be used in the current era of generic clopidogrel in the US is one the most debatable discussions in the interventional community. While it is well accepted that both ticagrelor and prasugrel offer a superior clinical outcomes when compared to clopidogrel, the use of both agents in the setting of ACS remains less common in the US compared to Europe. As despite that studies showed that both drugs are economically attractive options, their use is associated with a considerable economic burden on some patients in the US who may not have the appropriate insurance to cover the extra cost of these medications in comparison to generic clopidogrel. If the use of these agents is not feasible in all ACS patients, a choice can be made to use these drugs in the patients who are likely to benefit the most. This group can be identified based on available evidence from randomized control trials. For example, prasugrel use probably is more useful than clopidogrel in males, diabetics, younger patients (<65 years old) and those with GFR >60 . (28) Similarly, ticagrelor use probably offer better outcomes than that of clopidogrel in those presenting with STEMI and NSTEMI (but not UA).

7. Cost Effectiveness of Antithrombotic use in Acute Coronary Syndrome

The benefit of using unfractionated heparin (UFH) in addition to antiplatelet therapy in reducing the incidence of death and recurrent MI in the setting of ACS has been well established. (32, 33). However the use of UFH is associated with an unpredictable anticoagulant response secondary to its neutralization by protein binding and activated platelets. Furthermore, the discontinuation of unfractionated heparin is associated with increased incidence of cardiac events. (34) Therefore, several studies were performed to demonstrate the benefit of more predictable anticoagulation using enoxaparin/low molecular weight heparin (LWMH), anti-Xa inhibitors, and direct thrombin inhibitors.

7.1 Cost Effectiveness of Enoxaparin (LWMH)

The first comparison between unfractionated heparin and enoxaparin in the setting of non-STEMI ACS came from the Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events (ESSENCE) trial. This trial randomized 3171 patients with non-STEMI ACS to receive enoxaparin or continuous intravenous UFH. The use of enoxaparin was associated with a significant decrease in the incidence of the composite of death, MI, or recurrent angina at 30 days (19.8% vs. 23.3%, $P=0.016$), as well as the need for revascularization at 30 days (27.1% vs. 32.2%, $P=0.001$). Enoxaparin was associated with an increase in all bleeding (18.4 % vs. 14.2 %, $P=0.001$) primarily because of ecchymoses at injection sites, but a non-significant difference in the incidence of major bleeding (6.5% vs. 7.0 %, $P=NS$). (34) The economic evaluation of ESSENCE, reported in 1998, showed that the use of enoxaparin was associated with a net cumulative cost savings of \$1172 ($P=0.04$) at 30 days and was therefore dominant strategy. (35) The cost of enoxaparin in the contemporary era is even lower than when this comparison was done, and therefore it is expected that the results are still pertinent.

Data comparing enoxaparin and UFH in the setting of STEMI comes from the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment (ExTRACT)–Thrombolysis in Myocardial Infarction (TIMI) 25 study. ExTRACT-TIMI 25 randomly assigned 20,506 patients with STEMI who were scheduled to undergo fibrinolysis to receive enoxaparin throughout the index hospitalization or weight-based unfractionated heparin for at least 48 hours. The use of enoxaparin was associated with a significant reduction in the incidence of the composite of death, nonfatal MI, or urgent revascularization (11.7% vs. 14.5 %; $P<0.001$). However enoxaparin use was associated with increased incidence of major bleeding (2.1% vs. 1.4 %; $P<0.001$). (36) Cost effectiveness analysis of ExTRACT-TIMI 25 reported in 2009 showed that enoxaparin use in STEMI was associated with a higher cost at 30 days (\$102) and lifetime cost (\$1,207). However, patients receiving enoxaparin gained an average of 0.12 life-years relative to patients given UFH. Enoxaparin was shown to be an economically attractive option with an ICER of \$5,700 per LY gained. (37) However, these data may not represent the contemporary practice where patients are managed primarily with primary PCI instead of fibrinolytic therapy.

