SYSTEMATIC REVIEW

Pharmacoeconomics 2012; 30 (4): 303-321
1170-7690/12/0004-0303/$49.95/0

Cost Effectiveness of Anticoagulation in Acute Coronary Syndromes

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Abstract

Background: The benefit of unfractionated heparin (UFH) added to aspirin in patients with acute coronary syndromes (ACS) was described more than 20 years ago. Ever since, a wide variety of anticoagulant drugs have become available for clinical use, including low-molecular-weight heparins (LMWH), direct thrombin inhibitors and selective factor Xa inhibitors.

Objective: The aim of this study was to critically review the available evidence on the cost and incremental cost effectiveness of anticoagulants in patients with ACS.

Methods: Studies were identified using specialist databases (UK NHS Economic Evaluation Database [NHS EED] and Cost-Effectiveness Analysis [CEA] Registry), PubMed and the reference lists of recovered articles. Only studies based on randomized controlled trials were considered for inclusion. Finally, 22 studies were included in the review.

Results: Enoxaparin is the only LMWH that has been shown to reduce the risk of death or myocardial infarction in patients with non-ST-elevation ACS (NSTE-ACS). In economic studies based on the ESSENCE trial conducted in the late 1990s, enoxaparin was consistently associated with a lower risk of coronary events, a reduction in the number of revascularization procedures and a lower cost per patient than UFH. However, these results refer to patients managed conservatively, with little use of thienopyridines and glycoprotein IIb/IIIa inhibitors, and the results are difficult to extrapolate to moderate-to-high-risk patients managed with the present day early invasive strategy.

Available studies of LMWH in ACS with persistent elevation of ST-segment (STE-ACS) are limited to patients treated with thrombolysis. In this scenario, enoxaparin was shown to be a dominant alternative compared with UFH in a study based on the ASSENT-3 study and was considered an economically attractive alternative in three studies based on the ExTRACT-TIMI 25 study. However, these results should be interpreted cautiously due to the heterogeneity of the supportive randomized trials and the possible underestimation of bleeding costs.

The effectiveness and safety of bivalirudin, a direct thrombin inhibitor, were evaluated in the ACUITY study (NSTE-ACS patients managed invasively) and the HORIZONS-AMI study (STE acute myocardial infarction patients planned

for primary percutaneous coronary intervention). Bivalirudin monotherapy was not inferior to heparin plus a glycoprotein IIb/IIIa inhibitor and reduced the risk of major bleeding. The economic evaluations based on these studies suggest that bivalirudin is an attractive alternative to heparin plus a glycoprotein-IIb/IIIa inhibitor.

In the OASIS-5 trial, compared with enoxaparin, fondaparinux reduced the mortality in patients with NSTE-ACS, probably because of a reduced risk of bleeding. In three economic evaluations of fondaparinux versus enoxaparin based on this trial, fondaparinux was the dominant strategy in two of them, and still economically attractive in a third.

Taken as a whole, the usefulness of economic studies of anticoagulants in patients with ACS is undermined by the quality of the evidence about their effectiveness and safety; the narrow spectrum of the analysed scenarios; the lack of economic evaluations based on systematic reviews; the limitations of sensitivity analyses reported by the available economic evaluations; and their substantial risk of commercial bias.

Conclusions: The available studies suggest that enoxaparin is an economically attractive alternative compared with UFH in patients with NSTE-ACS treated conservatively and STE-ACS patients treated with thrombolysis. Bivalirudin in patients with ACS treated invasively is cost effective compared with heparin plus a glycoprotein IIb/IIIa inhibitor. In patients with NSTE-ACS, fondaparinux is cost effective compared with enoxaparin. The usefulness of these results for decision making in contemporary clinical practice is limited due to problems of internal and external validity.

Key points for decision makers

- Economic studies of anticoagulants in acute coronary syndromes uniformly reported favourable results for the treatment studied
- A large part of the studies have been conducted in clinical settings away from the current clinical practice and are obsolete
- There are no studies comparing the new anticoagulants head-to-head, so the evidence on their relative merits is indirect
- Economic evaluations should pay greater attention to costs associated with bleeding
- Economic studies are needed based on systematic reviews of the literature and studies that make use of extensive sensitivity analysis

Acute coronary syndromes (ACS) are defined as the sudden onset of cardiac ischaemia, including unstable angina and Q-wave and non-Q-wave acute myocardial infarction. An estimated 1.365 million of patients with ACS were hospitalized in the US in 2006,[1] with an approximate cost of $US150 billion.[2]

ACS are usually produced by the fissuring or rupturing of a plaque of atheroma with subsequent platelet activation, formation of fibrin and genera-

tion of a coronary thrombus.[3] This is frequently accompanied by persistent ST-segment elevation in the ECG (ST-elevation ACS [STE-ACS]) and is usually associated with the complete occlusion of a major coronary artery by a thrombus. In this case, the primary therapeutic goal is to establish reperfusion in the culprit artery either pharmacologically (thrombolysis) or mechanically (primary percutaneous coronary intervention [PCI]).[4] In other cases, there is no persistent ST-segment elevation in the ECG (non-ST-elevation ACS [NSTE-ACS]), which usually indicates that the coronary obstruction is incomplete or intermittent. Thrombolysis in these cases is not recommended, and a decision between an initial-conservative and an early invasive strategy must be made according to the patient's characteristics and available resources.[5]

Anticoagulant therapy, coupled with antiplatelet drugs and occasionally coronary revascularization, has a pivotal role in the treatment of ACS. A wide variety of anticoagulant drugs are currently available for clinical use, such as indirect thrombin inhibitors (unfractionated heparin [UFH] and low-molecular-weight heparins [LMWHs]), direct thrombin inhibitors (e.g. bivalirudin) or selective factor Xa inhibitors (e.g. fondaparinux).[6]

Unfortunately, choosing the optimal antithrombotic regimen is a complex task. No single anticoagulant 'fits all sizes', and the advantages and drawbacks of each specific anticoagulant depends on the clinical scenario in which they are used (patients with or without persistent ST-elevation, managed conservatively or invasively, with or without concomitant thienopyridine therapy, etc.). Furthermore, the rational clinical use of anticoagulants is complicated by the low quality of the evidence about the effectiveness and safety of anticoagulant drugs, as exemplified by the inconsistencies observed between the major clinical practice guidelines.[7,8] Additionally, most of the new anticoagulant drugs are expensive, so the recommendations should ideally consider cost effectiveness as well as risk-benefit profile.

The aim of this study was to critically review the available evidence on the cost and incremental cost effectiveness of anticoagulants in patients with ACS.

