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Original Research Article

Evaluation of management in acute coronary syndrome and extent of adherence to standard treatment guidelines

Aalesh Shah[1], Nehal R. Parikh[2,3], Devang Rana[1], Supriya Malhotra[1], Tejas Patel[4]*

[1]Department of Pharmacology, Smt. Nathiba Hargovandas Lakhmichand Municipal Medical College, Ellis-Bridge, Ahmedabad, Gujarat, India
[2]Raptim Research Pvt Ltd, Navi Mumbai, Maharashtra, India
[3]Department of Pharmacology, Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India
[4]Department of Cardiology, SVP Hospital, Ellis-Bridge, Ahmedabad, Gujarat, India

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***Correspondence:**
Dr. Tejas Patel,
Email: tejaspatel@apexheart.in

ABSTRACT

Background: India has the highest burden of acute coronary syndrome (ACS) in the world. This research is to evaluate prescriptions pattern and extent of adherence to American College of Cardiology (ACC)\American Heart Association (AHA) guidelines in the management of ACS with patient outcome.
Methods: Case record form containing patient's demographic, clinical profile, diagnosis, prescription drugs (with dose, duration and frequency) were noted. Pharmacotherapy was compared to ACC/AHA guidelines, to evaluate adherence, guideline adherence index (GAI-5) was used for 5 major drug groups for ACS. GAI was calculated as: number of patients using the prescribed medications/number of eligible patients multiplied by 100.
Results: A total of 172 patients diagnosed with ACS. 64 (37.20%) Patients with the highest preponderance to ACS belonged to 51-60 years age group with a 4.73:1 male to female ratio. ST-elevation myocardial infarction (STEMI) (44.77%) was the most common diagnosis and an average of 14.66±4.34 drugs were prescribed. Majority of the patients opted for percutaneous coronary intervention (PCI) with or without having received fibrinolytic therapy at onset. Adherence to the ACC/AHA guidelines being 93.75% and 118 prescriptions being 100% adherent to the guidelines. A positive correlation between adherence and number of drugs was statistically significant.
Conclusions: The success of evidence-based medicine (EBM) was well noted with a 0% in hospital mortality rate i.e. all of the 172 patients were discharged with therapeutic success. Despite the concept of EBM and its proven effectiveness, there is a paucity of availability of such guidelines in India, so this study, a first of its kind can serve as a starting point of generating national as well as local guidelines.

Keywords: Acute coronary syndrome, ACC/AHA guidelines, Guideline adherence index-5

INTRODUCTION

Acute coronary syndromes (ACS) encompass myocardial infarction, non-Q-wave myocardial infarction, and unstable angina, all of which are common causes of emergency hospital admission and a major cause of morbidity and mortality worldwide.[1,2] ACS refers to a spectrum of clinical presentations ranging from those for ST-segment elevation myocardial infarction (STEMI) to presentations found in non–ST-segment elevation myocardial infarction (NSTEMI) or in unstable angina. It is almost always associated with rupture of an atherosclerotic plaque and partial or complete thrombosis of the infarct-related artery.[3] India has the highest burden of ACS in the world.[4] In comparison with the people of

European ancestry, cardiovascular diseases (CVD) affect Indians at least a decade earlier and in their most productive midlife years.[4,5] For example, in Western populations only 23% of CVD deaths occur before the age of 70 years; in India, this number is 52%.[4,6]

ACS results from a sudden decrease in the blood flow to the heart, that is commonly due to a coronary artery obstruction or it can also be due to other causes like pulmonary embolism, severe heart failure, tachycardia etc. This inadequate blood supply, leads to imbalance in the myocardial demand-supply of oxygen (O_2) and precipitates as STEMI, NSTEMI myocardial infarction or unstable angina. Major risk factors predisposing to occurrence of ACS are smoking (40%), high blood pressure (38%), and diabetes (30%).[7] The 30-day mortality rate attributable to ACS was 8.2% for the poor in comparison with 5.5% for the rich.[7] This difference was largely accounted for by variations in in-hospital treatment and discharge medications. India accounts for the highest number ACS cases in the world, yet very little known is known about the treatments and the outcomes.