7.2 Cost Effectiveness of Anti-Xa Inhibitors

The impact of anti-Xa inhibitors fondaparinux on NSTEMI-ACS was evaluated in the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) trial. This trial randomized 20,078 NSTEMI ACS patients to fondaparinux or enoxaparin and reported no significant difference in the composite endpoint of death, MI, or refractory ischemia at 9 days (5.8% vs. 5.7%; $P=NS$), but fondaparinux did significantly reduce major bleeding events at 9 days (2.2% vs. 4.1 %; $P<0.001$). (38) The economic evaluation of this trial in 2009 showed that using fondaparinux instead of enoxaparin was associated with a cost savings of \$547 per patient at 180 days, and long-term cost-effectiveness analysis found fondaparinux to be the dominant therapy. (39)

The Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-6) trial reported in 2009 evaluated the role of fondaparinux in STEMI. While fondaparinux was superior to unfractionated heparin in preventing death or MI at 30 days in those receiving thrombolytic therapy ($HR=0.79$; $P=0.003$), there was a higher incidence of guiding catheter thrombosis in the PCI cohort treated with fondaparinux compared to control ($n=22$ vs. $n=0$, $p<0.001$). (40) This finding made the use of this drug harmful with PCI, and the drug not becoming the standard of care for the management of both STEMI and NSTEMI-ACS.

7.3 Cost Effectiveness of Direct Thrombin Inhibitors

The Acute Catheterization and Urgent Intervention Triage strategY (ACUITY) trial randomized 13,819 patients with NSTEMI-ACS to one of three antithrombotic regimens: unfractionated heparin or enoxaparin plus a GPI, bivalirudin plus a GPI or bivalirudin monotherapy. The results showed that bivalirudin monotherapy when compared to heparin plus GPI was associated with a noninferior rate of the composite of death, MI, or unplanned revascularization (9% vs. 8%.; $P=0.45$), MI (6% vs. 6%; $P=0.19$) and unplanned revascularization (3% vs. 3%; $P=0.87$). However the bivalirudin monotherapy was associated significantly reduced rates of major bleeding (3.0% vs. 5.7%; $P<0.001$). There was no difference in any of the outcomes between the use of unfractionated heparin or enoxaparin plus a GPI and that of bivalirudin plus a GPI. (41)

The economic evaluation of the US Cohort of the ACUITY trial, reported in 2008, showed that despite the higher drug cost of bivalirudin, the cumulative hospital stay costs were lowest with bivalirudin monotherapy (mean difference range: \$184 to \$1,081, $p < 0.001$ for overall comparison) with cost savings extending out to 30 days (mean difference range: \$123 to \$938, $p = 0.005$). This saving was primarily due to less major and minor bleeding with bivalirudin (\$8,658/event and \$2,282/event, respectively).(42) Figure 3 summarizes the cost assessment of the ACUITY trial.

The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial randomized 3602 patients with STEMI who presented within 12 hours after the onset of symptoms and who were undergoing primary PCI to treatment with heparin plus a GPI or to treatment with bivalirudin alone. Similar to the findings in ACUITY, the use of bivalirudin monotherapy was associated with reduced 30-

day rate of net composite of major bleeding and major adverse cardiovascular events (MACCE), including death, MI, TVR, and stroke (9.2% vs. 12%; $P=0.005$), lower rate of major bleeding (4.9% vs. 8.3%; $P<0.001$), lower 30-day cardiac death (1.8% vs. 2.9%; $P=0.03$) and death from all causes (2.1% vs. 3.1%; $P=0.047$). (43) The economic evaluation of the HORIZONS-AMI trial, reported in 2012, showed that the use of bivalirudin monotherapy was associated with a lifetime savings of £267 (£12 843 vs. £13 110). Probabilistic analysis showed that bivalirudin use was associated with higher quality-adjusted survival and lower costs in 95.0% of simulation runs. In 99.2%, cost-effectiveness was better than £20 000 per QALY gained, suggesting that bivalirudin monotherapy is cost effective strategy when compared to heparin and GPI. (44) Figure 4 summarizes The Cost Assessment Of The HORIZONS-AMI Trial.