1. Literature Search

We searched for economic analyses that assessed the cost and cost effectiveness of early anticoagulation in patients with ACS. Studies were identified using the UK NHS Economic Evaluation Database (NHS EED), Cost-Effectiveness Analysis (CEA) Registry and PubMed. Additional references were identified from the reference lists of published articles. MEDLINE search terms were:

- ('heparin', 'low molecular weight heparin', 'enoxaparin', 'lepirudin', 'argatroban', 'bivalirudin', 'fondaparinux', 'otamixaban', 'edoxaban', 'apixaban', 'rivaroxaban', 'varosaban' or 'YM-150');
- ('Acute Coronary Syndrome' [medical subject heading; MeSH], 'unstable angina', 'non-ST elevation', 'ST-elevation' or 'ST-segment elevation');
- ('Cost-Benefit Analysis' [MeSH], 'Costs and Cost Analysis' [MeSH] or cost-effective*[tiab]).

Searches were last updated to 20 May 2010. Only studies based on randomized controlled trials were considered for inclusion. The process of study selection is summarized in figure 1. In short, the database search and manual search identified 51 potentially relevant articles. After an initial examination of title and abstract, 23 of them were considered irrelevant and excluded from the review. The remaining studies were retrieved in full text for closer examination, which led to the exclusion of six additional studies because they were

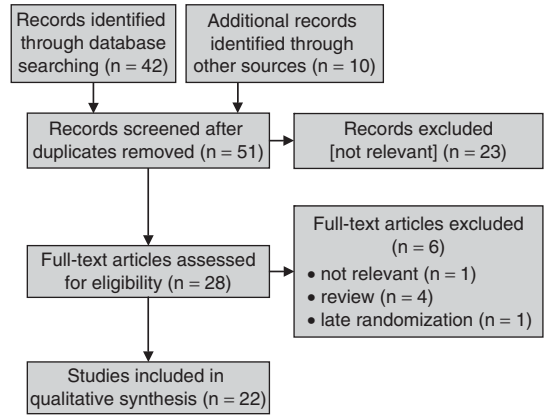

Fig. 1. Flow diagram of included and excluded studies.

considered irrelevant,[9] reviews[10-13] or deferred randomization studies.[14] The methodological quality of pharmacoeconomic studies was assessed using a preformed instrument adapted from Evers et al.[15] Both the selection and the quality assessment were performed in duplicate and discrepancies were resolved by consensus.

2. Indirect Thrombin Inhibitors

UFH is an indirect inhibitor of thrombin and factor Xa. Its major drawbacks are the need for intravenous administration; the requirement of frequent haematological monitoring; the possible rebound effect after withdrawal; and the risk of developing immune thrombocytopenia. LMWH are characterized by a lower inhibitory effect of thrombin and a more preferential effect on factor Xa, along with a reduced platelet activation and decreased plasma protein binding. They can be administered subcutaneously (SC) and have a more predictable anticoagulant action, so they can be administered without the need of blood clotting tests and have a much lower associated risk of immune thrombocytopenia.[6]

2.1 Non-ST-Elevation Acute Coronary Syndrome (ACS)

2.1.1 Effectiveness Studies

In a recent systematic review,[16] heparin (UFH or LMWH) compared with placebo reduced the risk of myocardial infarction in patients with NSTE-ACS (relative risk [RR] 0.40, 95% CI 0.25, 0.63) but failed to show reduction in mortality (RR 0.84, 95% CI 0.36, 1.98) [table I].

Enoxaparin is the only LMWH that has demonstrated superiority over UFH in several randomized controlled trials in NSTE-ACS patients.[17-19,26-28] In the ESSENCE study,[17] a randomized double-blind trial (see table II for definitions of trial acronyms), 3171 NSTE-ACS patients managed conservatively were allocated to receive enoxaparin (1 mg/kg/12 h SC) or UFH infusion for 2–8 days. The group treated with enoxaparin had a lower risk of the primary event (death, myocardial infarction or recurrent angina at 14 days), which was maintained at 30 days without increasing the risk of major bleeding (6.5% vs 7.0%), and with a reduction of percutaneous revascularization procedures (27.0% vs 32.2%; $p = 0.001$).The results of the ESSENCE study have been verified by other trials such as TIMI 11B.[18] However, the above-mentioned studies were conducted at a time when the use of thienopyridines, glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors and percutaneous revascularization procedures was not widespread. More recent studies, however, offered different results. For example, in the SYNERGY study,[19] a randomized non-blinded trial, 10 027 high-risk patients with NSTE-ACS under potent antiplatelet therapy were assigned to receive enoxaparin or UFH. The incidence of the primary endpoint (death from all causes or non-fatal myocardial infarction at 30 days) was comparable (odds ratio [OR] 0.96, 95% CI 0.86, 1.06), and the group treated with enoxaparin had a higher risk of major bleeding (9.1% vs 7.6%; $p = 0.008$). Moreover, the proportion of patients undergoing a coronary angiography was similar in the enoxaparin and UFH arms (92.1% and 92.0%, respectively). Further analyses showed that 75% of the patients had received pre-randomization antithrombin therapy and suggested that post-randomization crossover had an important impact on these trial results.

Recently, Murphy et al. reported a meta-analysis of six major studies of enoxaparin versus UFH.[29] A re-analysis of their results permitted the following conclusions: (i) there was no evidence that enoxaparin reduced mortality (RR 0.98, 95% CI 0.94, 1.14, $I^2 = 0\%$); (ii) enoxaparin reduced the risk of myocardial infarction (RR 0.88, 95% CI 0.81, 0.96, $I^2 = 0\%$); and (iii) regarding the risk of major bleeding, the results were heterogeneous from both a clinical (different definitions of major bleeding) and a statistical ($I^2 = 65.9\%$; $p = 0.0119$) point of view.

2.1.2 Economic Studies

Six *cost analyses* compared enoxaparin with UFH in patients with NSTE-ACS based on subcohorts of the ESSENCE trial[17] recruited in the US,[30] UK,[31,32] Latin America,[33] France[34] and Canada.[35] All the studies were performed from the perspective of the healthcare providers, with a time horizon of 30 days to 1 year. In ad-

Table I. Main randomized controlled trials on which the pharmacoeconomic studies are based

