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Original article

Patterns and determinants of cardiovascular drug utilization in coronary care unit patients of a tertiary care hospital

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ABSTRACT

Background: A wide variation exists in the patterns of pharmacotherapy among patients admitted with cardiovascular diseases. Very few studies have evaluated the potential determinants of drug utilization. Our objective was to evaluate the clinical characteristics and patterns of cardiovascular drug utilization among patients in coronary care unit (CCU) and assess the determinants of cardiovascular drug use among patients with coronary artery disease (CAD).

Methods: In this retrospective cohort study, the medical records of CCU patients were reviewed independently by two trained physicians over one year. Patients were analyzed as two groups – those with CAD and without CAD. Multivariate logistic regression was done to identify the determinants of cardiovascular drug utilization in the CAD group.

Results: Of 574 patients, 65% were males, 57% were <60 years. The five commonly prescribed drug classes were platelet inhibitors (88.7%), statins (76.3%), ACE-inhibitors/Angiotensin receptor blockers (72%), beta-blockers (58%) and heparin (57%). Poly-pharmacy (>5 drugs) was noticed in 71% of patients. A majority of patients had diagnosis of CAD (72.6%). CAD patients received significantly higher median number of drugs and had longer duration of CCU stay ($p < 0.0001$). Renal dysfunction for ACE-inhibitors [0.18 (0.09–0.36)], ST-elevation myocardial infarction for calcium channel blockers [0.29 (0.09–0.93)] and brady-arrhythmias for beta-blockers [0.3 (0.2–0.7)] were identified as determinants of decreased drug use in CAD group.

Conclusion: Predominance of male gender, age <60 and poly-pharmacy was observed in CCU. Antithrombotics, statins, ACE-inhibitors/Angiotensin receptor blockers and beta-blockers were the most frequently prescribed drugs. Clinical co-morbidities (renal dysfunction, arrhythmias) decreased the utilization of ACE-inhibitors, beta-blockers among CAD patients.

1. Introduction

Cardiovascular diseases (CVDs) have emerged as the leading cause of mortality with developing countries accounting for 80% of cardiovascular deaths.[1] The mortality data from first phase of the Million Death Study showed CVDs as the largest cause of deaths in India leading to 1.7–2 million deaths annually.[2]

According to the Global burden of diseases study in India, coronary artery disease is the largest contributor to CVD accounting for over 35% of disease burden.[3,4] As per predictions from studies by the National Commission for Macroeconomics and Health, Government of India, the number of patients with CAD is set to increase over 60 million by 2015.[5]

Drug therapies in critically ill patients are often complicated by the altered physiology and coexistence of multiple co-morbidities that warrants polypharmacy. Polypharmacy may increase the risk of adverse drug reactions (ADRs), medication errors and patient non-compliance with treatment.[6]

The American College of Cardiology Federation/American Heart Association (ACCF/AHA) guidelines – 2011 have recommended pharmacotherapy with anti-thrombotics, Angiotensin Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs) and beta-blockers based on results of multiple controlled trials to improve survival benefits in Acute Coronary Syndrome (ACS).[7–10] In spite of availability of standard guidelines, a wide variation exists in patterns of pharmacotherapy. An observational study which evaluated treatment practices for acute myocardial infarction (MI)

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across hospitals in South India observed appropriate use of thrombolytics, beta-blockers and ACE-inhibitors among 83%, 78% and 99.3% of patients respectively.[11] Only 40% of ACS patients received combined beta-blockers, statins and ACE-inhibitors in an Estonian study.[12]

Very few studies have evaluated factors that predict the utilization of pharmacotherapy in patients with cardiovascular diseases. Assiri et al[13] has reported that presence of diabetes predicts use of ACE-inhibitors [Adjusted Odds Ratio (aOR) = 1.496 (1.055–2.121)], whereas the diagnosis of unstable angina [aOR = 9.803 (1.312–71.42)] and ST-elevation MI (STEMI) [aOR = 8.064 (1.052–62.5)] predicted use of statins. Assessment of drug utilization patterns and potential determinants of utilization are highly essential to establish the optimal utilization of evidence-based therapies.

The objectives of this study were to evaluate the demographics, clinical characteristics and patterns of cardiovascular drug utilization among patients admitted to CCU and assess the potential determinants of utilization of cardiovascular drug classes among patients with CAD.

2. Methods and materials

2.1. Study setting, design and data collection

This was a retrospective cohort study conducted in CCU of St John's Medical College, Bangalore, India, which is a 1500 bed tertiary care teaching hospital. The study method and results on patterns, predictors and preventability of adverse drug reactions in the CCU of a tertiary hospital have been reported in our earlier paper.[14]

The case records of 574 consecutive patients admitted to CCU between 1st January 2008 and 31st December 2008 were retrospectively reviewed by two trained physicians independently. All patients admitted and treated for more than 24 h were included in the study. Data on demographics, clinical characteristics and drug prescription were collected in a specially designed case record form. Patients with missing details on relevant drug utilization data were excluded from analysis. Institutional Ethical Review Board (IERB) approved conduct of the study.

