INTRODUCTION

Cardiovascular diseases (CVDs)-related deaths in 2002 were more in India compared to other countries of the world. 52% of CVD in India occur below the age of 50 years and about 25% of acute myocardial infarction (AMI) in India occur below the age of 40 years. Disability-adjusted life years lost due to CAD per 1000 populations in India are three times higher than in developed countries, thus having sustainable implication on Indian growing workforce [1-4]. Rates of primary percutaneous coronary intervention (PCI) were lower while that of thrombolytic treatment was higher than in developed countries. This is probably because three-fourth of the patients in India have to pay directly for their own treatment. The rates of coronary artery bypass graft were even lower in Indian patients. The reasons for poor invasive cardiac procedures are numerous and evident [1]. In Indian condition with delayed access to a minimum number of catheter laboratories and insurance benefits being a rarity, pre-hospital and in-hospital thrombolytic has become the choice for patients with acute coronary syndrome (ACS), where many patients bear the economic burden of pharmacological thrombolytic. The present study was carried out to evaluate the pattern of prescribing of pharmacological thrombolytic agents in hospitalized ACS patients and associated cost burden.

METHODS

A prospective observational cohort study of prescription was conducted for in-patient admitted to intensive care unit for thrombolytic and antithrombotic drug utilization pattern. The direct cost analysis was performed from patient’s perspective where a direct cost was calculated using pharmacy bills. All other cost was assumed to be same.

Results: Data of 288 patients were collected from which 108 (37.5%) patients were ST-elevation myocardial infarction (STEMI) and 180 (62.5%) patients were non-STEMI. The mean number of drugs prescribed was 11±2 which constitutes a mean of 3.1±0.7 reperfusion drugs. 59% of patients were prescribed with enoxaparin (0.6 ml/seconds route) for the mean duration of 4 days. The average prescription cost for ACS admission was around Rs.7159.5±5137.2 (Rs.1101-Rs.22202). The average cost of pharmacological thrombolytic therapy was Rs.4557±468.3 (Rs.23-Rs.12542). The mean cost of pharmacological thrombolytic therapy was found to be 63% of the total direct cost of drugs borne by the patient. The cost of therapy was positively correlated with duration of stay (p=0.000) and insignificantly correlated with a number of drugs.

Conclusion: Antiplatelets were the most preferred followed by anticoagulants. The mean number of drugs per encounter was high but was rational as per standard guidelines. The mean cost for pharmacological reperfusion therapy was found to be more than half of mean prescription cost for the management of ACS.

Keywords: Acute coronary syndrome, Thrombolytic therapy, Cost, Medication management.

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entered for each distinct drug. Cost analysis was performed from patient's perspective. The cost of the drug was defined as the acquisition cost to the patient by the retail pharmacy within the hospital campus. Direct cost of pharmacological treatment was calculated using patient's pharmacy bills. In each case, the price was calculated finally on a per unit basis for the strength and form actually used and then multiplied by a number of units actually administered to determine the cost of each drug received by a patient. Cost figures were assembled for each drug received by a patient, for all drugs received during an admission, and for all drugs prescribed in hospitals. Finally, total cost for all drugs received by the patients during 12 months period was calculated.

Statistical analysis used
The standard descriptive statistics were used, and all the collected data were analyzed using Microsoft Excel spreadsheet and interpreted. The results were evaluated against the set criteria and thresholds and presented in tables and figures. The data were represented as mean, numbers, or percentages. Pearson's coefficient used to correlate between a number of drugs, stay in days, and cost of therapy. p<0.05 was considered statistically significant.

RESULTS
A total of 3201 drugs were prescribed in 288 patients. Mean number of drugs prescribed per patients was 11. Antiplatelet drugs were most frequently prescribed in 92.5% of the patients. Aspirin of drugs prescribed per patients was 11. Antiplatelet drugs were preferably, enoxaparin and unfractionated heparin (UFH) were equally practiced as anticoagulants either alone or together (administered on a different day) in each of the 171 (59%) patients. Streptokinase was used as initial fibrinolytic agent only limited to 108 (37.5%) patients (Table 2).

The other class of drugs prescribed was antihyperlipidemia (atorvastatin) and antiemetic (ondansetron) in 90.62%. Pantoprazole was prescribed in 87% patients. A total of 180 (62.5%) antimicrobial drugs were used among which commonly prescribed was ceftriaxone (31.25%).

Mean total cost of pharmacotherapy per patient was Rs. 7159.5±137.2 among which the mean cost for thrombolytic and antithrombotic therapy was Rs. 4557±468.3 (Fig. 2). Average number of drugs per patient was found to be 11±2. Duration of ICU stay was not positively correlated with number of drugs (Pearson’s correlation r=0.31, p=0.08). Cost of therapy was positively correlated with duration of stay (Pearson’s correlation r=0.59, p=0.000) and not positively correlated with number of drugs (Pearson’s correlation r=0.27, p=0.12).

