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Does The Pharmacological Management Of Unstable Angina Vary With Age And Gender – A Descriptive Study

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ABSTRACT

Purpose: Observational registries have shown the underutilization of evidence based therapies in women and elderly patients. While the burden of unstable angina is high in India, there is minimal data on the drug utilization patterns. Also, gender and age differences in the treatment have not been assessed. This study intends to present the data on drug utilization in the management of unstable angina in a tertiary care hospital and to detect the presence of significant gender or age related differences in the treatment. Method: The case record files of all patients who were admitted with unstable angina during January 2006 to December 2008 were studied. The demographical details, comorbidities, the duration of the hospital stay, outcomes and the drugs administered within 24 hours of admission and at discharge for each case was obtained. Results: Of the 318 patients, 63.2% were males and 55.7% were less than 65 years of age. The mean (± SD) age of the males was 60.64 (± 11.71) years as compared to the mean age of 64.21 (± 9.98) years in females (p=0.006). The overall mortality was 1.89 %. There was an underutilization of aspirin and betablockers in the elderly, while antiplatelet agents and angiotensin converting enzyme inhibitors were used to a lesser extent in females. The prescription rate of statins was high. Conclusion: There was an underutilization of drugs in the elderly and in female patients. The results are similar to the data reported from previous studies. The diagnosis and management of unstable angina poses a difficult challenge because these subgroups quite often present with atypical symptoms and have less extensive coronary artery disease.

Key words - Drug utilization, unstable angina, gender, age

Key Points: Observational registries have shown the underutilization of evidence based therapies in women and elderly patients with acute coronary syndrome. Our study in patients with unstable angina in India revealed similar findings. The presence of atypical symptoms, less extensive coronary disease and increased comorbidities in these groups might pose diagnostic and therapeutic challenges.

In recent years, considerable new information has come to light concerning the diagnosis and

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the subsequent management of patients with unstable angina (UA). The course and the prognosis of unstable angina is variable, but
there is a high risk of myocardial infarction and death during the initial 2-3 months [1]. While the short term mortality is low as compared to patients with ST-elevation myocardial infarction (STEMI), the long term outcomes for mortality and recurrent ischaemic events are higher [2]. Observational registries have shown the underutilization of evidence based therapies in women and elderly patients. Differences in cardiac care according to gender have been described over the past two decades. Two key areas which are responsible include the lower utilization of effective diagnostic strategies and the perception that women are at a lower risk than their male counterparts [3]. Some studies suggest an equal delivery of cardiac care to both the male and female genders, once the diagnosis is established [4]. However, a recent study which looked into the data of 35,875 patients with non ST-elevation acute coronary syndrome, who participated in the CRUSADE (Can rapid risk stratification of unstable angina patients suppress adverse outcomes with early initiative of the American College of Cardiology/American Heart Association guidelines) national quality improvement initiative, reported a less aggressive treatment of women than men, despite having a higher in-hospital risk of morbidity or mortality [5]. Elderly patients with unstable angina tend to have atypical presentations of disease, substantial comorbidity, ECG stress tests that are more difficult to interpret and different responses to pharmacological agents as compared to the younger patients [6].

While the burden of unstable angina is high in India, there is minimal data on the utilization of various evidence based medicines in the management of the disease. The largest study to date in India is based on the data from the CREATE registry, a prospective multicentre study which was done to determine the treatment and outcomes of acute coronary syndrome (ACS). However, gender and age differences in the treatment were not assessed in this study [7]. Also, the treatment received on hospital admission and discharge needs to be considered separately, since the early initiation of certain drugs can significantly decrease mortality or subsequent morbidity. This study intends to present the data on drug utilization in the management of unstable angina in a tertiary care hospital and to detect the presence of significant gender or age related differences in the treatment.

**Methods**

The study was done at a tertiary care hospital with a dedicated coronary care unit in Southern India. The inpatient registry was searched to identify the patients who were admitted with unstable angina during the period from January 2006 to December 2008. The initial case selection was based on the International Classification of Disease Code (ICD-10, I20), which was later confirmed by going through the patient history and investigations which were recorded in the case file. The patients who were referred from other hospitals were not included in the study. Mandatory approval from the Institutional Ethics Committee was obtained prior to the initiation of the study. The demographical details, comorbidities, the duration of the hospital stay, outcomes and the drugs administered within 24 hours of admission and at discharge for each case was obtained. The use of the following drugs was recorded – nitrates, antiplatelet agents, beta blockers, calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), diuretics, hypolipidaemics, nicorandil, Pfox inhibitors and anticoagulants.

Elderly patients were defined as those with ≥ 65 years of age. Drug utilization was defined as the percentage of patients receiving a particular drug.

The continuous variables have been presented as mean±SD and were compared by using the unpaired t test. The categorical variables have been compared by the Pearson’s Chi square test. The odds ratio and the adjusted odds ratio have been presented. The binary logistic regression model was used for this adjustment. The baseline variables which were adjusted for in the model were age, gender, hypertension, diabetes, hypercholesterolaemia, prior myocardial infarction, ischaemic heart disease and chronic...
kidney disease. P value of <0.05 was considered to be statistically significant. The SPSS version11.5 software package was used for statistical analysis.

