

# Pharmacoeconomics of Low molecular Weight Heparin in Unstable Angina: A Critical Review

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**Abstract** – Economics assessment basically deals with science of drug cost, benefits and hope of survival in patients suffering from serious disease. This review focuses of the pharmacoeconomical factors associated with the use of low molecular weight heparin (LMWH) in unstable angina. Unstable angina (UA) or non ST elevated myocardial infarction (NSTEMI) is one of common ischemic manifestation of acute coronary syndrome (ACS) and a large cause of hospitalization. The purpose of this article is to review and evaluate the available literatures on economic assessment of low molecular weight heparin (LMWH) over unfractionated heparin (UFH) in the management of unstable angina to establish their role in reducing therapy load, improve the effectiveness of care, optimize patient outcomes and overall cost of care by focusing on the most effective strategies. Economic analysis consistently demonstrated the efficacy of enoxaparin (LMWH) in reducing cardiovascular events and mortality in UA/NSTEMI. Investigators concluded that high cost of enoxaparin for the treatment of unstable angina was offset by the savings and cost effectiveness associated with fewer hospital admissions, less coagulation monitoring (aPTT), reduce frequency of death, myocardial infarction (MI) and invasive procedures such as catheterization and angioplasty compared to UFH.

**Keywords** – Pharmacoeconomics, Low molecular weight heparin, Unstable angina

## 1. Introduction

Low molecular weight heparin (LMWH) is associated with patient compliance as it is easy to administer, or self-administer and does not require monitoring in comparison to standard unfractionated heparin [1]. The antithrombotic potential of low molecular weight heparin is well established and effectively replaced unfractionated heparin in many parts of the world [2]. The reason behind the outgrowth in prescription and use of LMWH lies in the fact that patients can effectively use it without hospitalization [3]. However the cost effectiveness of the medicine cannot be overlooked. Increase health care expenditures considered as crucial burden for population worldwide.

### Pharmacoeconomics

Health care is a right of citizenship which should not be dependent on an individual income and wealth. The objective of health services is to maximize the impact on the nation's health of the resources available. Pharmacoeconomics deals with health economics of drugs (input) and drugs treatment (output) by making a significant contribution to increase access towards care and ensuring sustainability. It usually provides quality care and life with minimum resources and costs. Guidelines and resources are available for health care professionals to achieve an economic task (low cost with improved outcomes) Clinical outcomes include cure, comfort and survival while economic outcomes include expense, saving and cost avoidance.. Moreover, economical aspects facilitates different parameters (cost-savings, cost-effectiveness, cost- minimization, cost- utility) to decrease disease load, increase survival rate and satisfaction of health care based on long term treatment benefits where clinical

practitioners mainly focus to seek immediate savings and effectiveness. Economic analysis concerned with physicians to compare two or more alternatives in order to select best treatment option regarding clinical benefits and cost. [4, 5] National Institute for Health and Clinical Excellence (NIHCE) and National Health Services (NHS) provide guidance for use of new and existing medicines, treatment and procedures with respect to efficacy and cost effectiveness in terms of health quality [6].

### Unstable angina and Prevalence

Acute coronary syndrome (ACS) is a large cause of hospitalization, comprised of several ischemic conditions including unstable angina (UA), NSTEMI, and ST elevation myocardial infarction (STEMI), described by clinical manifestation of advanced atherosclerosis with significant mortality and morbidity, therefore, an appropriate treatment is a major focus for practicing clinicians to produce an impact on patient outcomes and to reduce ischemic complications as possible [7].

