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Original Article

Epidemiology of cardioprotective pharmacological agent use in stable coronary heart disease

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ABSTRACT

Objective: To determine use of class and type of cardioprotective pharmacological agents in patients with stable coronary heart disease (CHD) we performed a prescription audit.
Methods: A cross sectional survey was conducted in major districts of Rajasthan in years 2008–09. We evaluated prescription for classes (anti-platelets, β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), calcium channel blockers (CCB) and statins) and specific pharmacological agents at clinics of physicians in tertiary ($n = 18$), secondary ($n = 69$) and primary care ($n = 43$). Descriptive statistics are reported.
Results: Prescriptions of 2290 stable CHD patients were audited. Anti-platelet use was in 2031 (88.7%), β-blockers 1494 (65.2%), ACE inhibitors 1196 (52.2%), ARBs 712 (31.1%), ACE inhibitors − ARB combinations 19 (0.8%), either ACE inhibitors or ARBs 1908 (83.3%), CCBs 1023 (44.7%), statins 1457 (63.6%) and other lipid lowering agents in 170 (7.4%). Among anti-platelets aspirin–clopidogrel combination was used in 88.5%. Top three molecules in β-blockers were atenolol (37.8%), metoprolol (26.4%) and carvedilol (11.9%); ACE inhibitors ramipril (42.1%), lisinopril (20.3%) and perindopril (10.9%); ARB's losartan (47.7%), valsartan (22.3%) and telmisartan (14.9%); CCBs amlodipine (46.7%), diltiazem (29.1%) and verapamil (9.5%) and statins were atorvastatin (49.8%), simvastatin (28.9%) and rosuvastatin (18.3%). Use of metoprolol, ramipril, valsartan, diltiazem and atorvastatin was more at tertiary care, and atenolol, lisinopril, losartan, amlodipine and simvasatin in primary care ($p < 0.01$).
Conclusions: There is low use of β-blockers, ACE inhibitors, ARBs and statins in stable CHD patients among physicians in Rajasthan. Significant differences in use of specific molecules at primary, secondary and tertiary healthcare are observed.
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1. Introduction

Patients with coronary heart disease (CHD) are at higher risk for subsequent cardiac events and mortality. A number of drugs have been shown to reduce second cardiovascular events and mortality in large randomized controlled trials.[1] These are anti-platelets, β-blockers, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and cholesterol lowering statins.[2] Current guidelines for the prevention of cardiovascular events among individuals with established CHD recommend anti-platelets, β-blockers, ACE inhibitors and statins in all individuals.[3,4] However, there is substantial gap between recommendations and implementation of these medicines in routine clinical practice.[5]

Recent studies have also shown that second and third generation pharmacological agents among these cardioprotective drug classes have important pharmacological and clinical benefits. For example, metoprolol has been reported to be better than atenolol in reduction of cardiovascular events,[6] ramipril and perindopril are more cardiovascular protective as compared to first generation ACE inhibitors,[7,8] newer ARBs such as telmisartan are equivalent to ACE inhibitors in cardioprotective effects,[9] and newer statins such as atorvastatin and rosuvastatin have dosing ease and less toxicity over older statins.[10,11] Studies in developed countries have reported that there occurs a substantial change in pharmacological drug use over time and also newer molecules are rapidly absorbed into practice once the clinical trial evidence emerges.[12] Use of different pharmacological agents and, specifically, newer molecules has not been studied in patients with CHD in India. To evaluate the use of various cardioprotective medicines and to document the use of different pharmacological agents within the broad class of drugs, used for secondary prevention in CHD patients, we performed a cross sectional study.

2. Methods

The study was approved by the institutional ethics committee. Details of the study protocol and methods have been reported earlier.[13] In brief, a proforma was prepared that included demographic details of patients, diagnoses, and drug prescriptions. Data on demographic and personal detail of physicians were also collected. Physicians were classified as primary care physicians who had basic qualifications and were working in rural or urban clinics and dispensaries; secondary level physicians who were having a postgraduate qualification in internal medicine and practising independently or in government clinics, primary health centers or secondary level government or private hospitals; and tertiary level physicians were those with subspecialty qualification in cardiology or cardiac surgery and working at tertiary level hospitals with cardiac invasive and surgical management. The trade names of drugs were deciphered and classified into pharmacological groups that included aspirin, clopidogrel or other anti-platelets agents, β-blockers, ACE inhibitors or ARBs, statins, other lipid lowering medicines such as fenofibrate, short- and long-acting nitrates, dihydropyridine or nondihydropyridine calcium channel blockers (CCBs), potassium channel openers (eg, nicorandil), metabolic modulators (eg, trimetazidine), antioxidants, multivitamins, diabetic medications, and other medications.