Study[a]	Patients	Intervention vs comparator	Primary endpoint	Event rate (experimental vs control group)	Comments
ESSENCE[17]	NSTE-ACS	ENOX vs UFH	Death, myocardial infarction or recurrent angina at 14 d	16.6% vs 19.8%; p = 0.019	Most pts treated conservatively, low use of thienopyridine and IIb/IIIa antagonists
TIMI 11B[18]	NSTE-ACS	ENOX vs UFH	After 7 d, the primary endpoint was death, myocardial infarction or revascularization at 7 d	12.4% vs 14.5%; p = 0.048	Most pts treated conservatively, low use of thienopyridine and IIb/IIIa antagonists
SYNERGY[19]	High-risk NSTE-ACS pts	ENOX vs UFH	Death from all causes or non-fatal myocardial infarction at 30 d	14.0% vs 14.5%; p = 0.40	92% treated invasively. Higher risk of major bleeding in ENOX group (9.1% vs 7.6%; p = 0.008). Post-randomization crossover probably favoured bleeding
ESCAPEU[20]	Unstable angina	ENOX vs UFH	Myocardial infarction, cardiac death, recurrent angina and need for intervention	37% vs 62%; p = 0.04	Small study
ESCAPe-END[21]	Unstable angina	ENOX vs nadroparin vs dalteparin	Cardiovascular death, myocardial infarction, recurrent angina and need for intervention	24% vs 30 vs 28%; p = 0.526	Small study
ASSENT-3[22]	Pts with STE-ACS undergoing thrombolytic therapy	ENOX vs UFH	Death or non-fatal reinfarction at 30 d	7.6% vs 9.6%; p = 0.03	No reduction of 1 y mortality (8.2% in ENOX group vs 7.9% in UFH group)
ExTRACT-TIMI 25[23]	Pts with STE-ACS undergoing thrombolytic therapy	ENOX vs UFH	Death or non-fatal reinfarction at 30 d	9.9% vs 12%; p < 0.001	Higher risk of major bleeding but 'net clinical benefit' favourable to the ENOX group
ACUITY[24]	Medium-to-high-risk pts with NSTE-ACS managed with an early invasive strategy	BVD alone vs BVD + GPIIb/IIIa inhibitor vs heparin (LMWH or UFH) + GPIIb/IIIa inhibitor	Death, myocardial infarction or unplanned revascularization for ischaemia at 30 d	7.8% vs 7.7% vs 7.3%	Major bleeding events 3% in the BVD group vs 5.7%; p < 0.001
OASIS-5[25]	NSTE-ACS	FPX vs ENOX	Death, myocardial infarction or refractory ischaemia at 9 d	5.8% vs 5.7%	Major bleeding events 2.2% in the FPX group compared with 4.1% in the ENOX group (p < 0.001)

a See table II for definitions of trial acronyms.

BVD = bivalirudin; **ENOX** = enoxaparin; **FPX** = fondaparinux; **GP** = glycoprotein; **LMWH** = low-molecular-weight heparin; **NSTE-ACS** = non-ST-elevation acute coronary syndrome; **pt(s)** = patient(s); **STE-ACS** = ST-elevation acute coronary syndrome; **UFH** = unfractionated heparin.

dition to the costs of drug acquisition and administration, length of stay in the coronary care unit and the hospital ward, and the use of coronary angiography and revascularization procedures were quantified. The results were highly consistent across countries and showed that the higher drug acquisition costs of enoxaparin were offset by the reduction in catheterization and re-

Table II. Trial acronyms

ACUITY	Acute Catheterization and Urgent Intervention Triage Strategy
ASSENT	Assessment of the Safety and Efficacy of a New Thrombolytic Regimen
ESCAPe-END	Efficacy, Safety, Cost Effectiveness and Effect on PAI-1 Levels of the Three Low-Molecular-Weight Heparins: Enoxaparin, Nadroparin and Dalteparin
ESCAPEU	Efficacy, Safety, Cost and Platelet Aggregation Effects of Enoxaparin and Unfractionated Heparin
ESSENCE	Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events
ExTRACT	Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries
HORIZONS-AMI	Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction
OASIS	Organization to Assess Strategies in Acute Ischaemic Syndromes
SYNERGY	Superior Yield of the New Strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa Inhibitors
TIMI	Thrombolysis in Myocardial Infarction

PAI = plasminogen activator inhibitor.

vascularization procedures and a tendency for reduced hospital stay, resulting in overall cost savings. An additional cost analysis based on a small randomized trial conducted in India[20] had results consistent with these studies (tables III and IV).

Four additional studies have evaluated the cost effectiveness of enoxaparin versus UFH in patients with NSTE-ACS through a *cost-effectiveness*[36-38] or *cost-utility*[39] *analysis* performed from the perspective of the health systems of Canada,[36] Poland,[37] Spain[38] and the UK.[39] All studies were based on the data of events and effectiveness from the ESSENCE study and eventually the TIMI 11B study.[38,39] Enoxaparin was the dominant option in the base case in all studies, although this finding was not robust in the worst-case scenario. The average savings per patient ranged widely within a range between $US4 and $US1600 (actualized to year 2009 values). Interestingly, in the UK study,[39] the results were very sensitive to variation in rates of revascularization.

2.2 ST-Elevation ACS

2.2.1 Effectiveness Studies

Most economic studies comparing enoxaparin with UFH in patients with STE-ACS originate from randomized trials in patients undergoing thrombolytic therapy (table I).[22,23,51-54]

The ASSENT-3 study[22] compared enoxaparin (n = 2040) versus UFH (n = 2038) as adjunctive therapy in patients with STE-ACS treated with tenecteplase. The incidence of death or non-fatal reinfarction at 30 days was lower in the group treated with enoxaparin (7.6% vs 9.6%; p = 0.03), but this did not translate into lower mortality during the year (8.2% in enoxaparin group vs 7.9% in the UFH group).

In the ExTRACT-TIMI 25 study,[23] a randomized double-blind double-dummy controlled trial, 20 506 STE-ACS patients were allocated to receive enoxaparin until discharge or UFH for at least 48 hours as adjunctive therapy to thrombolysis. The primary outcome (death or non-fatal reinfarction at 30 days) occurred in 9.9% of the patients assigned to enoxaparin versus 12% of the patients assigned to UFH ($p < 0.001$). The group assigned to enoxaparin had a higher risk of major bleeding (2.1% vs 1.4%; $p < 0.001$), but the 'net clinical benefit' (incidence of death, non-fatal myocardial infarction, disabling stroke, bleeding or intracranial haemorrhage) was favourable to the enoxaparin group. The re-analysis of a recent meta-analysis of major trials comparing enoxaparin with UFH as adjunctive medication in patients with STE-ACS undergoing thrombolysis[29] permitted the following conclusions: (i) enoxaparin was associated with a trend to reduced mortality (RR 0.93, 95% CI 0.85, 1.02, $I^2 = 0\%$); (ii) although the pooled effect (random effects model) suggested a reduction in the incidence of reinfarction (RR 0.67, 95% CI 0.49, 0.92), the results were heterogeneous ($I^2 = 72\%$; $p = 0.006$); and (iii) enoxaparin increased the incidence of major bleeding as defined by the authors (RR 1.44, 95% CI 1.23, 1.69, $I^2 = 0\%$).