**Results**

The case record files of 318 patients who were admitted with unstable angina during the years from 2006-2008 were retrieved from the medical records section and were studied. 63.2% were males. 55.7% were less than 65 years of age. The mean (± SD) age of the males was 60.64 (± 11.71) years as compared to the mean age of 64.21 (± 9.98) years in females. The females were significantly older than the males \( p = 0.006 \).

The median (25th percentile, 75th percentile) duration of hospital stay was 6 (4, 8) days. The overall mortality was 1.89 %. The mortality rate in males, females, patients aged < 65 years and the elderly were 2.55, 0.86, 2.31 and 1.44 percent, respectively. The difference among the groups was not significant.

The distribution of comorbidities according to gender and age is shown in [Table/Fig 1]. A significantly larger percentage of elderly patients were hypertensive and had ischaemic heart disease and chronic kidney disease. With regards to gender, there were more hypertensives and hyperlipidaemics among the females than the males.

*Data obtained for 262 patients.

The utilization rates of various groups of drugs within 24 hours of admission and at discharge are shown in [Table/Fig 2]. The commonly prescribed drugs were as follows – isosorbide mononitrate among the nitrates, clopidogrel among the antiplatelet agents, metoprolol among the beta blockers, amlodipine among the CCBs, ramipril among the ACE inhibitors, atorvastatin among the hypolipidaemics and unfractionated heparin (UFH) among the anticoagulants.
Discussion

The gender distribution of the patients in our study was similar to that found in other studies, which showed the predominance of the male gender. The age at presentation was considerably lower as compared to those of the patients in the CRUSADE registry (Median age of 65 years in males and 73 years in females) [5]. Various studies have shown that the presentation of coronary disease occurs a decade earlier in Indians and other Asians [8]. The CREATE registry investigators reported a mean age of 59.31±11.83 years in patients with NSTEMI [7]. With the improvement in the standard of living and access to health care, there is a steady increase in the population which survives beyond 65 years of age. In our study, elderly patients constituted 44% of the total cases. The elderly patients significantly more often had hypertension (78.0% vs 59.9%), ischaemic heart disease (53.2% vs 40.7%) and chronic kidney disease (14.9% vs 5.1%) as compared to the younger patients. Similarly, a gender difference in the presence of
comorbidities was seen, with more hypertension and hyperlipidaemia in women. The CRUSADE investigators also showed that women with unstable angina were more hypertensive [5]. Similarly, the TIMI III Registry Study Group reported an increased likelihood of women to have a history of hypertension and diabetes mellitus [9]. Although in our study, more women had diabetes than men, which corroborated with previous studies, the difference was not significant.

More than 95% of the patients received antiplatelet agents and more than 90% received hypolipidaemics within 24 hours of hospital admission as well as on discharge. Among the antiplatelet agents, clopidogrel was utilized to a greater extent than aspirin. The CRUSADE investigators reported a greater use of aspirin (91.6% versus 41% for clopidogrel on admission, 90.4% versus 53.2% for clopidogrel on discharge) [5]. The reasons for the higher utilization of clopidogrel in our study include its better gastrointestinal safety profile and the numerous clinical trials over the past few years, supporting the use of dual antiplatelet therapy. The combination of clopidogrel plus aspirin has been shown to confer a 20% reduction in cardiovascular death, MI, or stroke as compared to aspirin alone, in both low and high-risk patients with UA/NSTEMI [10]. For secondary prevention, clopidogrel alone is at least as effective as or modestly more effective than aspirin [11]. In our study, 70.4% of the patients within 24 hours of admission and 66.3% of the patients at the time of discharge were prescribed a dual antiplatelet therapy of aspirin and clopidogrel. Numerous trials have shown that early initiation and long-term treatment with statins reduce the risk of recurrent ischaemic events post-ACS, despite only modest angiographic reductions in the severity of coronary stenoses [12],[13]. While the guidelines recommend the initiation of hypolipidaemic drugs prior to hospital discharge, there is evidence that initiation of a statin within 24 hours of admission lowers the incidence of death, stroke, reinfarction, heart failure and pulmonary oedema as compared to delayed administration of the drug [14]. Atorvastatin was by far the most commonly used hypolipidaemic agent in our study, being prescribed in 88.7% and 91.7% of the patients within 24 hours of admission and at discharge respectively. These prescription rates are much higher than those reported by the CRUSADE (59.65% for statins on discharge) or CREATE investigators (53.9% for hypolipidaemics during hospitalization) [5],[7].