The study was performed at all large districts of Rajasthan state over a period of 15 months from September 2007 to December 2008. Consent from the physicians prescribing at primary, secondary, and tertiary sites was obtained and the prescriptions were studied during a single day at the local pharmacy. This was to minimize bias and negate the influence of changing the prescribing habit once awareness of monitoring was apparent. We could evaluate prescriptions of 43 general practitioners or primary care physicians, 61

Table 1 – Cardiovascular pharmacological agents prescribed in stable CHD patients.

Pharmacological molecules	Patient numbers	Proportion within each drug class %
Anti-platelet agents ($n = 2031$)		
Aspirin alone	234	11.5
Aspirin–clopidogrel	1797	88.4
β-Blockers ($n = 1494$)		
Atenolol	566	37.8
Metoprolol	394	26.4
Carvedilol	178	11.9
Bisoprolol	139	9.3
Nebivolol	108	7.2
Propanolol	74	4.9
Others	35	2.3
Angiotensin converting enzyme inhibitors ($n = 1196$)		
Ramipril	504	42.1
Lisinopril	243	20.3
Perindopril	131	10.9
Enalapril	147	12.3
Captopril	87	7.3
Trandolapril	54	4.5
Others	30	2.5
Angiotensin receptor blockers ($n = 712$)		
Losartan	340	47.7
Valsartan	159	22.3
Telmisartan	106	14.9
Candesartan	70	9.8
Others	37	5.2
Calcium channel blockers ($n = 1023$)		
Amlodipine	485	47.5
Diltiazem	298	29.1
Verapamil	97	9.5
Nifedipine	46	4.5
Felodipine	47	4.6
Nicardipine	23	2.2
Others	27	2.6
Statins ($n = 1457$)		
Atorvastatin	726	49.8
Simvastatin	422	28.9
Rosuvastatin	267	18.3
Others	42	2.8
Other lipid lowering ($n = 170$)		
Fibrates	71	41.7
Niacin	29	17.0
Orlistat	35	20.6
Others	35	20.6

internists and 8 diabetologists or secondary care physicians, and 18 cardiologists in tertiary care. Interviews were organized with the patients after their consent and only those patients who had an established diagnosis of CHD were included. Approximately, 60% of eligible patients (3013/5000) recruited from the outpatient clinics of primary, secondary, and tertiary healthcare facilities or tertiary care hospitals agreed to provide details of prescriptions. Twenty prescriptions were illegible and 2993 were included in the initial prescription audit.[13] In the present study, we excluded prescriptions from patients recently discharged from tertiary care hospitals and therefore results of 2290 prescriptions are presented. The medicines obtained from these prescriptions were deciphered and trade names translated into pharmacological molecules.

2.1. *Statistical analyses*

All the data were computerized and SPSS statistical package used for analyses. Descriptive statistics are reported. Significance of difference in drug use at primary, secondary and tertiary care was evaluated by χ^2 test.

3. Results

A total of 2290 prescriptions obtained at different levels of care (297 primary, 1484 secondary and 509 tertiary) were audited. The mean age of patients was 60.9 ± 8 years and median duration of disease was 2 years. Majority of patients were male (67.3%) and from urban (86.1%) locations. Anti-platelet

Table 2 – Cardiovascular drug use at primary, secondary, and tertiary healthcare.