2.2.2 Economic Studies

To date, four economic evaluations comparing enoxaparin with UFH as adjunctive therapy

Table III. Pharmacoeconomic studies in patients with acute coronary syndromes[a]

Study population and setting	Analysis, perspective, model, time horizon	Data source (effectiveness, risk of events, costs)	Included costs	Results ($US)[b]	Sensitivity analysis
LMWH in NSTE-ACS (ENOX vs UFH, unless otherwise indicated)					
NSTE-ACS pts, ESSENCE US subcohort (n = 923)[30]	*Analysis*: cost analysis *Perspective*: US healthcare *Time horizon*: 30 d	*Effectiveness/risk*: ESSENCE *Costs*: local hospital billing data and Medicare physician fees	Drugs purchase, hospitalization, physician fees, cardiac catheterization, PCI, CABG	ENOX cost saving $1633 Cost saving 94% of bootstrap replications	Not performed
NSTE-ACS pts, ESSENCE UK subcohort (n = 191)[32]	*Analysis*: cost analysis *Perspective*: UK healthcare *Time horizon*: 30 d	*Effectiveness/risk*: ESSENCE, revascularization procedures in the UK *Costs*: local costs	Drugs purchase, hospitalization, physician fees, cardiac catheterization, PCI, CABG	ENOX cost saving $54	Not performed
NSTE-ACS pts, ESSENCE[31]	*Analysis*: cost analysis *Perspective*: UK healthcare *Time horizon*: 1 y	*Effectiveness/risk*: ESSENCE trial *Costs*: local costs	PCI, CABG	ENOX reduced revascularization costs by $404	Not performed
NSTE-ACS pts, ESSENCE Argentina/Uruguay subcohort (n = 256)[33]	*Analysis*: cost analysis *Perspective*: Argentina/Uruguay healthcare *Time horizon*: 30 d	*Effectiveness/risk*: ESSENCE *Costs*: local costs	Drugs purchase, hospitalization, cardiac catheterization, PCI, CABG	Cost saving $391 per pt	Not performed
NSTE-ACS pts, ESSENCE whole study group (n = 3171) and French subcohort (n = 133)[34]	*Analysis*: cost analysis *Perspective*: French healthcare *Time horizon*: 30 d	*Effectiveness/risk*: ESSENCE overall and French subsample *Costs*: resource use in the overall trial and French subgroup	Drugs purchase, hospitalization, cardiac catheterization, PCI	ENOX cost saving $402 for the whole population, $1476 for the French subsample	Deterministic sensitivity analysis. Results sensitive to the costing approach
NSTE-ACS pts, ESSENCE Canada subcohort (n = 1259)[35]	*Analysis*: cost analysis *Perspective*: Canadian healthcare *Time horizon*: 1 y	*Effectiveness/risk*: ESSENCE *Costs*: local costs (OCCP, regression model)	Drugs purchase, hospitalization, cardiac catheterization, PCI, CABG	Cost saving $1380. Cost saving 97% of bootstrap replications	Robust for two alternative hospitalization costs
Unstable angina, ESCAPEU trial (India) [n = 93][20]	*Analysis*: costs and results description *Perspective*: Indian healthcare *Time horizon*: 7 d	*Effectiveness/risk*: ESCAPEU *Costs*: trial-related cost analysis	Stay in the CCU and hospital, APTT monitoring, thrombolytic therapy, interventions	ENOX cost saving $17 per pt (non-significant)	Not performed
Unstable angina, ESCAPe-END trial (India) [n = 150][21] [c]	*Analysis*: costs and results description *Perspective*: Indian societal *Time horizon*: 30 d	*Effectiveness/risk*: ESCAPe-END *Costs*: trial-related costs	Stay in the CCU and hospital, drugs purchase, laboratory costs, thrombolysis, interventions, wages, travels	No significant differences in costs or efficacy (underpowered)	Not performed

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Table III. Contd

Study population and setting	Analysis, perspective, model, time horizon	Data source (effectiveness, risk of events, costs)	Included costs	Results ($US)[b]	Sensitivity analysis
NSTE-ACS hypothetical cohort (decision tree)[36]	*Analysis*: CEA *Perspective*: Canadian healthcare *Model*: decision tree analysis *Time horizon*: 30 d	*Effectiveness/risk*: ESSENCE *Costs*: Canadian costs (from literature)	Drug purchase, events, revascularization procedures, bleeding complications	ENOX dominant, cost saving $51 per pt	Deterministic sensitivity analysis on costs, cardiac events and bleeding (not robust)
NSTE-ACS hypothetical cohort (decision tree)[37]	*Analysis*: CEA *Perspective*: Polish hospital *Model*: decision tree analysis *Time horizon*: 30 d	*Effectiveness/risk*: ESSENCE *Costs*: resource use in the Polish GRACE sample and cost units in Poland	Drugs purchase, laboratory tests, hospitalization, revascularization and other procedures, salaries	ENOX cost saving $3.60	One-way/two-way deterministic analysis. Dominance sensible to variations in relative costs or effectiveness
NSTE-ACS hypothetical cohort[38]	*Analysis*: CEA *Perspective*: Spanish healthcare system *Time horizon*: 30–43 d and 1 y	*Effectiveness/risk*: ESSENCE (30 d–1 y) and TIMI 11B (43 d) *Costs*: resource use in the trials with Spanish unit costs	Drugs acquisition, administration and monitoring, hospitalization and revascularization procedures	ENOX dominant in the base case: 34 additional pts without complication per 1000 treated, while saving $483 968 (30–42 d) and $709 821 (1 y)	One-way deterministic sensitivity analysis. ENOX relatively robust (except for the worst-case analysis)
NSTE-ACS hypothetical cohort (model)[39]	*Analysis*: CUA *Perspective*: UK healthcare system *Time horizon*: 1 y	*Effectiveness/risk*: ESSENCE and TIMI 11B *Costs*: UK costs	Drugs acquisition and administration, length of stay, cardiac events, revascularization procedures	ENOX dominant (gain 0.013 QALYs while saving $689 per pt)	One-way deterministic analysis. Dominance sensitive to revascularization rates and cost
LMWH in STE-ACS (ENOX vs UFH)					
STE AMI treated with TNK-tPA, ASSENT-3 US subcohort (n = 975)[40]	*Analysis*: CEA *Perspective*: US healthcare ('societal') perspective *Time horizon*: 30 d and 1 y	*Effectiveness/risk*: ASSENT-3 *Costs*: resource use in ASSENT-3 (US subcohort and whole sample). Costs estimated from US DRGs and detailed billing data from GUSTO-2b	Drugs purchase and administration, length of stay, catheterization, PCI, CABG	ENOX cost saving at 30 d $98 (DRG-based) to $670 (GUSTO-2b-based) ENOX dominant (80% at 30 d, 71% at 1 y)	Not performed