The use of ACEI/ARBs was similar in extent, while the use of beta blockers and heparin was less as compared to that reported by the CRUSADE registry. ACE inhibitors improve endothelial dysfunction, reduce the progression of atherosclerosis and prevent plaque rupture and thrombosis, apart from their well known benefits in patients with LV dysfunction and in post-MI patients [15],[16]. ACEIs are useful if hypertension, diabetes, LV systolic dysfunction or heart failure complicates ACS. If tolerated, an ACEI may be used in all post-ACS patients [17]. Among the beta blockers, metoprolol was commonly prescribed. Beta blockers are effective when used singly in UA and in combination with nitrates to reduce subsequent MI or recurrent ischaemia [18]. The CREATE investigators reported the use of beta blockers in 61.9% of the NSTEMI patients. Various studies have reported the use of beta blockers ranging from 44.7% to 81.6% [5],[7],[9]. In our study, unfractionated heparin was used in 36.8% of the patients and enoxaparin was used in 25.2% of the patients. Enoxaparin has several advantages over UFH, namely, the more effective inhibition of thrombin generation and less thrombocytopaenia [19]. The American College of Cardiology (ACC) and the American Heart Association (AHA) guidelines recommend enoxaparin over UFH. However, due to the higher cost of enoxaparin, its utilization was less in our study. In the study conducted by Malhotra S et al., the use of enoxaparin was more than that of UFH (57% vs 33%). But, enoxaparin accounted for about 60% of the total expenditure on a prescription [20].

With respect to age, a significantly less utilization of aspirin and beta blockers was seen in elderly patients. The difference was seen after the adjustment for baseline demographics and co-morbid conditions, as well. Similar findings
have been reported by other studies [9],[21]. Although older age and the presence of comorbidities would tend to increase the benefit of treatment, these characteristics are often associated with under-treatment, probably due to the fear of complications or the lack of adequate clinical trial evidences in the elderly. Studies have reported the increased use of nitrates, diuretics and CCBs in elderly patients. Similar findings were seen in our study. The increased use of nitrates on discharge was probably due to an increased risk of recurrent angina in the elderly. CCBs tend to be overused in the elderly patients despite their detrimental effects on the survival [15]. One of the likely causes is the presence of comorbid hypertension. In our study, CCBs were more commonly used in the elderly, but the difference was not significant after adjusting for the baseline factors.

Previous studies have reported that women are less likely to receive antiplatelet agents, ACEI/ARBs, statins and heparin as compared to men. Our study revealed a significant underutilization of aspirin on admission along with clopidogrel and ACEI on discharge. In one of the largest studies to date, the National Registry of Myocardial Infarction-1 investigators found that similar treatment disparities existed among the STEMI patients [16]. The pattern of relative underuse was similar, considering older, more established therapies such as aspirin, or newer ones such as clopidogrel, despite greater cardiac disability in women. However, the ACC/AHA guidelines are clearly gender neutral.

The under-treatment of women with UA was possibly due to multiple reasons. Women are more likely to have atypical symptoms such as dyspnoea and to have chest pain which is unrelated to coronary artery disease [22],[23]. Elevated biomarkers are less often seen in women [5]. Coronary artery disease tends to be non-obstructive and less extensive, as revealed by angiography studies [24]. This profile makes it challenging to confirm the diagnosis of UA/NSTEMI and is a likely cause of underutilization. As women present at an older age, many have high-risk baseline features. This often leads to underutilization of drugs due to the fear of complications. One possible reason for aspirin underutilization is an increased incidence of bleeding in older women.

Limitations of the study

The major limitation of this study was that it was conducted in a tertiary care hospital and therefore, it was not representative of all hospitals in India. It would be beneficial to conduct further studies in other regions of India in order to compare the prescribing practices and take corrective measures, if any.

We have not looked into the long term outcome of patients who were treated for unstable angina. Therefore, although there was data to suggest the underutilization or the overutilization of drugs in certain groups, whether this difference in the drug prescribing patterns altered the outcome of the disease or not, cannot be said. However, since there is no difference in the in-hospital mortality, it can be said that the observed treatment differences did not adversely affect the immediate survival. Also, the statement about the underutilization of drugs is a relative one. The comparison between the genders and the age groups with adjustment for the baseline variables provides a reliable estimate. However, the determination of absolute underutilization would require the recording of other variables like cardiac markers, the TIMI (thrombolysis in myocardial infarction) score, the presence of contraindications for drugs, etc., which has not been done in our study. Similarly, general statements about underutilization wherever mentioned is in comparison to other similar studies.

Conclusion

This study identified the underutilization of drugs in females and in elderly patients, particularly antiplatelet drugs, despite a high overall use. Determining the specific causes for underutilization requires a more elaborate study. Our results are similar to the data reported from previous studies done in Europe and America. The prescription rate of statins was considerably high, as compared to that in other studies. There was no difference in the in-hospital mortality.
among any groups. The diagnosis and the management of unstable angina in women and the elderly poses a difficult challenge, because these subgroups of patients quite often present with atypical symptoms and have less extensive coronary artery disease. The clinicians need to keep in mind these differences when prescribing drugs for unstable angina.

References