However, data from both ACUITY and HORIZONS-AMI did not utilize a treatment arm with heparin monotherapy. It stands to reason that heparin monotherapy may be as effective, if not more effective than bivalirudin monotherapy at a decreased cost. The How Effective Are Antithrombotic Therapies in Primary PCI (HEAT-PPCI) trial that randomly assigned 1917 STEMI patients undergoing emergency angiography to either UFH or bivalirudin showed that the use of bivalirudin compared to heparin was associated with higher incidence of the primary composite outcome of death, MI, CVA and TVR (8.7% vs. 5.7%; $P=0.01$) without changing the incidence of major bleeding (3.5% vs. 3.1%; $P=0.59$). (45) The cost analysis of this trial has not been reported yet; however, heparin is less expensive than bivalirudin and giving that its use is associated with lower cost and better outcomes without increasing the risk of complications, heparin will probably be a dominant strategy according to this trial

On the other hand, the Bivalirudin in acute myocardial Infarction vs. Glycoprotein IIb/IIIa and Heparin Trial (BRIGHT Trial) showed contrasting results to those of HEAT-PPCI. In this trial 2194 patients were randomized in a 1:1:1 fashion to receive either bivalirudin alone, heparin alone, or heparin + tirofiban. The results showed that the composite 30-day net adverse clinical event (NACE) endpoint (MACCE + bleeding) was lower in the bivalirudin arm compared with both heparin monotherapy and heparin + tirofiban arms (8.8% vs. 13.2% vs. 17%, $p < 0.001$). This was driven predominantly by a reduction in the risk of Bleeding Academic Research Consortium (BARC) 3-5 (major) bleeding (0.5% vs. 1.5% vs. 2.1%, $p = 0.04$) and BARC 2-5 bleeding (1.2% vs. 3.6% vs. 5.1%, $p < 0.001$). Stent thrombosis rates at 30 days were similar (0.6% vs. 0.9% vs. 0.7%, $p = 0.77$). Similarly, at 1 year, NACE rates were lowest in the bivalirudin arm (12.8% vs. 16.5% vs. 20.5%, $p < 0.001$); MACCE rates were similar (6.7% vs. 7.3% vs. 6.8%, $p = 0.9$). (46) The cost effectiveness data for this trial has been reported yet. A cost effectiveness comparison between bivalirudin monotherapy and heparin monotherapy will be crucial for decision makers especially giving the conflicting clinical outcomes and huge discrepancy of the cost of both strategies.

In summary, the choice of anticoagulation in the setting ACS may differ depending on many factors including the presentation (STEMI vs. NSTEMI-ACS) and the invasive approach. As while multiple studies showed that the use of more predictable anticoagulation with enoxaparin in the medical management of NSTEMI-ACS was associated with cost saving when compared to unfractionated heparin, these economic comparison are based on a study where

only 26%-32% underwent coronary revascularization (with only 18-22% of patients undergoing percutaneous transluminal coronary angioplasty (PTCA)). In fact, a part of the cost saving with enoxaparin was related to a lower rate of both diagnostic catheterization and PTCA in the enoxaparin group. Furthermore, the revascularization in these patients was done in average within 6 days. (34) Therefore, whether enoxaparin is still necessarily more cost effective in the contemporary era with early revascularization done in the first 48 hours and more potent antiplatelet agents being used is debatable. As for fondaparinux, the higher incidence of catheter thrombosis diminished its use in NSTEMI-ACS to a great extent. On the other hand, the use of enoxaparin in STEMI was not cost saving, but was still an attractive economical choice. However, giving the improvement in door to balloon time and the increase evidence of potential benefit of UH in PCI, and the potential increase risk of bleeding reported with LMWH, the use of LMWH in STEMI may be impractical.

During primary PCI, the use of bivalirudin monotherapy seems to be a more attractive option than the combined use of UH or enoxaparin with GPI in both NSTEMI-ACS and STEMI. Cost effectiveness analysis showed that bivalirudin is a dominant strategy. This led to increase adoption of bivalirudin use in the US and further decline in the routine use of GPI. However, there is an argument that the use of heparin monotherapy might be an attractive alternative to bivalirudin monotherapy both clinically and economically. This was supported with HEAT-PPCI trial and a large meta-analysis that showed heparin to be superior to bivalirudin. (45, 47) However, another RCT (BRIGHT Trial) and a meta-analysis using RCTs data showed that bivalirudin was associated with similar efficacy outcomes with lower rate of bleeding. (46, 48) The debate on the appropriate anticoagulation use in ACS will continue for a while and cost effectiveness comparing both agents might offer an insight to direct the decision.