Drugs were classified based on WHO's Anatomic Therapeutic Chemical Classification System.[15] They were divided into groups based on organ system (1st level), therapeutic and chemical characteristics (2nd, 3rd, 4th levels). The total number of drugs and cardiovascular drugs prescribed per person was noted. Among the cardiovascular drugs prescribed, those from the WHO Essential Drug list were noted.[16]

The patient population was considered as two groups: those with diagnosis of CAD and those without CAD (Non-CAD group). The diagnoses were defined based on clinical presentation, definite ECG changes, Echocardiography/angiography findings and other investigation values using International Classification of Diseases version-10 (ICD-10).[17] Renal dysfunction was defined based on the estimated creatinine clearance (ml/min) values calculated using the Cockcroft–Gault equation. Baseline characteristics, co-morbidities and treatment patterns were compared across both groups. The characteristics of CAD patients were analyzed to identify potential factors affecting utilization of cardiovascular drug classes.

2.2. Statistical analysis

Descriptive measures (mean ± SD, median, inter-quartile range) were used to summarize numerical variables. For categorical variables, percentages were used. Chi-square test, Unpaired-*t* test and Mann–Whitney *U* test were used to analyze differences in baseline characteristics between CAD and non-CAD group. Multivariate logistic regression was used to identify the determinants of drug utilization among patients with CAD. Univariate analyses were done with set of eleven independent variables and nine cardiovascular drug classes. The variables considered for the first step of regression analysis included demographic data (gender and age) and clinical co-morbidities [hypertension, diabetes mellitus, STEMI, NSTEMI, unstable angina, ischemic heart disease (IHD), congestive cardiac failure (CCF), renal dysfunction and arrhythmias]. Binary logistic regression was done with independent variables found significant in the univariate analysis ($p < 0.2$) to identify potential factors affecting utilization of adjunctive pharmacotherapy among CAD patients. The data were entered and analyzed in SPSS version-20 software. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographic and clinical characteristics

During the study period, a total of 574 consecutive patients were admitted to CCU. 417 (72.6%) had a diagnosis of CAD (CAD group) and 157 (27.3%) were hospitalized for conditions other than CAD (Non-CAD group). Majority were males (65.1%) and were <60 years (57.1%). Patients in CAD group were older (60 vs 50.5; $p < 0.0001$), had a significantly longer median duration of CCU stay [3 (2–3) vs. 2 (2–3); $p < 0.0001$] and received significantly higher median

Table 1
Baseline characteristics of patients with CAD and non-CAD.

Variables	Overall $N = 574$ (100%)	CAD (417; 72.6%)	Non-CAD (157; 27.3%)	*p*-Value*
Gender[a]; *n* (%)				0.768
•Males	374 (65.1)	274 (65.7)	100 (63.6)	
•Females	200 (34.8)	143 (34.2)	57 (36.3)	
Age; Mean (±SD)[b]	57.39 (15.1)	60.00 (13.4)	50.52 (17.0)	<0.0001
<60[a]	328 (57.1)	216 (51.8)	112 (71.3)	
>60[a]	246 (42.9)	201 (48.2)	45 (28.7)	<0.0001
Median hospital stay (days)[c]	6 (4–10)	6 (4–11)	6 (4–10)	0.052
Median CCU stay (days)[c]	3 (2–3)	3 (2–3)	2 (2–3)	<0.0001
Median no. of drugs[c]	10 (8–10)	10 (9–12)	8 (6–10)	<0.0001
Median no. of cardiovascular drugs[c]	7 (5–7)	7 (6–9)	5 (4–6.5)	<0.0001
Median no. of comorbidities	3 (2–4)	3 (2–4)	2 (1–3)	<0.0001

Abbreviations: CAD (Coronary Artery Disease); Non-CAD (Non Coronary Artery disease); CCU (Coronary Care Unit).
* – $p < 0.05$ is considered statistically significant.
Data are given as:
[a] Number (*n*) of patients with percentages (%) in parentheses or as,
[b] Mean ± standard deviation or as,
[c] Median with interquartile range in parentheses.

Table 2
Common comorbidities among CAD and non-CAD patients at discharge.

Comorbidities	Overall[a] $N = 574$	CAD group[a] $N = 417$	Non-CAD group[a] $N = 157$	p-Value*
Hypertension	326 (64.6)	266 (63.8)	60 (38.2)	<0.0001
Diabetes mellitus	249 (43.4)	211 (50.6)	38 (24.2)	<0.0001
Dyslipidemia	136 (23.7)	112 (26.9)	24 (15.3)	0.002
Heart failure	122 (21.3)	82 (19.7)	40 (25.5)	0.138
LRTI	109 (19.0)	72 (17.3)	37 (23.6)	0.095
Renal dysfunction	101 (17.6)	79 (18.9)	22 (14)	0.178
Arrhythmias	91 (15.9)	50 (12)	41 (26.1)	<0.0001
Cardiomyopathy	34 (5.9)	12 (2.9)	22 (14)	<0.0001
CVA/Old-CVA	29 (5.1)	20 (4.8)	9 (5.7)	0.671
Peripheral vascular disease	28 (4.9)	20 (4.8)	8 (5.1)	0.831
Valvular heart disease	20 (3.5)	3 (0.7)	17 (10.8)	<0.0001
Pulmonary thromboembolism	15 (2.6)	1 (0.2)	14 (8.9)	<0.0001
Pulmonary hypertension	9 (1.6)	0 (0)	9 (5.7)	<0.0001

*$p < 0.05$ considered statistically significant (Chi-square test).
LRTI – Lower Respiratory Tract Infection; CVA – Cerebrovascular Accident.
[a] Data are given as number (n) of patients with percentages (%) in parentheses.

number of drugs [10 (9–12) vs. 8 (6–10); $p < 0.0001$] than those in non-CAD group (Table 1).