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Table III. Contd

Study population and setting	Analysis, perspective, model, time horizon	Data source (effectiveness, risk of events, costs)	Included costs	Results ($US)[b]	Sensitivity analysis
STE AMI with thrombolysis (hypothetical cohort) [model][41]	*Analysis*: CEA *Perspective*: Canadian healthcare ('societal') *Time horizon*: lifetime	*Effectiveness/risk*: ExTRACT-TIMI 25 plus Framingham survival data *Costs*: Canadian costs (DRGs)	Drugs purchase and administration, length of stay, catheterization, PCI, CABG, IABCP, scanner, MRI, adverse cardiac and bleeding events	$4613 per life-year gained ENOX cost effective (99%)	One-way sensitivity analysis on marginal time costs and life-years gained (robust)
STE AMI treated with fibrinolysis, ExTRACT-TIMI 25 (n = 20 479)[42]	*Analysis*: CEA and CUA *Perspective*: healthcare ('societal') *Time horizon*: 30 d and lifetime	*Effectiveness/risk*: ExTRACT-TIMI 25 plus Framingham life expectancy and literature-based utilities *Costs*: US costs (DRGs and Current Procedural Terminology)	Drugs purchase and administration, length of stay, catheterization, PCI, CABG, IABCP, scanner, MRI, adverse cardiac and bleeding events	Total lifetime cost $1360 higher for ENOX. Cost per QALY gained with ENOX $5294 ($6421 per life-year gained)	One-way sensitivity analysis on life-years gained and probabilistic microsimulation. ICER <$US50 000 in 90% of samples
STE AMI with thrombolysis (hypothetical cohort) [Markov model][43]	*Analysis*: CEA and CUA *Perspective*: UK healthcare system *Time horizon*: lifetime	*Effectiveness/risk*: ExTRACT-TIMI 25 plus Scottish survival data *Costs*: not fully specified	NR	$US25 333 per life-year gained, $US31 608 per QALY gained (£, year 2007–8 values)	One-way/two-way sensitivity analysis for duration of ENOX therapy, drug wastage analysis and utility scores
BVD (BVD vs heparin plus glycoprotein IIb/IIIa antagonist)					
NSTE-ACS managed invasively, ACUITY US subcohort (n = 7851)[44]	*Analysis*: CEA *Perspective*: US healthcare system *Time horizon*: 30 d	*Effectiveness/risk*: ACUITY *Costs*: ACUITY US subcohort (prospective resource counting plus billing data)	Drugs purchase and administration, procedures (catheterization, PCI, CABG), cardiac events, bleeding complications, length of stay, physician fees	BVD monotherapy cost saving ($134–1022; $p < 0.005$)	Not performed
NSTE-ACS managed invasively (hypothetical cohort) [Markov model][45]	*Analysis*: CUA *Perspective*: UK NHS *Time horizon*: lifetime	*Effectiveness/risk*: ACUITY study plus GRACE UK cohort and UK survival data *Costs*: ACUITY study plus GRACE UK cohort and UK unit costs	Drugs purchase and administration, procedures (catheterization, PCI, CABG), cardiac events, major and minor bleeding	$20 315–25 175 per QALY gained with monotherapy BVD (£, year 2007–8 values)	Extensive deterministic sensitivity analysis and probabilistic microsimulation. BVD cost effective: 72% (ACUITY-based) and 67% (GRACE-based)

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Table III. Contd

Study population and setting	Analysis, perspective, model, time horizon	Data source (effectiveness, risk of events, costs)	Included costs	Results ($US)[b]	Sensitivity analysis
FPX (FPX vs ENOX)					
NSTE-ACS[46]	*Analysis*: CUA *Perspective*: French healthcare system *Time horizon*: 180 d and lifetime	*Effectiveness/risk*: OASIS-5 plus literature-based data *Costs*: NR	NR	FPX cost effective ($4163 per QALY)	NR
NSTE-ACS OASIS-5 (decision model)[47]	*Analysis*: CUA *Perspective*: US healthcare system *Time horizon*: 180 d and lifetime	*Effectiveness/risk*: OASIS-5 plus US survival tables *Costs*: OASIS-5 trial, US subcohort (n = 759) and US unit costs	Drugs purchase and administration, length of stay, cardiac catheterization, PCI, CABG, cardiac events, stroke, blood transfusions	FPX dominant (+0.04 QALYs while saving $200)	FPX dominance robust under most of the scenarios
NSTE-ACS managed with an early invasive strategy (hypothetical cohort) [Markov model][48]	*Analysis*: CUA *Perspective*: Spanish healthcare system *Time horizon*: lifetime	*Effectiveness/risk*: OASIS-5 plus Spanish survival data *Costs*: Spanish published costs	Drugs purchase and administration, length of stay, PCI, CABG, cardiac events, bleeding events	FPX dominant (+0.023 QALYs while saving $55)	FPX dominance, robust for changes in age, severity score, relative risk of events and baseline risk of bleeding
Various anticoagulants[d]					
NSTE-ACS medium-high risk, managed with an early invasive strategy (hypothetical cohort) [decision model][49]	*Analysis*: CEA *Perspective*: healthcare provider *Time horizon*: 30 d	*Effectiveness/risk*: SYNERGY, ACUITY and OASIS-5 *Costs*: US DRGs	Drugs purchase, AMI, urgent revascularization, major bleeding, minor bleeding	Base case: BVD dominant over UFH and ENOX. FPX more costly and effective than BVD ($2569 per each additional pt treated without complications)	Microsimulation: toss-up for BVD vs FPX (50+/−5%)

a See table II for definitions of trial acronyms used within this table.

b Currencies are converted to $US; all values are actualized to year 2009 $US using the Consumer Price Index statistics from the annual *Statistical Abstracts of the United States*.[50]

c Intervention vs comparison group is ENOX vs nadroparin vs dalteparin.

d Four strategies were used: (i) ENOX plus eptifibatide; (ii) UFH plus eptifibatide; (iii) BVD alone; and (iv) FPX plus eptifibatide.

ACS = acute coronary syndromes; **AMI** = acute myocardial infarction; **APTT** = activated partial thromboplastin time; **BVD** = bivalirudin; **CABG** = coronary artery bypass graft; **CCU** = cardiac care unit; **CEA** = cost-effectiveness analysis; **CUA** = cost-utility analysis; **DRG** = diagnosis-related group; **ENOX** = enoxaparin; **FPX** = fondaparinux; **GRACE** = Global Registry of Acute Coronary Events; **IABCP** = intra-aortic balloon pump counterpulsation; **ICER** = incremental cost-effectiveness ratio; **LMWH** = low-molecular-weight heparin; **NR** = not reported; **NSTE** = non-ST-elevation; **OCCP** = Ontario Case Costing Project; **PCI** = percutaneous coronary intervention; **pt(s)** = patient(s); **STE** = ST-elevation; **TNK-tPA** = tenecteplase; **UFH** = unfractionated heparin.