8. Cost Effectiveness of Different Antiplatelet and Anticoagulation agents in ACS

Another aspect of the current debate in the interventional community is related to the choice of the best combination of available antiplatelet and anticoagulation that can offer the best results clinically and economically. The only data from RCT that address this important issue in the setting of ACS comes from The Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 study that was reported recently in 2014. The trial originally aimed to randomize 1240 STEMI patients to prasugrel plus bivalirudin or clopidogrel plus heparin. The study was stopped prematurely after enrolling 548 patients and showed no difference between prasugrel plus bivalirudin and clopidogrel plus heparin in NACE (15.6% vs. 14.5%; $P = 0.68$), MACCE (4.8% vs. 5.5%; $P = 0.894$) and bleeding (14.1% vs. 12.0%; $P = 0.543$). (48) However this trial was stopped prematurely due to slow enrollment and therefore may be underpowered. More studies are needed to provide an insight to this crucial issue.

9. Conclusion

The use of an ideal antiplatelet as second agent changed over time depending not only on the effectiveness and safety, but also in part on the cost effectiveness of these agents. Several considerations should be taken in account when deciding which agents to use. These include

the effectiveness of studies agent in reducing major adverse cardiac and cerebrovascular event, the associated increase or decrease of bleeding rate. The cost consideration is not only linked to the direct cost of the drug itself, but also to the decrease or increase cost associated with added or reduced benefit or risk of using any agent when compared to either placebo or other available therapeutic options. The debate of the most attractive choice of antiplatelet and anticoagulation agents will continue. In the next five years the first patent for prasugrel (2017) and ticagrelor (2018) will expire which may allow for generic form of both drugs to be available. Furthermore, more data addressing comparative and cost effectiveness of studies comparing UH and bivalirudin will be available and hopefully will provide an insight on the best agent to be used. The debate of the effectiveness of longer versus 12 months of DAPT especially in high-risk ACS patients and cost effectiveness of each approach may impact our choice of therapy. (49) More studies similar to BRAVE4 comparing comparative and cost effectiveness of different antiplatelet and anticoagulation agents are expected to help guide decision-making.

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Key points

- ❖ Several considerations should be taken in account when deciding cost effectiveness of antiplatelet and anticoagulant drugs.
- ❖ The use of dual antiplatelet therapy with aspirin and P2Y₁₂ receptor antagonist represent the most attractive clinical and economic option in patients presenting with ACS.
- ❖ The debate about the comparative and potential cost effectiveness of heparin versus bivalirudin monotherapy is the focus of contemporary studies.
- ❖ The comparative clinical and cost effectiveness of different combinations of antiplatelet and antithrombotic therapy will be the focus of future studies.

Figure-1.
The Cost Assessment Of TRITON-TIMI-38 Trial.

Figure 2.
The Cost Effectiveness Of PLATO Trial.

Figure 3.
The Cost Assessment Of The ACUITY Trial.

Figure 4.
The Cost Assessment Of The HORIZONS-AMI Trial.

Table-1**Comparative and Cost Effectiveness Trials of Antiplatelet Therapy in ACS**

Agent/ trial name	Comparison	Primary outcome	Results	Cost Effectiveness
Tirofiban / RESTORE (21, 22)	Tirofiban vs. Placebo in ACS patients	Composite of death, MI and TVR	Tirofiban use was associated with a non-statistically significant reduction of the primary outcome at 30 days (10.3 % vs. 12.2%; P=0.16).	The cost of tirofiban use was not significantly higher than placebo at 30 days (\$12,446 ± 5,814 tirofiban vs. \$12,402 ± 6,147 placebo; P = 0.87)
Eptifibatide / PURSUIT (23, 24)	Eptifibatide vs. Placebo in ACS	Composite of death, MI	Eptifibatide use was associated with a reduction in the primary outcome at 30 days (14.2 % vs. 15.7 %; P=0.04).	ICER for eptifibatide therapy was \$16,491 per LY gained and \$19,693 per QALY
Clopidogrel /PCI-CURE (26, 27)	Clopidogrel vs. Placebo in ACS	Composite of death, MI and TVR	Clopidogrel use was associated with a reduction in the primary outcome at 30 days (4.5 % vs. 6.4 %; P=0.03).	ICER of \$2856 to \$4775 per LY without PCI and \$935 per LY in the early PCI subgroup.
Prasugrel / TRITON-TIMI-38 (28, 29)	Prasugrel vs. Clopidogrel in ACS	Composite of death, MI and stroke	Prasugrel use was associated with a reduction in the primary endpoint (9.9% vs. 12.1%; P < 0.001)	Prasugrel was shown to be a dominant strategy when compared to “branded clopidogrel”
Ticagrelor/ PLATO (30, 31)	Ticagrelor vs. Cloidogrel in ACS	Composite of death, MI and stroke	Ticagrelor use was associated with a reduction in the primary outcome (9.8% vs.11.7%; P<0.001).	The use of ticagrelor was an economically attractive option with an ICER of \$2753 per QALY gained and \$2372 per LY gained