Molecules used	Primary care (297)	Secondary care (1484)	Tertiary care (509)	X^2 (p-value)
Anti-platelets ($n = 2031$)				
Aspirin	48 (24.7)	162 (11.9)	24 (5.0)	0.0001
Aspirin–clopidogrel	146 (75.2)	1192 (88.0)	459 (95.0)	0.0001
β-Blockers ($n = 1494$)				
Atenolol	84 (41.2)	366 (39.3)	116 (32.2)	0.21
Metoprolol	27 (13.2)	249 (26.8)	118 (32.7)	0.0001
Carvedilol	17 (8.3)	120 (12.9)	41 (11.4)	0.36
Bisoprolol	23 (11.3)	89 (9.5)	27 (7.5)	0.36
Nebivolol	8 (3.9)	53 (5.7)	47 (13.0)	0.0001
Propanolol	23 (11.3)	43 (4.6)	8 (2.2)	0.0001
Others	22 (10.8)	10 (1.1)	3 (0.8)	0.0001
Angiotensin converting enzyme inhibitors ($n = 1196$)				
Ramipril	34 (24.8)	289 (38.2)	181 (59.9)	0.0001
Lisnopril	36 (26.3)	170 (22.5)	34 (11.2)	0.0006
Perindopril	3 (2.2)	79 (10.4)	51 (16.9)	0.0001
Enalapril	33 (24.1)	98 (12.9)	16 (5.3)	0.0001
Captopril	23 (16.8)	61 (8.1)	3 (0.9)	0.0001
Trandolapril	4 (2.9)	38 (5.0)	12 (4.0)	0.0001
Others	4 (2.9)	21 (2.8)	5 (1.6)	0.54
Angiotensin receptors blockers ($n = 712$)				
Losartan	40 (54.7)	249 (48.6)	51 (40.1)	0.0008
Valsartan	9 (12.3)	117 (22.8)	33 (26.0)	0.009
Telmisartan	8 (10.9)	69 (13.5)	29 (22.8)	0.14
Candesartan	14 (19.1)	50 (9.7)	6 (4.7)	0.009
Others	2 (2.7)	27 (5.3)	8 (6.3)	0.35
Calcium channel blockers ($n = 1023$)				
Amlodipine	106 (61.6)	321 (46.5)	56 (35.0)	0.0001
Diltiazem	27 (15.7)	206 (29.9)	65 (40.6)	0.08
Verapamil	8 (4.6)	67 (9.7)	22 (13.7)	0.36
Nifedipine	11 (6.4)	33 (4.8)	2 (1.2)	0.003
Felodipine	12 (6.9)	33 (4.8)	2 (1.2)	0.001
Nicardipine	2 (1.1)	9 (1.3)	12 (7.5)	0.002
Others	6 (3.5)	20 (2.9)	1 (0.6)	0.04
Statins ($n = 1457$)				
Atorvastatin	27 (40.9)	478 (50.7)	221 (52.3)	0.0001
Simvastatin	35 (53.0)	283 (30.0)	104 (24.6)	0.0053
Rosuvastatin	3 (5.3)	157 (16.6)	76 (18.0)	0.0001
Others	1 (1.7)	25 (2.6)	21 (5.0)	0.0003
Other lipid lowering drugs ($n = 170$)				
Fibrates	2 (66.7)	47 (42.3)	22 (39.3)	0.01
Niacin	0 (0.0)	24 (21.6)	5 (8.9)	0.06
Orlistat	0 (0.0)	30 (27.0)	5 (8.9)	0.01
Others	1 (33.3)	10 (9.0)	24 (42.8)	0.0001

was used in 2031 (88.7%), β-blockers in 1494 (65.2%), ACE inhibitors in 1196 (52.2%), ARBs in 712 (31.1%), ACE inhibitors – ARB combinations in 19 (0.8%), either ACE inhibitors or ARBs in 1908 (83.3%), CCBs in 1023 (44.7%), statins in 1457 (63.6%) and other lipid lowering agents in 170 (7.4%) (Table 1). In the anti-platelet class of drugs, 11.5% patients were on aspirin and 88.5% were on aspirin–clopidogrel combination. Top three molecules prescribed among β-blockers were atenolol (37.8%), metoprolol (26.4%) and carvedilol (11.9%); among ACE inhibitors were ramipril (42.1%), lisinopril (20.3%) and perindopril (10.9%); among ARBs were losartan (47.7%), valsartan (22.3%) and telmisartan (14.9%); among CCBs were amlodipine (46.7%), diltiazem (29.1%) and verapamil (9.5%); and among statins were atorvastatin (49.8%), simvastatin (28.9%) and rousvastatin (18.3%). Details of use of other pharmacological entities are shown in Table 1.

Use of various cardiovascular pharmacological drugs at different levels of care is shown in Table 2. At primary, secondary and tertiary care levels, respectively, the use of leading molecules was aspirin–clopidogrel in 75.2, 88.0 and 95.0%; atenolol in 41.2, 39.3 and 32.2%; metoprolol in 13.2, 26.8 and 32.7%; ramipril in 24.8, 38.2 and 59.9%; lisinopril in 26.3, 22.5 and 11.2%; losartan in 54.7, 48.6 and 40.1%; valsartan in 12.3, 22.8, 26.0%; amlodipine in 61.6, 46.5 and 35.0%; diltiazem in 15.7, 29.9 and 40.6%; atorvastatin in 40.9, 50.7 and 52.3%; and simvastatin in 53.0, 30.0 and 24.6%. Use of metoprolol, ramipril, valsartan, diltiazem and atorvastatin was more at tertiary care while at primary care atenolol, lisinopril, losartan, amlodipine and simvasatin use was more (χ^2 test for intergroup difference, $p < 0.01$).