Majority of the patients presenting with the complaint of chest pain do not have ACS and are at low risk for morbidity and mortality. Therefore, it is imperative to establish and implement a prediction model or a diagnostic protocol to differentiate those with a benign condition, low risk patients and high-risk patients who require earlier surveillance, aggressive treatment and hospitalisation. Diagnostic protocol includes history taking with emphasis on prevalence of cardiovascular diseases in the family, past history of cardiac complications, presence of precipitating factors; lead electrocardiogram (ECG) and measurement of troponin levels. Additionally, treadmill test, rest scintigraphy, coronary computed tomography (CT) angiography, stress imaging may also be conducted if required.[8,12]

According to the 2014 American College of Cardiology (ACC)\American Heart Association (AHA) guidelines for initial hospital care include prescribing sublingual nitro-glycerine for persistent ischemic pain and given sublingually causes coronary artery vasodilatation. Intravenous (IV) morphine for continued ischemic chest pain despite maximally allowed dosage of anti-ischemic medication. Aspirin or clopidogrel are prescribed for antithrombotic- antiplatelet effects. No other non-steroidal anti-inflammatory drug (NSAID) is to be prescribed except aspirin due to the increased risk of major adverse cardiac events (MACE) associated to their use. Beta-blockers, angiotensin converting enzyme (ACE) inhibitors, calcium channel blockers along with statins are also prescribed in respective cases provided contraindications for the same are absent. Supplemental oxygen is also prescribed to prevent oxygen saturation from dipping below 90% in specific cases.[9,10] If STEMI is detected reperfusion therapy, such as percutaneous coronary intervention (PCI) is required immediately to remove the red blood clot that has caused the STEMI.

Very little is known about how these recommendations are implemented in 'real life' and even lesser is known about the outcome of the patients with the different presentations of ACS. Hence, we had undertaken this research.

METHODS

The study began after obtaining permission from the Indian Council of Medical Research (ICMR) and the institutional ethics committee and a written consent of the patient were obtained in their vernacular language.

All patients diagnosed with ACS attending the cardiology department of a tertiary care hospital as well admitted in intensive cardiac care unit (ICCU) during the 8-week study period were enrolled in this study. The prescription of the patient including the drug prescribed, dose, frequency and duration of the treatment was noted. The data was analysed for demographic characteristics, presenting complaints, morbidity pattern, co-morbid conditions, and distribution of patients as per ACHA/ACC classification and drug utilisation patterns for ACS as well as co-morbid conditions. Adherence to ACC/AHA guidelines for management of ACS was also analysed quantitatively as well as qualitatively.

Objective of this study were to evaluate drugs used in the management of ACS, to evaluate the prescriptions and extent of adherence to ACC\AHA guidelines and to correlate prescription adherence to guidelines adherence with patient outcome.

Criteria for inclusion were patients of age 18 years or more, diagnosed of specific type of ACS by cardiologist and who had given written and informed consent.

Criteria for exclusion were who were not willing to give informed consent and refused to participate in the study.

Statistical analysis

The collected data were entered in Microsoft excel, 2016 version and analyzed using statistical package for sciences (SPSS) version 23.0 (IBM Corporation, California). Pearson correlation coefficient test was used. P value less than 0.05 considered as statistically significant. Pearson correlation coefficient was used to find out the correlation between different variables like number of drugs per patient and hospital stay in days.

Unpaired t test and Fisher's exact test were applied between prescription adherent and non-adherent patients for comparison of different variables like age, drug therapy and co-morbidities.