Table IV. Quality of the studies

	[30]	[33]	[35]	[36]	[34]	[20]	[21]	[37]	[38]	[39]	[32]	[31]	[40]	[42]	[41]	[43]	[44]	[45]	[47]	[48]	[49]
Study population clear?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
Competing alternatives clear?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Economic study design appropriate to stated objective?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time horizon appropriate to include relevant costs?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Sources of cost and healthcare resource use stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Unit costs provided?	N	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Year of costing clear?	N	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N
Source of clinical outcome data stated?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Quality of clinical data good?	Y	Y	Y	Y	Y	N[a]	N[b]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
All important/relevant outcomes for each alternative identified?	NA	NA	NA	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
All outcomes measured appropriately?	NA	NA	NA	N[c]	NA	Y	N	N[c]	N[c]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
All future costs/outcomes discounted appropriately?	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	NA	Y	Y	Y	NA	Y	Y	Y	NA
Important variables, with uncertain values subjected to sensitivity analysis?	N	N	N	Y	Y	N	N	Y	Y	Y	N	N	N	Y	N	N	N	Y	Y	Y	Y
Generalizability of results discussed?	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Low risk of commercial bias?[d]	N	N	N	Y	N	N	N	Y	N	Y	N	N	N	N	N	N	N	Y	N	Y	N
Ethical and distributional issues discussed?	N	N	Y	N	N	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N	N

a Unblinded RCT; unclear concealed randomization; no intention to treat; underpowered.

b Small RCT; single blind; unclear concealed randomization; underpowered.

c Composite endpoint (death, myocardial infarction or refractory angina).

d Low risk means that the study is not funded by the industry *and* the paper includes a conflict of interest disclosure.

N = no; **NA** = not applicable; **RCT** = randomized controlled trial; **Y** = yes.

in ACS-STE with thrombolysis have been published (tables III and IV).

Kaul et al.[40] performed a cost-effectiveness analysis with a time horizon of 30 days and 1 year based on the ASSENT-3 trial[22] and US costs. In the bootstrap analysis, enoxaparin-based thrombolysis was more effective and less costly than thrombolysis based on UFH in 80% of cases at 30 days and 71% of cases at 1 year. The relative performance of enoxaparin and UFH in the US cohort and the entire ASSENT-3 study were comparable in both clinical outcomes and costs.

Three additional studies based on the ExTRACT-TIMI 25 study[23] have evaluated the cost effectiveness of enoxaparin versus UFH in patients with thrombolysis with data from the US,[42] Canada[41] and UK,[43] with a lifetime time horizon. In all three cases, the average cost per patient was higher in the enoxaparin-based strategy, but the incremental cost-effectiveness ratio (ICER) was within the limits usually accepted as cost effective. In one study[42] that conducted probabilistic sensitivity analysis, the cost per QALY gained was less than $US50 000 in 90% of cases; however, the unit cost of bleeding used in this study ($US200, range for the sensitivity analysis from $US100–1000) was well below that estimated in other studies.[44,47,49,55-57]

3. Direct Thrombin Inhibitors

Thrombin plays a central role in the mechanisms of coagulation, platelet activation and tissue injury.[58] Indirect thrombin inhibitors do not act on the level of thrombin included in the thrombus, which maintains its activity on coagulation factors and platelets. Direct thrombin inhibitors, acting both on fluid-phase thrombin and fibrin-bound thrombin, have an advantage over indirect upstream inhibitors on the accretion of thrombi. Its theoretical counterpart would be the risk of upstream accumulation of prothrombotic factors leading to the risk of rebound.[6]

3.1 Effectiveness Studies

Many direct thrombin inhibitors are available for therapeutic use. A meta-analysis published in 2002[59] found that the bivalent inhibitors (hirudin and bivalirudin) were more effective compared with UFH than univalent inhibitors, which seemed to be harmful compared with UFH. In addition, bivalirudin was associated with fewer bleedings than UFH, while other direct thrombin inhibitors were associated with more bleedings. It is not surprising, therefore, that the main trials of direct thrombin inhibitors in patients with ACS[24,60,61] have evaluated bivalirudin (table I).

The ACUITY trial[24] included medium-to-high-risk patients with NSTE-ACS managed with an early invasive strategy, and these patients were randomly allocated to one of three antithrombotic treatments: bivalirudin alone, bivalirudin associated with a GPIIb/IIIa inhibitor or heparin (LMWH or UFH) plus a GPIIb/IIIa inhibitor. Compared with heparin plus a GPIIb/IIIa inhibitor, bivalirudin monotherapy met the criteria of non-inferiority and was associated with a lower risk of major bleeding (3% vs 5.7%; $p < 0.001$) and net clinical effect (10.1% vs 11.7%; $p < 0.02$).

3.2 Economic Studies

Economic studies available are limited to the use of bivalirudin in NSTE-ACS managed invasively (tables III and IV).

Pinto et al.[44] reported an economic evaluation from the perspective of the health system based on the US subcohort of the ACUITY trial ($n = 7851$). The incidence of ischaemic events at 30 days was similar in the three groups. The risk of major and minor bleeding was lower in the group treated with bivalirudin monotherapy. Although the cost of the drug was lower in patients treated with heparin, the costs accrued at 30 days were lower in patients treated with bivalirudin monotherapy (actualized cost saving between $US134 and $US1022). Regression analysis showed that savings were caused by the reduction of both major and minor bleeding. In the simulation, the probability of cost savings with bivalirudin monotherapy compared with heparin plus upstream GPIIb/IIIa inhibitor was 85.3%.

A recent study[45] evaluated the cost utility of bivalirudin monotherapy versus heparin plus a GPIIb/IIIa inhibitor in patients with NSTE-ACS

treated with an early invasive strategy from the perspective of the UK NHS and based on the ACUITY study. A second parallel analysis compared bivalirudin with the usual strategy in the UK, using data from the Global Registry of Acute Coronary Events (GRACE).[62] Survival data, utilities and unit costs (actualized to year 2007/08 values) were derived from sources in the UK. The ICER was between £9.906 (ACUITY) and £12.276 (GRACE) per QALY gained. The probabilistic sensitivity analysis showed a cost per QALY below £20 000 in 72.1% (ACUITY) to 67% (GRACE) of cases.