According to Global disease burden (GDB) and World Health Organization (WHO),

Angina is considered as class 2 disability [8]. Unstable angina is a life threatening disorder and a leading cause of death worldwide. Treatment cost is a biggest issue due to required diagnostic and invasive procedures. It is reported in United State as main cause of every five deaths [9] or an average of one death at every 33 seconds was due to cardiovascular disease [10]. Cardiology Society of India, World Health Organization (WHO), National Institute of Health and Family Welfare (NIHFW), Indian Council of Medical Research (ICMR) estimated coronary artery disease

as number one killer in India by 2020 [11]. According to CRUSADE registry, more than 180,000 patients of unstable angina were admitted in US during period of 2001-2006 [12]. During (2008-2009), unstable angina cases were 25,040 in different Canadian province and calculated hospitalization cost per patient was \$6,445 by the Ontario province [13]. Reported number of unstable angina hospitalization in France (2009) was 62,254, in Italian region (2009) was 35,282, in United Kingdom (2009) was 52,296 and hospitalization cost for unstable angina in UK was 25,298 (pounds sterling) including hospital stay charges, laboratory charges,

consultant fee and cost of therapy [14].

### Summary of Guidelines and Recommendations for LMWH and UFH

Guidelines and recommendations are intended to assist physicians and cardiologist to standardize treatment pattern along with quality improvement tools. It reflects consensus of expert opinion after a thorough review of the available current scientific evidence to improve patient care with UA/NSTEMI

World Health Organization (WHO) [15]	Enoxaparin sodium is the first International low molecular weight heparin (LMWH) reference standard.
Food Drug and Administration (FDA) [16, 17]	The U.S FDA approved Enoxaparin sodium (Lovenox) as first LMWH. Furthermore recommendation based on the ESSENCE (efficacy and safety of subcutaneous enoxaparin in non-Q wave coronary events) trial compared enoxaparin with unfractionated heparin (UFH) for prevention and treatment of unstable angina and non-Q wave myocardial infarction. The FDA approved Dalteparin on the basis of the FRISC (fragmin during instability in coronary artery disease) trial, comparison of dalteparin with placebo for prevention and treatment of unstable angina and non-Q wave myocardial infarction.
American Heart Association/ American College of Cardiology 2002 [18, 19]	For early conservative management of UA/NSTEMI patients, use Enoxaparin or unfractionated heparin (Class IA). For early invasive treatment strategy, enoxaparin is considered preferable to unfractionated heparin unless coronary angio bypass grafting (CABG) is planned within 24 hours. Guideline recommend enoxaparin sodium (Lovenox) on the basis of clinical trials ESSENCE, TIMI and meta-analysis showed 20% significant reduction in ischemic events over UFH in acute management of UA/NSTEMI.
American College of Chest Physician 2008 [20]	For UA/NSTEMI, early invasive strategy, recommend UFH over LMWH and for early conservative strategy or delayed invasive strategy recommend LMWH over UFH.
American Heart Association/ American College of Cardiology 2007 [21], 2012 [22], 2013 [23]	For UA/NSTEMI patients, invasive strategy select enoxaparin and UFH For initial conservative strategy, enoxaparin is preferable to UFH unless coronary artery bypass graft surgery (CABG) is planned within 24 h.

### Economic considerations of LMWH

Economic outcomes play important role to assess the true value of healthcare interventions. Economic evaluation remain essential during almost all stages of pharmaceutical design and use Quality of care along with cost found to be the main. objective Review of several studies mainly focused the economic analysis of low molecular weight heparins (LMWH) for unstable angina (UA), common reason of hospitalization and contribute major cost of care. Unfractionated heparin (UFH) has traditionally been the treatments of choice but recently, a number of randomized controlled trials have been conducted to evaluate the role of low-molecular-weight heparins (LMWH) and emerging evidence suggest that LMWH offer potential advantages over UFH in terms of cost effectiveness, cost savings in the management of patients with unstable angina or non-ST elevated myocardial infarction.

The World Health Organization (WHO) and United States Food and Drug Administration (US-FDA) regard LMWHs as individual drugs that cannot be used interchangeably [24].