Pharmacotherapy was compared to ACC/AHA guidelines, to evaluate adherence, guideline adherence index (GAI-5) was used for 5 major drug groups for ACS.

$$GAI = \frac{No.\,of\ patients\ using\ the\ prescribed\ medications}{No.\,of\ eligible\ patients} \times 100$$

RESULTS

Population characteristics

A total of 172 patients who visited cardiology department and diagnosed with ACS were involved in this study. 64 (37.20%) patients with the highest preponderance to ACS were belong to 51-60 years age group followed by 50 (29.06%) patients in 61-70 years age group followed by 26 (15.11%) patients in 41-50 years age group followed by 18 (10.46%) patients in 71-80 years age group followed by 7 (4.06%) patients in 31-40 years age group followed by 6 (3.46%) patients in 81-90 years age group. Males had greater preponderance, with a 4.73:1 male to female ratio. Out of total 19 patients were addicted to smoking and tobacco.

Symptoms characteristics

Chest pain was the most common symptom. Out of total 127 (72.83%) patients had chest pain at admission. 41 (23.83%) patients were complained of Gabhraman at time of admission. 42 (24.41%) patients had complained of excessive perspiration at the time of admission. Other complains were uneasiness followed by chest discomfort and breathlessness. Out of total 77 (44.76%) patients were diagnosed with STEMI followed by 55 (31.97%) patients with Unstable Angina and 40 (23.25%) patients with NSTEMI.

Amongst ACS patient's coronary artery disease (CAD) was detected in 166 (96.51%) patients, out of which 56 patients were detected with double vessel CAD followed by 51 patients with single vessel disease followed by 48 patients with Triple vessel disease followed by 11 patients with left main CAD. Left ventricular dysfunction (LVD) was detected in 109 (63.37%) patients, out of which 61 patients diagnosed with mild LVD followed by 31 patients with severe LVD followed by 17 patients with moderate LVD. Most common co-morbidities observed were hypertension in 91 (52.90%) patients followed by diabetes mellitus type 2 in 69 (40.11%) patients followed by hypothyroidism in 15 (8.72%) patients.

Prescription pattern

Most common drug classes prescribed were P2Y12 inhibitors (frequency=283) followed by aspirin (frequency=279) followed by statins (frequency=195) followed by beta blockers (frequency=135) as shown in Figure 1.

Some of the drugs were prescribed to patients in different dosage patterns and combinations and hence exceed the total number of patients under study (n=172). Most frequently prescribed drugs from the time of admission till one month after discharge were aspirin (frequency=279) followed by ticagrelor (frequency=171) followed by rosuvastatin (frequency=146) followed by heparin (frequency=145) followed by clopidogrel (frequency=107).

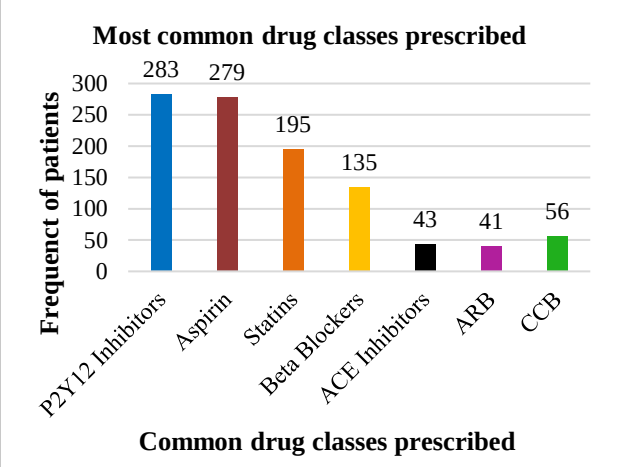

Figure 1: Most common drug classes prescribed.

Average adherence was 93.75% (calculated as per 2014-ACC/AHA Guidelines for UA/NSTEMI and 2013-ACCF/AHA guidelines for STEMI) as shown in Table 1.

Table 1: Frequency distribution of observed adherence patterns.

Adherence (%)	No. of patients
50.0	2
60.0	2
68.0	1
70.0	2
75.0	5
80.0	13
85.0	24
88.0	4
90.0	1
100.0	118

Highest adherence observed was with drug aspirin followed by other medication as shown in Table 2.