ACS was the most common admission diagnosis in CAD group accounting for 72.5% cases [STEMI (38.6%); NSTEMI (24.2%); unstable angina (9.6%)]. Stable angina or a prior diagnosis of MI (IHD) constituted the remaining 27.5% of CAD cases. The common co-morbidities among CAD and Non CAD patients are presented in Table 2. The median number of co-morbidities was significantly more in CAD group than in non-CAD group [3 (2–4) vs. 2 (1–3); $p < 0.0001$]. Hypertension (64.6%) and diabetes (43.4%) were the most common co-morbidities.

3.2. Utilization patterns of cardiovascular drugs among CAD and non-CAD patients

A total of 5532 drugs prescribed to 574 patients were categorized into 14 groups based on the first anatomical level of ATC classification. Distribution of drugs in different categories is shown in Fig. 1. The five frequently prescribed drugs were aspirin (8.3%), atorvastatin (7.8%), clopidogrel (7.6%), pantoprazole (6.8%) and ramipril (5.7%). Cardiovascular drugs (ATC class B and C) accounted for 69.3% of drugs prescribed. 70.5% of patients received more than five cardiovascular drugs. 77.4% of cardiovascular drugs prescribed were from WHO essential list.

Table 3 shows patterns of utilization of major cardiovascular drug classes among CAD and non-CAD groups (ATC 3rd & 4th levels). The detailed table on utilization of drug classes and individual drugs among CAD and non-CAD groups is given in Appendix 1. Among 3832 cardiovascular drugs, the five commonly prescribed subgroups were platelet aggregation inhibitors excluding heparin (23.5%), statins (11.4%), heparin group (9.4%), ACE-inhibitors (8.9%) and selective beta-blocking agents (7.3%). The utilization of majority of drug classes was significantly more among patients with CAD with the exception of vitamin-K antagonists (CAD, 4.8% and non-CAD, 24.2%; $p = 0.0001$) and digitalis (CAD, 6% and non-CAD, 22.3%; $p < 0.0001$).

Aspirin (88.7%) and clopidogrel (89.7%) were the most frequently used drugs among CAD group. Use of glycoprotein IIB/IIIA receptor antagonists were reported in 3.8% patients with CAD, with eptifibatide being prescribed more frequently (3.1%)-(Appendix 1). 79% patients with ACS received heparin. Direct thrombin inhibitors-fondaparinux was utilized in 5.2% patients of whom 3.5% presented with ACS. 81% of patients in the non-CAD group were prescribed antithrombotics (platelet aggregation-inhibitors/heparin group/vitamin-K antagonists). Common diagnoses included arrhythmias (21%), valvular heart disease (9.5%), cardiomyopathy (8.2%), pulmonary thromboembolism (8.2%).

Beta-blockers and ACE-inhibitors/ARBs were prescribed to 67% and 79% of patients with ACS respectively. Out of 22 patients of cardiomyopathy in non-CAD group, 17 were on ACE-inhibitors/ARBs. Calcium channel blockers (CCBs) were prescribed to 28% patients of which amlodipine was the most frequently used (22.5%).

Of 47% patients with CAD on diuretics, 33% had a diagnosis of ACS. 17% patients with ACS utilized aldosterone antagonists. Newer anti-anginal agents (nicorandil, ranolazine and trimetazidine) were prescribed to 32.4% patients (Appendix 1). Cardiac glycosides were prescribed significantly more in non-CAD group (22.3%) where the common clinical diagnoses were cardiomyopathy (10.2%) and valvular heart disease (5.73%) complicated by heart failure (15.3%).