On the basis of FRISC (Fragmin during Instability in Coronary Artery Disease) and FRIC (Fragmin in Unstable Coronary Artery Disease) trials, dalteparin found to be

effective as heparin. ESSENCE (Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events), TIMI 11B trial and meta-analysis revealed significant reduction in death, recurrent angina, urgent revascularization and myocardial infarction by the use of enoxaparin [25]. Evidence and clinical trials for the use of dalteparin from cost effective and cost saving point of view was insufficient to support its use in UK clinical practice as compared to enoxaparin. Cost effectiveness usually expressed in terms of cost per QALY gained (Quality adjusted life yearly) and calculated reduced cost was £317 per person with a QALY gain of 0.013 treated UA/NSTEMI patients with enoxaparin against unfractionated heparin. Results from UK perspective analysis showed enoxaparin sodium as cost effective during hospitalization at 30 days and 1-year follow-up compared with UFH. ESSENCE trial represents low cost of enoxaparin (£10.80/day over UFH £12.16/day) similarly reduced dose regimen of enoxaparin 0.75mg/kg from usual dose 1mg/kg also supported cost savings [26, 27]. Various pharmacoeconomic evaluations conducted in Canada, France, United State, United Kingdom, South America described cost savings associated with enoxaparin [28]. Economic studies based on ESSENCE trial suggested enoxaparin as an attractive alternative LMWH among available choices over UFH due to lesser number of revascularization procedures in patients of

UA/NSTEMI [29]. Economic analysis of ESSENCE trial from US perspective showed the mean cost of enoxaparin for 2.5 days was \$155 and for UFH was \$80 but due to reduced number of percutaneous coronary intervention (PCI) and diagnostic catheterization, enoxaparin saved \$763 at hospital discharge and \$1172 at 30 days rather than UFH [30, 31, 32, 33]. Cost effective analysis from a Canadian hospital perspective showed the average total direct medical cost per patient was \$Can848 with the enoxaparin strategy versus \$Can892 with the unfractionated heparin strategy [31]. The main contribution relates with cost savings included less number of laboratory assays, reduced length of hospitalization, low need of cardiac procedures, decreased nursing hours, simple administration technique by subcutaneous (S/C) injection rather than (I/V) injection in case of unfractionated heparin, such reasons have made enoxaparin as recommendation of preferable antithrombotic agent for acute coronary syndromes in recent guidelines [34, 35, 36]. French sub study of ESSENCE trial also support enoxaparin as cost saving due to significant reduction in angioplasty and angiography, automatically decrease hospitalization stays [37]. Enoxaparin considered to be more cost-effective around the globe than unfractionated heparin (UFH) for acute coronary syndrome due to lesser number of revascularization procedure and those do not require urgent cardiac catheterization because major cost contribution are associated with occurrence of MI and revascularization like percutaneous coronary intervention (PCI) or coronary angiobypass grafting (CABG), no sufficient economic data available for other low molecular weight heparin [29, 38, 39].

## 2. Conclusion

Increasing health care cost is a major concern in the developing world and has increased the individual economical burden. Unstable angina patients are mainly affected by the high price regimen associated with consultant fee, drug cost, lab monitoring and diagnostic charges, cardiac catheterization or revascularizations. Therefore, pharmacoeconomics are essential for physicians to prescribe individualized drug based on minimal costs and cost-effectiveness of the drug therapy.

Several economic studies conducted on low molecular weight heparin concluded that although the acquisition costs of enoxaparin is higher than those of conventional unfractionated heparin, but this greater expenditure is offset by decrease in total costs because of improved clinical outcomes (reduced myocardial infarction (MI), death, recurrent angina, lesser need of revascularization procedures), shorter hospital stays and absence of routine anticoagulation monitoring. The pharmacoeconomic evaluation clearly demonstrate significant cost savings, cost effectiveness and sustained clinical benefits in favor of enoxaparin over unfractionated heparin in patients with unstable angina. Investigators furthermore need to analyze the costs and benefits of health care interventions.

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