4. Selective Factor Xa Inhibitors

Fondaparinux is a synthetic pentasaccharide that selectively inhibits factor Xa through an indirect mechanism dependent on antithrombin-III. It has a long half-life, and it can be administered SC once daily.[6]

4.1 Effectiveness Studies

The evidence on the effectiveness and safety of fondaparinux in NSTE-ACS comes from the OASIS-5 trial[25] and from a meta-analysis[63] of individual data of the studies OASIS-5 and OASIS-6[64] (conducted in patients with STE-ACS) [table I]. Because the available economic studies of fondaparinux in ACS refer to patients with NSTE-ACS, the effectiveness and safety of fondaparinux in STE-ACS is out of the scope of this paper.

In the OASIS-5 study,[25] 20 078 patients with NSTE-ACS were randomly allocated to receive fondaparinux (2.5 mg/day SC) or enoxaparin (1 mg/kg/12 h SC) for 8 days or until hospital discharge. The primary endpoint (death, myocardial infarction or refractory ischaemia) occurred in 5.8% of patients in the fondaparinux group versus 5.7% in the enoxaparin group, fulfilling criteria for non-inferiority. Major bleeding events were 2.2% in the fondaparinux group compared with 4.1% ($p < 0.001$) in the enoxaparin group. Interestingly, patients undergoing catheterization and treated with fondaparinux had more frequent catheter thrombosis (0.9% vs 0.4%; $p < 0.001$). At 6 months, the fondaparinux group showed a reduced risk of the composite endpoint (11.3% vs 12.5%; $p = 0.007$) and mortality (5.8% vs 6.5%; $p = 0.05$). This reduction in mortality seemed attributable to the reduction of bleeding during the acute phase.

The explanation for the low risk of haemorrhage from fondaparinux treatment has been the subject of intense debate. Indeed, the use of post-randomization UFH has been criticized for being more frequent in the enoxaparin group (13.4% vs 4.3%; $p < 0.0001$), suggesting the possibility of bias due to co-intervention.[65] However, the risk of major bleeding was consistently lower in all subgroups analysed, including patients who did not receive UFH after randomization.[66] It has been discussed whether the reduction of bleeding in the group treated with fondaparinux was due to the different safety profile of both drugs or to the use of non-comparable doses of enoxaparin and fondaparinux.[67,68] In a recent study, Anderson et al.[68] showed that fondaparinux 2.5 mg/day compared with enoxaparin 1 mg/kg twice daily produced a less variable and less intense anticoagulant effect, which could explain the reduced risk of bleeding with fondaparinux compared with enoxaparin, suggesting that less intense anticoagulation than that used in the past may be sufficient to prevent ischaemic events in patients with ACS treated with aspirin and clopidogrel.

4.2 Economic Studies

Sculpher et al.[46] reported a cost-utility study of fondaparinux versus enoxaparin in patients with NSTE-ACS performed from the French healthcare system perspective, based on data from the OASIS-5 (table III). At 6 months, fondaparinux was associated with a gain of 0.001 QALYs while saving €132. In the long term, the cost savings associated with fondaparinux disappeared, but the ICER remained within acceptable levels (€2758 per QALY gained).

Similarly, Sculpher et al.[47] conducted a cost utility from the perspective of the US healthcare system; the study had a time horizon of the patient's life and was based on the OASIS-5 study (tables III and IV). It was assumed that differences in the effectiveness between the two treatments

disappeared after 16 days. Costs during the first 6 months were estimated from resource consumption of 759 patients in the US subcohort of the OASIS-5 study. Utilities were calculated from the EQ-5D scale. Fondaparinux was associated with a saving at 180 days of $US547 (95% CI 207, 924) per patient. In the long term, fondaparinux was the dominant strategy in most scenarios examined. The dominance was lost only when including a covariate in the regression model, but the cost per QALY gained was within acceptable limits.

Latour-Pérez and de-Miguel-Balsa[48] reported a cost-utility analysis based on a Markov model from the Spanish health system perspective with a time horizon of the patient's lifetime, that compared the strategy of fondaparinux 2.5 mg/day versus enoxaparin plus an upstream GPIIb/IIIa inhibitor in patients with NSTE-ACS managed with an early invasive strategy (tables III and IV). It was assumed, according to data from the OASIS-5 trial, that the differential effects after day 30 were due entirely to the bleeding risk associated with each agent. The long-term survival and costs were obtained from Spanish sources. In the long term, fondaparinux was the dominant strategy, with a cost saving of $US55 per patient (actualized to year 2009 values). This dominance was robust within the reasonable range of variables (including patients at low risk of bleeding) and structural assumptions. The net health benefit increased directly with the risk of bleeding, the protective effect of fondaparinux and the bleeding severity score, and was inversely associated with age.

5. Multiple Comparisons

Two economic studies compared more than two anticoagulants (tables III and IV).

Shafiq et al.[21] conducted a randomized trial in India that compared the costs and clinical outcomes of enoxaparin, nadroparin and dalteparin in patients with NSTE-ACS. Unfortunately, the study lacked statistical power, and the results were inconclusive.

Maxwell et al.[49] performed a cost-effectiveness analysis based on a decision tree, which compared four strategies in medium-to-high-risk patients with NSTE-ACS: (i) UFH plus a GPIIb/IIIa inhibitor; (ii) enoxaparin plus a GPIIb/IIIa inhibitor; (iii) bivalirudin monotherapy; and (iv) fondaparinux plus a GPIIb/IIIa inhibitor. The final outcome was the absence of ischaemic or haemorrhagic complications. The data were obtained from the SYNERGY,[19] ACUITY[24] and OASIS-5[25] studies. In the baseline analysis, bivalirudin monotherapy dominated the strategy based on UFH or enoxaparin and was cost effective compared with fondaparinux. In the probabilistic sensitivity analysis, bivalirudin and fondaparinux showed a 'toss-up' situation. Unfortunately, differences in the profiles of patients included in each of the alternatives (obtained from trials with different inclusion criteria) and the difficult interpretation of the terminal nodes (which assigns equal weight to a death and to a minor haemorrhage) seriously limit the usefulness of these results for decision making.

6. Narrative Synthesis and Discussion

In this review, we identified 22 economic studies on anticoagulation in ACS. Thus far, nearly half of them were related to the use of enoxaparin as an alternative to UFH in patients with NSTE-ACS treated conservatively (table V). Only six studies reported on the cost effectiveness of new anticoagulants (factor Xa inhibitors and direct thrombin inhibitors), and none of them compared the new anticoagulants head-to-head, so the evidence is necessarily indirect.[49] On the other hand, the available economic studies focused on answering specific questions, which cover only a narrow spectrum of the potential scenarios that are relevant for the management of patients with ACS. Therefore, the availability of economic studies to inform clinical decisions about the use of anticoagulants in ACS is limited.