There was statistically significant and positive correlation between extent of prescription adherence to standard treatment guidelines and total number of drugs prescribed. Statistically significant and negative correlation between extent of prescription adherence to standard treatment guidelines and age of patient as shown in Table 3.

ACE inhibitor were the most omitted and aldosterone antagonist was the most overprescribed drug class as shown in Table 4.GAI-5 was 86.46% as mentioned in Table 5.

Table 2: Adherence pattern.

Generic name	Frequency	COR	LOE	Adherence frequency
Metoprolol	98	I	A/B*	95
Aspirin	242	I	A	242
Atorvastatin	51	I	A/B*	51
Clopidogrel	107	I	B	107
Rosuvastatin	146	I	A/B*	146
Ticagrelor	171	I	B	171
Glimepiride + metformin	33	I	C	33
Ramipril	40	I	A	29
Torsemide + spironolactone	43	I	B	22
Amlodipine	39	I	B	38
Telmisartan	27	I	B	20
Heparin	145	I	B/C*	145
Rabeprazole + domperidone	40	IIa	C	40

*The different level of evidence (LOE) mentioned are according to the UA/NSTEMI and STEMI guidelines respectively

Table 3: Correlation between extent of prescription adherence to standard treatment guidelines.

Correlations	Total no. of drugs	Adherence	Age
Total no. of drugs prescribed			
Pearson correlation	1	0.186*	0.104157
Sig. (2-tailed)		0.014742958	0.176472
N	172	172	170
Extent of prescription adherence to standard treatment guidelines			
Pearson correlation	0.186*	1	-0.156*
Sig. (2-tailed)	0.014742958		0.042478
N	172	172	170
Age of the patient			
Pearson correlation	0.104156643	-0.156*	1
Sig. (2-tailed)	0.176472447	0.042478471	
N	170	170	172

*Correlation is significant at the 0.05 level (2-tailed)

Table 4: Frequency distribution of non-adherence to standard treatment guidelines.

Non adherence	No. of patients
P2Y12 inhibitor omitted	10
Statin omitted	1
Ace inhibitor omitted	31
Ace inhibitor prescribed extra	11
Aldosterone antagonist prescribed extra	21
Aldosterone antagonist omitted	4
ARB prescribed extra	20
Beta blocker omitted	16
Beta blocker prescribed extra	3
CCB prescribed extra	1

Table 5: GAI 5.

Drugs	Aspirin	P2Y12 inhibitors	Statins	Beta blockers	ACE inhibitors/ ARB
Adherence	172	162	171	116	32
***Non adherence**	0	10	1	16	31
****Total**	172	172	172	132	63
% Adherence	100	94.18	99.41	87.87	50.79
Score out of 20	20	18.84	19.88	17.58	10.16

*Only patients who were under-prescribed the particular drug have been considered in non-adherence, **adherence of drugs is calculated according to the number of patients who need the drug group (patients who were overprescribed have not been considered in the total

DISCUSSION

ACS comprises of three diagnoses namely, STEMI, NSTEMI and unstable angina (UA). As the term 'infarction' suggests, at a molecular level, there is an oxygen demand–supply deficit in the myocardium inducing degenerative processes in the myocardial cells which manifest as one of the diagnoses mentioned above. India accounts for the highest number of ACS cases in the world, very little information is available on the prevalent drug prescription patterns and subsequent patient outcome.[4]

This prospective follow up study was carried out for 8 weeks and a total of 172 patients with ACS were included. The purpose of this study was to evaluate the prevalent prescription patterns from time of admission to discharge, adherence to standard treatment guidelines and co-relate the same with patient outcome at the end of one week.