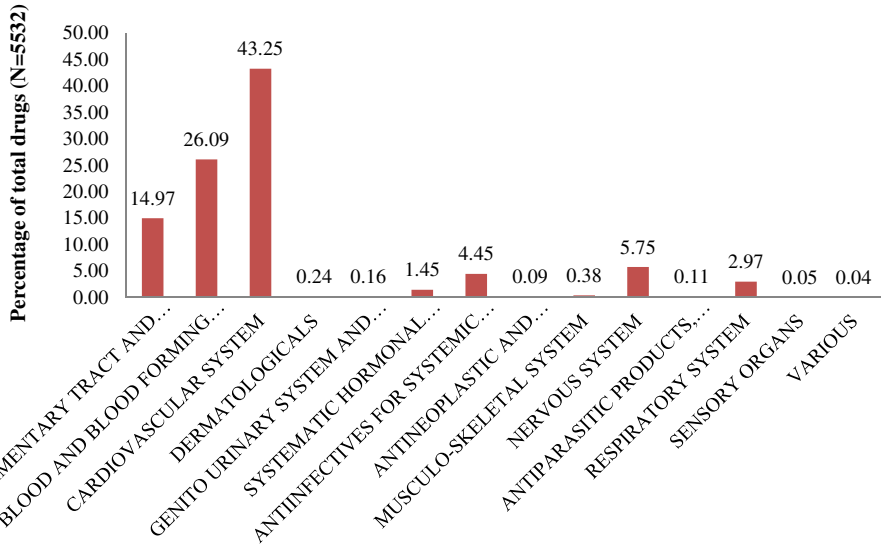

Fig. 1. Distribution of drugs in different categories based on ATC level 1 ($N = 5532$) in CCU patients.

Table 3
Utilization patterns of common cardiovascular drug classes in CAD and non-CAD patients.

Drug classes (as per ATC 3rd & 4th levels)	Overall ($N = 574$)[a]	CAD group ($n = 417$)[a]	Non-CAD group ($n = 157$)[a]	p-Value*
Vitamin-K antagonists [B01AA]	58 (10.1)	20 (4.8)	38 (24.2)	**0.0001**
Heparin group [B01AB]	327 (57)	269 (64.5)	58(36.9)	**0.0001**
Platelet aggregation inhibitors [BO1AC]	509 (88.7)	409 (98.1)	100 (63.7)	**0.0001**
Enzymes [B01AD]	47 (8.2)	39 (9.4)	8 (5.1)	**0.124**
Other antithrombotic agents [B01AX]	30 (5.2)	27 (6.5)	3 (1.9)	**0.033**
Digitalis [C01AA]	60 (10.5)	25 (6)	35 (22.3)	**<0.0001**
Antiarrythmics-class 111 [C01BD]	53 (9.2)	33 (7.9)	20 (12.7)	**0.104**
Adrenergic & dopaminergic agents [C01CA]	32 (5.6%)	22 (5.3)	10 (6.4%)	**0.683**
Organic nitrates [C01DA]	211 (36.8)	179 (42.9)	32 (20.4)	**0.0001**
Other vasodilators used In cardiac disease [C01DX]	105 (18.3)	103 (24.7)	2 (1.3)	**0.0001**
Other cardiac preparations [C01EB]	86 (15)	74 (17.7)	12 (7.6)	**0.002**
Diuretics	264 (46)	197 (47.2)	67 (42.7)	**0.348**
Thiazides [C03A]	10 (1.7)	8 (1.9)	2 (1.2)	
Low ceiling diuretics excl thiazides [C03B]	5 (0.9)	1 (0.2)	4 (2.5)	
High Ceiling Diuretics [C03C]	245 (42.7)	177 (42.4)	68 (43.3)	
Aldosterone antagonists [C03D]	101 (17.6)	78 (18.7)	23 (14.6)	
Beta-blockers [C07]	334 (58.2)	270 (64.7)	64 (40.8)	**0.0001**
Non-selective beta-blockers [C07AA]	2 (0.3)	2 (0.5)	0 (0)	
Selective beta-blockers [C07AB]	276 (48.1)	229 (54.9)	47 (29.9)	
Alpha and beta-blocking [C07AG]	63 (11)	45 (10.8)	18 (11.5)	
Calcium channel blockers [C08]	161 (28)	117 (28.1)	44 (28)	**1.00**
Selective CCBs with mainly vascular effects [C08C]	131 (22.8)	97 (23.3)	34 (21.7)	
Selective CCB with direct cardiac effects [C08D]	33 (5.7)	23 (5.5)	10 (6.4)	
ACE inhibitors [C09AA]	340 (59.2%)	280 (67.1)	60 (38.2)	**0.000**
Angiotensin 11 antagonists [C09CA]	74 (12.9)	58 (13.9)	16 (10.2)	**0.26**
Statins [C10AA]	438 (76.3)	364 (87.3)	74 (47.1)	**0.0001**

* – $p < 0.05$ considered as statistically significant (Chi square test).
[a] Data are given as number (n) of patients with percentages (%) in parentheses.

3.3. Determinants of utilization of cardiovascular drug classes in CAD

Four hundred and seventeen patients with diagnosis of CAD were analyzed to identify the potential factors affecting utilization of nine cardiovascular drug classes (platelet aggregation inhibitors, statins, vasodilators, CCBs, beta-blockers, diuretics, heparin and other antithrombotics, ACE-inhibitors/ARBs and anti-arrhythmics). The results of six drug classes are presented as the remaining three showed no significant difference in utilization across selected variables (Table 4).

Logistic regression analysis was done adjusting for variables significant in univariate analysis (significance set at $p < 0.2$) to identify the determinants of drug use among patients with CAD (Table 5).