ACS, acute coronary syndromes; CURE, Clopidogrel in Unstable angina to prevent Recurrent Events; ICER, incremental cost-effectiveness ratio; LY life year; MI, myocardial infarction; PCI-CURE, Percutaneous Coronary Intervention Substudy of the CURE trial; PLATO, The Study of Platelet Inhibition and Patient Outcomes; PURSUIT, The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; QALY, quality-adjusted life year; RESTORE, The Randomized Efficacy Study of Tirofiban for Outcomes and REstenosis; TRITON-TIMI-38, The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel Thrombolysis in Myocardial Infarction; TVR, target vessel revascularization

Table-2**Comparative and Cost Effectiveness Trials of Antithrombotic Therapy in ACS**

Agent/ Trial name	Comparison	Primary outcome	Results	Cost effectiveness
Enoxaparin/ ESSENCE (34, 35)	Enoxaparin vs. UH in NSTEMI-ACS patients	Composite of death, MI and recurrent angina	Enoxaparin use was associated with a reduction in the primary outcome at 30 days (19.8% vs. 23.3%, P=0.016)	The use of enoxaparin was associated with a net cumulative cost savings of \$1172 (P=0.04)
Enoxaparin/ ExTRACT-TIMI 25 (36, 37)	Enoxaparin vs. UH in STEMI patients	Composite of death, nonfatal MI, or urgent TVR	Enoxaparin use was associated with a reduction in the primary outcome (11.7% vs. 14.5 %; P<0.001)	Enoxaparin was shown to be an economically attractive option with an ICER of \$5,700 per LY gained.
Fondaparinux/ OASIS-5 (38, 39)	Fondaparinux vs. enoxaparin in NSTEMI-ACS patients	Composite of death, MI and refractory ischemia at 9 days	No significant difference in primary outcome (5.8% fondaparinux vs. 5.7% enoxaparin; P=NS)	Using fondaparinux instead of enoxaparin was associated with a cost savings of \$547 per patient at 180 days
Bivalirudin/ ACUTY (41, 42)	UH / LMWH plus a GPI vs. bivalirudin plus a GPI vs. bivalirudin alone in ACS patients in NSTEMI-ACS	Composite of death, MI, or unplanned revascularization P=0.32)	Bivalirudin monotherapy use was associated with a noninferior rate of primary outcome compared to UH / LMWH plus a GPI (7.8% vs. 7.3%,	The cumulative hospital stay costs were lowest with bivalirudin monotherapy (mean difference range: \$184-\$1,081, p < 0.001) with cost savings extending out to 30 days (mean difference range: \$123-\$938, p = 0.005).
Bivalirudin/ HORIZONS-AMI (43, 44)	Bivalirudin vs. UH plus a GPI in STEMI patients	Composite of major bleeding and MACCE	The use of bivalirudin monotherapy was associated with reduced 30-day rate of primary outcome (9.2% vs. 12.1%; P=0.005),	The use of bivalirudin alone was associated with a lifetime savings of £267 (£12 843 bivalirudin vs. £13 110 Heparin + GPI).

ACUTY, The Acute Catheterization and Urgent Intervention Triage strategy trial; ESSENCE, The Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q Wave Coronary Events trial; ExTRACT-TIMI 25, Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment -Thrombolysis in Myocardial Infarction 25 study; GPI, glycoprotein IIb/IIIa receptor inhibitor; HORIZONS-AMI, The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction trial; ICER, incremental cost-effectiveness ratio; LMWH, low-molecular weight heparin; MACCE, Major Adverse Cardiovascular and Cerebral events; MI, myocardial infarction; NSTEMI-ACS, non ST-segment elevation acute coronary syndromes; OASIS-5, The Organization to Assess Strategies in Acute Ischemic Syndromes-5 trial; STEMI, ST-segment elevation myocardial infarction; TVR, target vessel revascularization; UH, unfractionated heparin.