In our study out of 172 patients 142 (82.6%) were males and 30 (17.4%) were females which is a higher than 67% and 33% respectively as observed in the study conducted by Kumar et al.[11] Most of the patients belonged to the age groups of 51-60 years (37.2%) and 61-70 (29%). The mean±standard deviation in our study was calculated to be 59.24±11.314 which is similar to the one found in a study conducted by Mohanan et al in 2013, where it was determined to be 60±12 years.[12]

In the study, 127 patients (73%) reported of chest pain and 28 (16.2%) reported of left arm/shoulder pain which is little lower as compared to the study of King-Shier et al where the same were reported to be 89.3% and 46.6% respectively. In the same study 70% of the patients were diagnosed with UA/NSTEMI with NSTEMI being the most common diagnosis, while 30% of the patients were diagnosed with STEMI. This is in contrast to our study where the most common diagnosis was STEMI (44.72%) followed by UA (31.97%) and NSTEMI (23.25%).[13]

There were a total of 2520 drugs prescribed to 172 patients from the time of admission to discharge. On an average 14.66±4.34 drugs were prescribed to the patient during the time period.

Out of all the patients (n=172), 100% were prescribed aspirin, 94.18% were prescribed P2Y12 inhibitors, 99.4% were prescribed statins, 81.9% were prescribed ACE inhibitors and 90.70% were prescribed beta blockers, this is comparatively higher to a study conducted in Qatar by El Hajj et al which reported that aspirin was prescribed to 96.0%, clopidogrel to 92.0%, statins to 97.7%, ACE inhibitors to 63.5% and β-blockers to 90.6% of the patients included in the study.[14]

Although the role of aspirin in acute and prophylactic therapy of ACS is universally accepted, uncertainties exist regarding the optimal dose of aspirin for the prevention and treatment of cardiovascular disease has resulted in wide geographic variations in practice patterns. In our study patients were prescribed a loading dose of 350 mg/325 mg followed by a 75 mg once daily dosage. Indirect comparisons in trials evaluating different doses of aspirin versus placebo have shown similar reductions in vascular events, observational analyses have suggested a dose-dependent increase in the risk of bleeding associated with aspirin.[15]

Clopidogrel, prasugrel and ticagrelor are anti-platelet agents and inhibit platelet aggregation by irreversibly blocking adenosine diphosphate (ADP) P2Y12 inhibitor. In the study an overwhelming majority of the patients underwent PCI after admission and 162 (94.18%) were prescribed dual antiplatelet therapy (DAPT) i.e. a combination of P2Y12 inhibitor and aspirin. This is in accordance with the findings of CURE trial where patients presenting within 24 hours after the onset of symptoms suggestive of ACSs (n=12,562) were randomized to receive clopidogrel (300 mg immediately, followed by 75 mg once daily; 6,259 patients) or placebo (6,303 patients) in addition to aspirin for 3-12 months, and it was observed that the deaths resulting from cardiovascular causes, nonfatal myocardial infarction (MI), or stroke (first primary outcome) was significantly lower in the clopidogrel group compared to placebo (9.3% versus 11.4%).[16]

It has been shown that long-term, intensive statin therapy may also decrease Lp-PLA2 levels by more than 20%; this is, however, largely due to the fact that most Lp-PLA2 is bound to apoB-containing particles, the concentration of which is reduced by statin.[17]

Beta blockers occupy a central role in treatment of ACS provided there are no contraindications for its use. This class of drugs function to reduce the oxygen demand of the myocardium, which is beneficial in cases of low tissue perfusion due to thrombosis, vasospasm or atherosclerotic plaque in the coronary arteries. In addition, the drugs function to prevent re-infarction and ventricular arrhythmias.