3.3.1. ACE-inhibitors and ARBs

In univariate analysis, age <60 [2.19 (1.30–3.69)] and renal dysfunction [0.20 (0.11–0.36)] were significant predictors of ACE-inhibitor/ARB use. Their utilization was decreased by 42% in patients with diabetes [0.58 (0.35–0.97)]. In multivariate analysis, renal dysfunction was identified as the significant determinant, which decreased utilization by 80% [0.18 (0.09–0.36)].

3.3.2. Calcium channel blockers (CCBs)

In univariate analysis, the utilization of CCBs was significantly more in patients with hypertension [3.26 (1.89–5.65)], IHD [1.62 (0.99–2.63)] and renal dysfunction [2.84 (1.66–4.87)]. A diagnosis of STEMI decreased the utilization of CCBs by 65% [0.35 (0.21–0.59)]. Logistic regression identified hypertension [3.70 (1.95–7.03)], renal dysfunction [2.85 (1.61–5.06)] and STEMI [0.29 (0.09–0.93)] as major determinants for CCB use.

3.3.3. Heparin and other antithrombotics

STEMI [3.53 (1.16–10.73)] and NSTEMI [4.86 (1.41–16.72)] were two significant predictors in multivariate analysis.

3.3.4. Beta-blockers

Patients <60 years were 2.96 times more likely to be on beta-blockers than older patients 2.96 (1.91–4.60)]. Diagnosis of STEMI increased use by 1.63 times [1.63 (1.04–2.55)]. CCF [0.49 (0.29–0.83)], renal dysfunction [0.58 (0.34–0.99)] and arrhythmias including heart blocks [0.34 (0.18–0.65)] decreased utilization (Table 4). Multivariate analysis identified STEMI [1.58 (1.01–2.46)] and brady-arrhythmias [0.365 (0.2–0.7)] as significant determinants of beta-blocker use (Table 5).

3.3.5. Diuretics

Renal dysfunction [4.37 (2.29–8.29)] and heart failure [11.26 (4.47–28.33)] were the significant determinants that increased their utilization. Patients <60 years were less likely to be on diuretics than those >60 years [0.34 (0.20–0.55] (Table 5).

3.3.6. Anti-arrhythmics

Logistic regression identified arrhythmias [7.10 (3.20–15.76)], CCF [3.03 (1.33–6.92)] and NSTEMI [3.44 (1.1–10.8)] as significant predictors of increased use.

4. Discussion

In this study, we analyzed data of 574 patients admitted to CCU of a tertiary hospital in India over one year and assessed their baseline characteristics, clinical co-morbidities and drugs prescribed during the duration of hospital stay. This study has provided a picture of cardiovascular drug prescribing patterns and identified the potential predictors of drug utilization among patients with CAD.

4.1. Demographic and clinical characteristics

Patients in our study were younger (57 ± 15) than those in observational studies done in developed countries (63–69 years) (Table 1).[18,19] Early age at onset of CAD has been documented as one

Table 4
Univariate analysis showing potential predictors of utilization of six cardiovascular drug classes in CAD patients.