The overall quality of pharmacoeconomic studies included in this review is summarized in table IV. Some aspects should be highlighted. First, most of the studies made no declaration of conflicts of interest and/or were funded by the pharmaceutical industry. Therefore, the risk of commercial bias is not negligible.[69] Second, only 50% of the studies conducted sensitivity analyses,[34,36-39,42,45,47-49] and in many of them, this did not include important determinants of cost such as bleeding.[57] Third, the

Table V. Spectrum of pharmacoeconomic studies of anticoagulation in acute coronary syndromes

Patients	n	UFH	ENOX	BVD	FPX	RCT[a]
NSTE-ACS	12	X	X			ESSENCE (10 studies[b])
	2	X	X	X		ACUITY
	3		X		X	OASIS-5
	1		X	X	X	ACUITY + OASIS-5 + SYNERGY
STE-ACS	4	X	X			ASSENT-3 (1 study) + ExTRACT-TIMI 25 (3 studies)

a See table II for definitions of trial acronyms.

b Only ten of 12 studies were based on the ESSENCE trial. Malhotra et al.[20] and Shafiq et al.[21] were based on other trials.

BVD = bivalirudin; **ENOX** = enoxaparin; **FPX** = fondaparinux; **n** = number of studies; **NSTE-ACS** = non-ST-elevation acute coronary syndrome; **RCT** = randomized controlled trial; **STE-ACS** = ST-elevation acute coronary syndrome; **UFH** = unfractionated heparin.

outcome analysed was considered inadequate in almost one-third of the studies[21,36-38,49] mainly because of the unavoidable use of composite endpoints (i.e. 'death or non-fatal infarction'), which seriously hampers the significance of the cost-effectiveness ratios.

Clinical data were considered unreliable in only three studies.[20,21,49] However, the data on the effectiveness and safety of anticoagulation that support the economic studies are partly derived from studies with low levels of evidence.[8] On the other hand, none of the reported economic evaluations relied primarily on systematic reviews, which raises serious doubts about whether these studies were based on the best available evidence.[70,71] To the extent that the denominator of the ICER is the incremental effectiveness, the low quality of evidence on the effectiveness and adverse effects of anticoagulants seriously compromises the credibility of economic evaluations.

Regarding patients with NSTE-ACS, most studies concluded that enoxaparin is cost saving compared with UFH. Despite the high consistency between studies, it should be noted that these studies were not independent because nearly all of them were based on the ESSENCE study.[17] Secondly, cost saving in these studies was attributable to a reduction in the number of PCIs, which is feasible in the context of patients treated medically, but it may not be reasonable to expect in the context of an early invasive strategy, in which the prevalence of cardiac catheterization is much higher.[11] For example, in the SYNERGY trial,[19] which was conducted using a predominant invasive strategy, the proportion of coronary angiography performed during the first 30 days was virtually identical in the groups treated with enoxaparin and UFH.

Regarding patients with STE-ACS, the cost effectiveness of enoxaparin as an alternative to UFH has only been evaluated as an adjunctive therapy in patients undergoing thrombolysis. Although studies based on the ExTRACT-TIMI 25 trial[23] have shown favourable results for enoxaparin, some reservations exist pertaining to the possible underestimation of bleeding costs in these studies. On the other hand, the effect of enoxaparin on the risk of reinfarction was highly inconsistent ($I^2 = 72\%$), so the magnitude of the benefit is uncertain.

The cost effectiveness of bivalirudin in patients with NSTE-ACS treated with an early invasive strategy has been evaluated using data from the ACUITY trial.[24] The results favoured the use of bivalirudin alone compared with heparin plus a GPIIb/IIIa inhibitor[44,45] because of reduced incidence of bleeding. However, there are uncertainties about whether this economic benefit will continue in the context of increasing use of radial approaches in coronary angiography, which are less prone to bleeding.[72] Following the ACUITY study, the efficacy and safety of bivalirudin for patients with STE-ACS planned for primary PCI was assessed in another large trial (HORIZONS-AMI).[61] In this study, anticoagulation with bivalirudin alone, as compared with heparin plus GPIIb/IIIa inhibitor, resulted in significantly reduced 30-day rates of major bleeding and net adverse clinical events. Recent pharmacoeconomic studies published after the

journal acceptance of this manuscript suggest that the implementation of a bivalirudin-based strategy, instead of a heparin plus GPIIb/IIIa inhibitor-based strategy, would be cost saving from a hospital perspective in patients with STE-ACS undergoing primary PCI.[73]

Finally, fondaparinux was associated with a reduction in mortality in patients with NSTE-ACS at the expense of the reduction in bleeding.[25] The available economic evaluations based on the OASIS-5 trial were relatively consistent and suggested that fondaparinux may be cost effective as compared with enoxaparin (at the actual recommended doses) in patients with NSTE-ACS.[46-48] Unfortunately, at this moment, there are no data on the cost effectiveness of fondaparinux in STE-ACS.[64]

7. Conclusions

- Evidence on the cost effectiveness of anticoagulants is insufficient to inform the wide variety of clinical situations that occur in the management of patients with ACS. In particular, more studies are needed to examine the cost effectiveness of new anticoagulants in patients with STE-ACS and to compare the new anticoagulants among themselves.
- Taken together, the usefulness of economic studies on anticoagulants in ACS is compromised by the quality of the evidence on clinical effectiveness and safety; the lack of economic evaluations based on systematic reviews; the limited sensitivity analyses performed; and the risk of commercial bias.
- In patients with STE-ACS treated with fibrinolysis, enoxaparin compared with UFH increased the risk of haemorrhage but improved the 'net benefit'. Although the available studies reported a favourable cost-effectiveness ratio, these results should be interpreted cautiously because of the heterogeneity of the supportive randomized trials and the possible underestimation of bleeding costs.
- According to the available evidence, the use of enoxaparin (instead of UFH) reduced the average cost in patients with NSTE-ACS treated conservatively, but enoxaparin may not be a cost-effective alternative in patients managed with an early invasive strategy.
- The use of fondaparinux seems to be an economically attractive strategy over enoxaparin at usual doses in patients with NSTE-ACS.
- Bivalirudin monotherapy compared with heparin plus GPIIb/IIIa is probably a cost-effective strategy for the management of patients with ACS treated with an early invasive strategy.

Acknowledgements

This review was commissioned by the journal. The preparation of the manuscript was not supported by any external funding. The authors have no conflicts of interest that are directly relevant to the content of this review and the opinions expressed are those of the authors.

Dr Latour-Pérez contributed to the conception and design of the study; literature research; data extraction; data analysis and interpretation; and manuscript preparation and revision, and approved the final version of the manuscript.

Dra de-Miguel-Balsa contributed to the literature research; data extraction; data analysis and interpretation; and manuscript editing and revision, and approved the final version of the manuscript.

Dr Latour-Pérez is the guarantor of the overall content of this review.

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