DISCUSSION
The study was carried out with the aim to estimate the cost incurred for pharmacological thrombolytic and antithrombotic therapy during a hospital stay in ACS patients and to identify the indicators that decline the cost of the same. The mean age of patients in our study was slightly lower when compared to a study that reported 60.45±12.45 and 64 years [6]. The majority of the patients in our study were male which is comparable to earlier Indian and foreign studies [7,8]. In our study, prevalence of hypertension and type 2 diabetes is generally 50%. However, in our study, the prevalence of these comorbid conditions was lower than in Indian study performed [9]. A pattern of comorbid condition varies within study population. Mean stay in ICU was higher.
Table 2: Percentage prescribing and cost (Rs.) accrued for individual pharmacological thrombolytic therapy

<table>
<thead>
<tr>
<th>Drug group</th>
<th>Drugs</th>
<th>ATC code</th>
<th>Number of patient, n (%)</th>
<th>Total cost (Rs.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet</td>
<td>Aspirin</td>
<td>B01AC06</td>
<td>90 (93.75)</td>
<td>179.1</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>B01AC04</td>
<td>87 (90.62)</td>
<td>2772</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>Enoxaparin</td>
<td>B01AB05</td>
<td>57 (59.37)</td>
<td>329920.8</td>
</tr>
<tr>
<td></td>
<td>UFH</td>
<td>B01AB03</td>
<td>57 (59.37)</td>
<td>21840</td>
</tr>
<tr>
<td></td>
<td>Warfarin</td>
<td>B01AD04</td>
<td>3 (3.12)</td>
<td>90</td>
</tr>
<tr>
<td>Fibrinolytic</td>
<td>Streptokinase</td>
<td>B01AD01</td>
<td>36 (37.5)</td>
<td>82285.5</td>
</tr>
</tbody>
</table>

UFH: Unfractionated heparin

compared with other studies [10,11]. The possible reasons may be due to difference in practice policies in different hospitals. Duration of ICU stay was not positively correlated with a number of drugs which contradicts the known fact [12], possibly due to the management strategy followed in ACS.

In an Indian study [13], mean number of drugs was more than 10, which was also observed in our study but was in contrast to a study that reported prescribing of <10 drugs per patient [6]. This difference can be due to difference in morbidity pattern and different prescribing practices in different countries. As per ACC/AHA guidelines, there are three classes of recommendations. Class 1 drugs are those having highest benefit-risk ratio and recommended. Class 2 drugs are those with somewhat less benefit-risk ratio compared with class 1 and are probably recommended. Class 3 drugs are those that are not recommended or potentially harmful. In our study considering rationality based on ACC/AHA guidelines for ACS in all NSTEMI patients, guidelines were adhered to. As far as drug therapy for STEMI is concerned, majority of prescriptions adhered to the guidelines in the form of Classes 1 and 2 recommendations. The use of aspirin, clopidogrel, UFH, LMWH, and fibrinolytics was used as clot dissolving and prevention cocktail strategies according to standard ACC/AHA guidelines [14].

AntiplaeteLet drugs were most frequently prescribed, it was found to be similar and comparable to other studies [15]. Aspirin and clopidogrel were mostly preferred for inhibition of blood clots in coronary artery and peripheral vessels in majority of the patients. In our study, none of the patients received GP IIb/IIIa receptor antagonist as none of our patients underwent primary PCI. Only one-third of the patients received fibrinolytics depending on their early presentation, and more than 50% were prescribed with enoxaparin and UFH. Streptokinase was not commonly used agent compared to LMWH and UFH though it is the least expensive option available. This is due to questionable effect on late presentation to hospital and possible adverse effects [16]. Other studies had a higher use of thrombolitics as compared to our study in suspected ACS [17-19]. UFH alone has been used for anticoagulation in the majority of patients after undergoing fibrinolysis (streptokinase). Even LMWH has been preferred alone as well as after fibrinolysis in STEMI patients. More than one-third of the patients were prescribed initially with UFH and then switched to LMWH after 1-2 days. This strategy is probably used because of half-life of UFH is 30-60 minutes as compared to enoxaparin having half-life of 4-6 hrs [20]. Switching strategy is preferred as many evidence suggest LMWH as an effective alternative antithrombotic therapy to UFH because of its favorable pharmacokinetic profile and clinical advantages [15,21,22]. In our study, LMWH has been used in more than 60% of patients because of its safety profile compared to UFH. Warfarin is least preferred among all the anticoagulant because of its side effects’ profile and frequent monitoring.

Mean cost of pharmacotherapy was higher compared to other few Indian studies [8]. Among all drugs, 41.1% were administered parenterally adding a significant cost burden to patients. About 83% of total cost of pharmacological therapy was attributed to these parenteral drugs. It was found that about 64% of cost was attributed to reperfusion therapy from the total cost. LMWH alone accrued 48% of cost burden on patients from cost of reperfusion therapy. This is due to high cost of LMWH available in the market ranging from Rs. 409 to 579. Enoxaparin (Rs. 579) has been the preferred LMWH in mean dose 0.6 ml administered subcutaneously for a mean duration of 4 days. Fondaparinux is the least preferred in our study though one of the studies reported it to be cost saving alternative among the available LMWH [23].

Recommendations
1. Including a cost-effective alternative of enoxaparin brand available in the market can reduce the price burden from 48% to 32%. This can be properly implemented if there would have been a formulary guided by pharmacist and proper drug utilization studies.
2. Another strategy to overcome the price burden would be to continue with streptokinase followed by UFH (least cost) for the in-patients associated with least risk factors and no observed contraindications as they are under continuous monitoring in the ICU.

These recommendations may require a formulary-based intervention study to measure the cost burden on the patient for the management of ACS.

CONCLUSION
Antiplaetelets were the most preferred followed by anticoagulants. Mean number of drugs per encounter was high but was rational as per standard guidelines. The mean cost for pharmacological reperfusion therapy was found to be more than half of mean prescription cost for management of ACS. LMWH (Enoxaparin) was found to accommodate the maximum cost of treatment per patient. Incorporating a cheaper cost-effective LMWH can save one-third of pharmacological cost and one-fourth of total prescription. Streptokinase and UFH can be preferred strategy to reduce the substantial cost burden of reperfusion therapy, until unless contraindicated.

REFERENCES
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