Variables N	ACE I & ARBs[c]		CCB		Heparin & antithrombotics[c]		Beta blockers		Diuretics		Antiarrhythmics	
	n (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]	*n* (%)	OR (95% CI)[a]
Sex												
M (274)	221 (80.7)	1.20 (0.71–2.03)	68 (24.8)	0.63 (0.40–1.01)	191 (69.7)	0.80 (0.50–1.30)	175 (63.9)	0.89 (0.57–1.40)	124 (45.3)	0.79 (0.52–1.21)	24 (8.8)	1.43 (0.61–3.42)
F (143)	111 (77.6)	$p = 0.465$	49 (34.3)	$p = 0.042$	106 (74.1)	$p = 0.344$	95 (66.4)	$p = 0.603$	73 (51.0)	$p = 0.261$	9 (6.3)	$p = 0.376$
Age												
<60 (216)	185 (85.6)	2.19 (1.30–3.69)	53 (24.5)	0.70 (0.44-1.09)	164 (75.9)	1.61 (1.03-2.53)	165 (76.4)	2.96 (1.91–4.60)	72 (33.3)	0.30 (0.20–0.46)	9 (4.2)	0.32 (0.13–0.75)
>60 (201)	147 (73.5)	$p = 0.001$	64 (31.8)	$p = 0.196$	133 (66.1)	$p = 0.03$	105 (52.2)	$p < 0.0001$	125 (62.1)	$p < 0.0001$	24 (11.9)	$p = 0.012$
HTN												
Yes (266)	215 (80.8)	1.23 (0.73–2.05)	95 (35.7)	3.26 (1.89–5.65)	184 (69.2)	0.75 (0.47–1.21)	174 (65.4)	1.08 (0.70–1.68)	128 (48.1)	1.10 (0.72–1.68)	17 (6.4)	0.58 (0.27–1.24)
No (151)	117 (77.5)	$p = 0.415$	22 (14.6)	$p = 0.001$	113 (74.8)	$p = 0.220$	96 (63.6)	$p = 0.706$	69 (45.7)	$p = 0.634$	16 (10.6)	$p = 0.126$
DM												
Yes (211)	159 (75.4)	0.58 (0.35–0.97)	63 (29.9)	1.20 (0.76–1.88)	147 (69.7)	0.86 (0.55–1.34)	129 (61.1)	0.73 (0.47–1.11)	110 (52.1)	1.49 (0.99–2.23)	12 (5.7)	0.53 (0.24–1.17)
No (206)	173 (84)	$p = 0.029$	54 (26.2)	$p = 0.408$	150 (72.8)	$p = 0.478$	141 (68.4)	$p = 0.118$	87 (42.2)	$p = 0.043$	21 (10.2)	$p = 0.088$
STEMI												
Yes (161)	130 (80.7)	1.12 (0.67–1.89)	26 (16.1)	0.35 (0.21–0.59)	132 (82.0)	2.51 (1.52–4.16)	115 (71.4)	1.63 (1.04–2.55)	71 (44.1)	0.81 (0.54–1.23)	13 (8.1)	1.04 (0.47–2.26)
No (256)	202 (78.9)	$p = 0.650$	91 (35.5)	$p = 0.0001$	165 (64.5)	$p < 0.001$	155 (60.5)	$p = 0.024$	126 (49.2)	$p = 0.308$	20 (7.8)	$p = 0.923$
NSTEMI												
Yes (101)	78 (77.2)	0.83 (0.47–1.48)	36 (35.6)	1.61 (0.97–2.67)	83 (82.2)	2.20 (1.21–4.01)	63 (62.4)	0.87 (0.53–1.41)	53 (52.5)	1.32 (0.82–2.12)	4 (4.0)	0.41 (0.12–1.26)
No (316)	254 (80.4)	$p = 0.494$	81 (25.6)	$p = 0.051$	214 (67.7)	$p = 0.005$	207 (65.5)	$p = 0.567$	144 (45.6)	$p = 0.226$	29 (9.2)	$p = 0.091$
Unstable Angina												
Yes (40)	31 (77.5)	0.87 (0.38–2.06)	15 (37.5)	1.62 (0.78–3.35)	23 (57.5)	0.51 (0.25–1.04)	25 (62.5)	0.90 (0.44–1.86)	12 (30.0)	0.44 (0.21–0.94)	1 (2.5)	0.28 (0.01–1.97)
No (377)	301 (79.8)	$p = 0.727$	102 (27.1)	$p = 0.162$	274 (72.7)	$p = 0.044$	245 (65.0)	$p = 0.754$	185 (49.1)	$p = 0.022$	32 (8.5)	$p = 0.182$
IHD[b]												
Yes (115)	94 (81.7)	1.13 (0.64–2.02)	41 (35.6)	1.62 (0.99–2.63)	59 (51.3)	0.27 (0.17–0.44)	68 (59.1)	0.69 (0.44–1.11)	61 (53.0)	1.35 (0.86–2.11)	15 (13.0)	2.33 (1.07–5.08)
No (302)	238 (79.1)	$p = 0.655$	76 (25.1)	$p = 0.040$	238 (79.0)	$p < 0.001$	202 (66.8)	$p = 0.104$	136 (45.0)	$p = 0.175$	18 (5.9)	$p = 0.018$
CCF												
Yes (82)	60 (73.2)	0.63 (0.35–1.15)	26 (31.7)	1.24 (0.71–2.7)	62 (75.6)	1.32 (0.73–2.39)	42 (51.2)	0.49 (0.29–0.83)	71 (86.6)	10.7 (5.26–22.28)	12 (14.6)	2.56 (1.13–5.77)
No (335)	272 (81.2)	$p = 0.106$	91 (27.2)	$p = 0.412$	235 (70.1)	$p = 0.328$	228 (68.1)	$p = 0.004$	126 (37.6)	$p = 0.001$	21 (6.3)	$p = 0.012$
Renal dysfunction												
Yes (79)	43 (54.4)	0.20	37 (46.8)	2.84 (1.66–4.87)	56 (70.9)	0.98 (0.55–1.74)	43 (54.4)	0.58 (0.34–0.99)	61 (77.2)	5.03 (2.76–9.27)	10 (12.7)	1.98 (0.84–4.62)
No (338)	289 (85.5)	(0.11–0.36)	80 (23.7)	$p = 0.001$	241 (71.3)	$p = 0.941$	227 (67.2)	$p = 0.033$	136 (40.2)	$p = 0.001$	23 (6.8)	$p = 0.083$
Arrhythmias												
Yes (50)	36 (72)	0.62 (0.3–1.27)	14 (28.0)	1 (0.49–2.01)	37 (74)	1.17 (0.57–2.42)	21 (42)	0.34 (0.18–0.65)	31 (62.0)	1.98 (1.04–3.79)	14 (28)	7.12 (3.1–16.5)
No (367)	296 (80.7)	$p = 0.189$	103 (28.1)	$p = 1.00$	260 (70.8)	$p = 0.74$	249 (67.8)	$p = 0.0001$	166 (45.2)	$p = 0.034$	19 (5.2)	$p = 0.0001$

ACEI & ARB: ACE-inhibitors and Angiotensin Receptor blockers; CCBs: Calcium Channel Blockers; CCF: Congestive cardiac failure; DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; STEMI: ST-Elevation Myocardial Infarction, NSTEMI: Non-ST-Elevation Myocardial Infarction.