ACE inhibitor (ACE–I) or angiotensin receptor blockers (ARB) have been shown to prevent ventricular remodelling, reduce risk of heart failure and overall cardiac mortality in various studies.[18] ACE-I potentially prevent coronary plaque rupture by suppressing angiotensin II-induced vasoconstriction. In addition, it also protects against re-infarction of the myocardium.[19]

Ivabradine's anti-anginal effect has been demonstrated in the INITIATIVE trial while the BEAUTIFUL trial reported on the positive effects of Ivabradine on cardiac outcomes in patients with coronary artery disease, left ventricular dysfunction and baseline heart rate ≥70 bpm.[20]

In a prospective double-blind study conducted by Gokhroo et al, it was observed that Ivabradine is well tolerated in

acute inferior wall STEMI patients for lowering the heart rate with significant lesser risk of AV blocks.[21]

27 patients (15.69%) of the patients in our study were prescribed nicorandil, a drug which hasn't been included in the guidelines as of yet. However, studies such as the one conducted by Wu et al has shown that nicorandil prior to reperfusion is associated with improvement of coronary reflow as well as suppression of ventricular arrhythmia, and further improves left ventricular function in patients who suffered from AMI and underwent primary PCI.[22]

It was observed from statistical analysis that total number of prescribed had a positive correlation with extent of adherence to standard treatment guidelines (AHA/ACC guidelines) and was statistically significant (p=0.0147). Extent of adherence to standard treatment guidelines had a negative correlation with the age of the patient and this correlation was also statistically significant (p=0.0147). It can thus be inferred that with rise in the age of the patient, the prescriptions tend to be more varied and stray away from the actual guideline recommendations.

Relatively significant errors were encountered in our study, with regards to both overprescribing and under prescribing. 10 (5.81%) patients were not prescribed P2Y12 inhibitors and 1 (0.58%) was not prescribed statin during hospital stay.

It was also observed that 11 (6.39%), 21 (12/120%), 20 (11.62%), 3 (1.74%) and 1 (0.58%) of the patients were overprescribed ACE-I, aldosterone antagonists, ARB's, beta blocker and calcium channel blocker respectively.

In another study conducted by Mas et al, 150 patients admitted to the coronary care unit were included in a prospective observational study and 5790 prescription items reviewed. 523 (9.0%) prescribing errors were identified. Errors frequently encountered with drugs such as aspirin, enoxaparin, beta-blockers followed by ACE-I and clopidogrel.[23]

The results of our study ought to be discussed with the prescribers and reasons for not prescribing or prescribing a certain drug need to be elicited.

Patients with ACS in low/middle-income countries were less likely to be revascularized and to receive evidence-based medications at discharge.[24] Our study has found that there was an average adherence of 93.75% in the study population (n=172), an overwhelming majority of the patients underwent PCI procedure and 0% hospital mortality rate or 100% survival rate at the time of discharge. This highlights the success of evidenced based medicine (EBM) in India and serves as a benchmark for further progress.

*In another study t*he most commonly prescribed drug classes for main indications in ACS were anti-platelet drugs 600 (100%) followed by antihypertensives (96.16%) and anti-hyperlipidemics (91.16%). Extensive polypharmacy (9.68 drugs per prescription) was noticed in the prescriptions.[25]

A study published in The Lancet by Aronow et al, has shown that lipid-lowering therapy was associated with a smaller proportion of deaths at 30 days and that prescription of a lipid-lowering agent at discharge remained associated with a reduced risk of death at 6 months.[26]

According to the LVD study, ACE-I therapy resulted in a significantly lower mortality during the first year, and an even 20% relative reduction in the total mortality during the 4-year follow up. The effects of ACE-I were even more prominent in more severe myocardial dysfunction, as it was well known that they could slow or stop unfavourable myocardial remodelling.[27]

In the observational, retrospective and multi-centric study with 2,553 patients which was conducted by Soeiro et al, it was concluded that patients with acute coronary syndrome who underwent early intervention with oral beta-blockers during the first 24 hours of hospital admission had a lower in-hospital death rate and experienced fewer major adverse cardiovascular events with no increase in cardiogenic shock or sustained ventricular arrhythmias compared to patients who did not receive oral beta-blockers within this timeframe.[28]

Data from the Unité de Soins Intensifs Coronaires (USIC) registry and the Swedish registry of cardiac intensive care also suggest that prehospital fibrinolytic therapy may lower STEMI mortality rates.[29]