4. Discussion

This study shows a substantial under-prescribing of cardiovascular evidence based medications in stable community dwelling patients with CHD. There is low use of β-blockers, ACE inhibitors and statins. The lowest use is at the primary care level as reported earlier.[13] Dual anti-platelet therapy is widely used. Among β-blockers, ACE inhibitors, ARBs, CCBs and statins, the most used molecules are atenolol, ramipril, losartan, amlodipine and atorvastatin, respectively. Use of second and third generation molecules in these drug classes is significantly greater at tertiary healthcare level compared to secondary and primary healthcare levels.

Recent studies in Europe and North America have reported a high use of evidence based drugs in patients with CHD for secondary prevention.[14] The serial EURO-ASPIRE studies in Europe[15] and large US based registries[16] reported continuous improvement in use of anti-platelets, β-blockers, ACE inhibitors or ARBs and statins. Only limited studies exist in low income countries.[17] There is also no systematic collection of information of cardiovascular drug use in India and prescription trends are usually available from marketing research conducted via pharmaceutical companies[18] and not through academic approach. The present study is an important landmark where we conducted the study to document the current treatment trends for secondary prevention of CHD in Rajasthan. Results of the present study have been compared with the international studies performed since 2000's (Table 3) and

Table 3 – Comparative analysis of prescribing frequency (%) of secondary preventative cardiovascular medicines in stable community dwelling CHD patients (data source: reference[19]).

	Present study	EURO-ASPIRE III study 2010	Turley et al 2008	EHS II study 2006	Martin et al 2005	Fox et al 2005	GRACE study 2005	WHO-PREMISE study 2005	MINAP study 2004	EHS I study 2002	EURO-ASPIRE II study 2001
Sample size	2290	8996	2749	7994	875	100	390	8483	150,902	9798	5556
Aspirin	89	91	92	95	86	92	94	81	90	90	90
β-Blockers	65	80	79	83	NA	70	76	48	83	77	66
ACE inhibitors	84[a]	71[a]	55	72[a]	NA	26	51	40	72	61[a]	38
Statins	63	78	92	77	70	73	75	21	84	50	43

a ACE inhibitors or ARBs, EHS = Euro Heart Survey.

show lower use of β-blockers, ACE inhibitors and statins as compared to studies in high income countries.[19] However, use of various drugs classes is significantly greater than WHO-PREMISE study[17] performed in eight low and middle income countries.

This study also shows significant differences in use of different pharmacological molecules at primary, secondary and tertiary levels of healthcare. While use of first generation molecules in various drug classes was the greatest at primary care, second and third generation pharmaceutical molecules were more frequently used at tertiary care level. These findings are similar to studies from high income countries.[20] Use of first generation molecules such as atenolol, enalapril and lisinopril, losartan and simvastatin is high among the primary care physicians while second and third generation drugs are more used in secondary and tertiary care.[20]

Physician behaviors are influenced by multiple factors.[21] Studies in high income countries have reported large number of factors such as government guidelines, continuing medical education, insurance coverage, peer-opinion, industry sponsored educational events, self-education and experiential knowledge. Reasons for low use of evidence based cardioprotective molecules have not been studied in India but factors that influence the physician mind-lines (reported above) could be important. Other factors could be poor dissemination and uptake of results of study data from Caucasian (non-Indian/Asian) populations, inequities in health services, and resistance (by both doctor and patients) to the cost and complexity of prescribing multiple cardiovascular medications. Barriers to adopting guideline recommendations by doctors may include lack of understanding or translation to clinical practice and patient profile.[22] Although polypill concept[23] may improve compliance, greatest advance would be to conduct studies in Indian subcontinent which would lead to more acceptable interpretation of the study results in the indigenous population.[24] Additionally, continued medical education directed on evidence based medicine rather than experience based medicine may augment secondary prevention and assist in reducing the anticipated growing burden of CHD in India. The study has multiple limitations, reported earlier,[13] related to patient inclusion criteria (broad array of CHD patients), sampling (healthcare facility based and not population based), non-random physician selection and study performed in a single state of India.

In conclusion, despite availability of evidence based medicines at affordable prices there are significant gaps in use of these secondary preventive medicines in India as observed in the present study. We believe that the results can be transposed to the whole country as Rajasthan is at the median of national human development index.[25] Larger prospective national registries are required for future outcomes research.

Conflicts of interest

All authors have none to declare.

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