[a] OR (95% CI) – unadjusted odds' Ratio with 95% confidence interval. $p < 0.05$ is considered as statistically significant.

[b] IHD: includes patients with past diagnosis of myocardial infarction and stable angina who are currently not admitted for an acute coronary event.

[c] ACEI & ARB: includes patients on ACEI alone or ARB alone or combined; heparin & antithrombotics: includes patients on heparin group alone or Vitamin-K antagonists alone or other antithrombotics agents or any combination.

Table 5
Determinants of cardiovascular drug utilization in CAD patients.

Drug classes	Adjustment variables	Significant variables	Adjusted OR with 95% CI
ACE-inhibitors & ARBs	Age, sex, DM, CCF, renal dysfunction, arrhythmias	Renal dysfunction	0.18 (0.09–0.36)
CCBs	Age, sex, HTN, NSTEMI, STEMI, unstable angina, IHD, renal dysfunction	HTN	3.70 (1.95–7.03)
		STEMI	0.29 (0.09–0.93)
		Renal Dysfunction	2.85 (1.61–5.06)
Heparin & antithrombotics	Age, sex, HTN, STEMI, NSTEMI, unstable angina, IHD	STEMI	3.53 (1.16–10.73)
		NSTEMI	4.86 (1.41–16.72)
Beta-blockers	Age, sex, DM, STEMI, renal dysfunction, CCF, arrhythmias	Age	0.96 (0.95–0.98)
		STEMI	1.58 (1.01–2.46)
		Arrhythmias	0.36 (0.20–0.68)
Diuretics	Age, DM, NSTEMI, unstable angina, CCF, renal dysfunction, IHD, arrhythmia	Age	0.34 (0.20–0.55)
		Renal dysfunction	4.37 (2.29–8.29)
		CCF	11.26 (4.47–28.33)
Antiarrhythmics	Age, HTN, DM, NSTEMI, unstable angina, IHD, CCF, renal dysfunction, arrhythmias	CCF	3.03 (1.33–6.92)
		Arrhythmias	7.09 (3.20–15.76)
		NSTEMI	3.44 (1.10–10.80)

CI: Confidence Interval; OR: Odds' Ratio.
Abbreviations: ACEI & ARB: ACE-inhibitors and Angiotensin Receptor blockers; CCBs: Calcium Channel Blockers; CCF: Congestive cardiac failure; DM: Diabetes Mellitus; HTN: Hypertension; IHD: Ischemic Heart Disease; NSTEMI: Non-ST-Elevation Myocardial Infarction; STEMI: ST-Elevation Myocardial Infarction.

of the unique barriers of the optimal management of CAD in India.[20] The alarming rates of hypertension (65%) and diabetes (43%) are a disturbing trend (Table 2). Prevalence of hypertension in India, for the last three decades has increased by about 30 and 10 times among urban and rural residents respectively.[21] It is projected that India would contribute to more than one fifth of worlds' total diabetic population by 2030.[22] Hypertension and diabetes mellitus are major and modifiable risk factors which when controlled can significantly reduce CVDs morbidity and mortality.[23]

The percentage of patients receiving more than five drugs (70.5%) was quite high. Polypharmacy may be justified as this was a tertiary critical care setting where majority of patients were hospitalized with multiple co-morbidities. The interplay of polypharmacy and multiple comorbidities are proven risk factors for ADRs, which significantly increase the duration of hospital stay.[24] This explains the increased median duration of hospital stay in CAD group compared to non-CAD group (3 vs 2; $p < 0.0001$). The percentage of drugs prescribed from the essential drug list was optimal (77%). This reflects on the increasing use of newer antithrombotic and anti-anginal agents, which are not yet available in the list.

4.2. Utilization patterns of cardiovascular drugs among CAD and non-CAD patients

Almost all patients with CAD received antiplatelet agents (98%) similar to rates recorded in other tertiary care centers in South India.[11,25] Clopidogrel was prescribed at a higher rate (90%) (Table 3) than seen across other registries (50%–80%).[18,19] This is in line with updated 2007 recommendation of dual antiplatelet therapy in ACS, which has proven to confer a 20% reduction in cardiovascular events in both low and high risk patients.[26,27]

The utilization of anticoagulants at 78% among ACS patients was similar to patterns observed in other Indian studies (75%–85%).[20,28] Guidelines recommend regimens other than unfractionated heparin (enoxaparin/fondaparinux) when anticoagulant therapy is given for more than 48 h because of the risk of heparin induced thrombocytopenia.[7,26]

The utilization of other evidence based treatments in CAD especially ACE-inhibitors (81%) and statins (87%) were optimal and similar to previous studies.[20,25] However the lower use of beta-blockers (65%) though similar to that reported in CREATE registry (61%) could be improved provided there are no signs of cardiogenic shock, heart blocks (greater than first degree) and other relative contraindications to beta-blockade. A study among ACS patients in Saudi Arabia also showed sub-optimal prescribing of beta-blockers (69%) and ACE-inhibitors (59%).[13]

This study has documented the use of newer anti-anginal drugs and vasodilators like nicorandil, trimetazidine and ranolazine. Several randomized controlled trials with nicorandil and trimetazidine among patients with chronic angina have shown their efficacy in significantly reducing surrogate cardiac events on follow-up.[29,30] The MERLIN-TIMI 36 trial, which randomized 6560 hospitalized patients (NSTE-ACS) to either ranolazine or placebo recorded significantly lower incidence of arrhythmias in the first week after admission in ranolazine group.[31] However they did not reduce the rates of death or recurrent MI.