In the Euro heart survey of ACS, fibrinolytic (thrombolytic) therapy using streptokinase, urokinase, tenecteplase or any other agent should not be used in patients with UA and NSTEMI.[30] As stated by Gibson et al, coronary arteriography, performed in the acute period following NSTEMI, demonstrates that the infarct-related artery is not occluded in 60 to 85 percent of cases.[31]

Morphine is frequently used in ACS due to its analgesic effect. A meta-analysis published in the BMJ Open by Caldeira et al, which included 5 RCTs and 12 observational studies, enrolling 69 993 participants, showed that Morphine was associated with an increased risk of in-hospital mortality and major adverse cardiac events (MACE) and that morphine decreases the antiplatelet effect of P2Y12 inhibitors.32

In another study published in the American Heart Journal by Meine et al, patients treated with any morphine had a higher risk of death, likelihood of death and increased in hospital mortality. Use of morphine either alone or in combination with nitroglycerin for patients presenting with NSTE ACS was associated with higher mortality.[33] Observational data collected by Cian et al suggests that

morphine administration during MI may have negative consequences.[34]

Primary PCI of the infarct artery is preferred to fibrinolytic therapy when time-to-treatment delays are short and the patient presents to a high-volume, well-equipped center with experienced interventional cardiologists and skilled support staff.

Early diagnosis combined with precise treatment of ACS is mandatory to achieve best possible patient outcome. Data suggest up to half of patients with ACS experience sudden death prior to arrival in the emergency department (ED). In addition, degree of myocardial necrosis is related to length of the ischemic episode.[13] The ACC/AHA guidelines provide an extensive framework for selection of an appropriate treatment regimen for the patients based on numerous studies being conducted around the world. However, there appears to be a general lack of data and inadequacy of studies measuring the adherence to the guidelines correlating the same to patient outcome, notably more so in the Indian subcontinent. This study is a small step in that direction with the aim to shed some light on the area.

Strengths

Despite the concept of EBM and its proven effectiveness, there is a paucity of availability of such guidelines in India, so this study, a first of its kind can serve as a starting point of generating national as well as local guidelines.

Limitations

The study was conducted in a limited duration of 8 weeks as specified by the ICMR and hence the long-term patient outcome could not be correlated with the extent of adherence to standard treatment guidelines. Quality of life index (Qol) was not determined in the study as the patient was only followed up till discharge and as such the correlation between the two could not be determined. These limitations can be overcome in subsequent studies undertaken in the direction.

CONCLUSION

ACS has a strong male preponderance with a 4.73:1 male to female ratio observed in the study. STEMI (44.77%) was the most common diagnosis and an average of 14.66±4.34 drugs were prescribed to a patient from the time of admission till discharge. Majority of the patients opted for PCI with or without having received fibrinolytic therapy at onset.

Although no concrete Indian guidelines exist, an earnest effort to adhere to the ACC/AHA guidelines was observed with the average adherence being 93.75% and 118 prescriptions being 100% adherent to the guidelines. The success of EBM was well noted with a 0% in hospital mortality rate i.e. all of the 172 patients were discharged with therapeutic success. ACE-I were the most under prescribed drug while aldosterone antagonists were the most commonly overprescribed drug in the study.

A positive correlation between adherence and number of drugs was observed which was found to be statistically significant. A statistically significant negative correlation between extent of adherence to standard treatment guidelines and age of the patient was also observed. It may be due to the wide array of complications that encountered with old age that the prescribers were compelled to look for alternatives to the standard practice.

ACS is extensively prevalent around the world and the Indian subcontinent specifically, contributes a majority of the load. The prescriptions patterns and therapeutic outcomes have not been studied in the subcontinent. Despite the concept of EBM and its proven effectiveness, there is a paucity of availability of such guidelines in India, so this study, a first of its kind can serve as a starting point of generating national as well as local guidelines.

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