Guidelines recommend vitamin-K antagonists along with low dose aspirin therapy in patients with rheumatic valvular disease complicated by atrial fibrillation or thrombo-embolic episodes.[32] This explains increased use of vitamin-K antagonists in the non-CAD group (24%) where 20% patients had diagnosis of valvular heart disease and pulmonary thromboembolism. Arrhythmias were seen significantly more in non-CAD group (26%). The significantly increased use of digoxin (22%) and adenosine (1%) among non-CAD patients is probably explained by their efficacy in supraventricular arrhythmias. Majority of patients with cardiomyopathy were managed with recommended treatments, which included ACE-inhibitors, beta-blockers, diuretics and digoxin.

4.3. Determinants of cardiovascular drug use among CAD patients

We studied factors that may predict the utilization of these evidence-based treatments among patients with CAD (Table 5). Renal dysfunction was found to significantly decrease the utilization of ACE-inhibitors. ACE-inhibitors can interfere with the autoregulation of GFR mediated by angiotensin-II and lead to deterioration of renal function especially in patients with bilateral renal artery stenosis. Large controlled trials have proved their efficacy in reducing proteinuria and slowing the progression of kidney disease.[33] Hence National Kidney Foundation guidelines recommend ACE-inhibitors and ARBs as the preferred agents for diabetic and non-diabetic kidney disease with proteinuria.[34] In univariate analysis, utilization of ACE-inhibitors and ARBs was decreased among diabetics (Table 4). On exploring factors, which contributed to this pattern, renal dysfunction emerged significant. Therefore in an acute care setting, physicians may choose to avoid ACE-inhibitors to prevent further deterioration, however with careful

monitoring, most patients with CKD can be maintained on these drugs, even at low levels of GFR.[34]

Utilization of CCBs was increased by 3.7 times among hypertensives. This probably reflects the high percentage of hypertensive patients in our study (64%) and their requirement for drugs like CCBs and ACE-inhibitors that have a neutral effect on glucose and lipid metabolism. A diagnosis of STEMI decreased CCB use by 70% (Table 5). A meta-analysis on CCBs has reported no beneficial effect on the incidence of deaths or myocardial infarction.[35]

Heart failure, renal dysfunction and brady-arrhythmias significantly decreased beta-blocker use in univariate analysis whereas age <60 and a diagnosis of STEMI increased their use. Their mortality benefit has been well established in several large trials among patients with mild-moderate heart failure.[36,37] However guidelines recommend exclusion of patients from beta-blocker use in an ICU setting and to initiate therapy once stabilized.[38] On adjusted analyses, age <60 and a diagnosis of STEMI were important predictors for increased use in line with current recommendation to initiate beta-blocker therapy as soon as STEMI diagnosed.[26] Brady-arrhythmias emerged as the significant determinant that decreased beta-blocker use (Table 5). Atrioventricular blocks (greater than first degree) are known to contraindicate beta-blocker use. NSTEMI and congestive heart failure are known to be complicated by life threatening arrhythmias and heart blocks, which explain the increased utilization of anti-arrhythmics in both.

5. Limitations

We have attempted to study the broader spectrum of cardiovascular drug use in CCU. Further we identified the determinants of evidence based drug utilization in a real world setting. However there are some limitations. It was a retrospective study in a tertiary care setup based on review of medical records where medications as received by the patient during duration of hospital stay were recorded. Though retrospective designs are acceptable methods for drug utilization, prospective studies generate more accurate data due to more intense data collection. Also, patterns of drug utilization based on population characteristics like socioeconomic status could not be assessed.

6. Conclusion

In conclusion, this study provides an insight on the various cardiovascular disorders encountered in a CCU setting and the spectrum of cardiovascular drug utilization in them. Predominance of male gender, age <60 years and poly-pharmacy were observed. The data on patterns of drug utilization was largely similar to those recorded in hospital and registry-based studies in India. However, it has identified areas to further rationalize and optimize patterns of polypharmacy and evidence based use of medications like beta-blockers, newer anticoagulants/antiplatelet agents and newer anti-anginal agents. The results on the major determinants of cardiovascular drug use in CCU matched with the existing indications and cautions for use with each drug class.

Conflicts of interest

All authors have none to declare.

Disclosures

The authors declare no conflict of interest. The authors declare that they had no financial or personal relations to other organizations whose interests could have affected the content of this article in any way, either positively or negatively.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcdr.2013.12.001.

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