Indian Heart Journal 69 (2017) 447–452

Contents lists available at ScienceDirect

Indian Heart Journal

journal homepage: www.elsevier.com/locate/ihj

Prevalence and control of cardiovascular risk factors in stable coronary artery outpatients in India compared with the rest of the world: An analysis from international CLARIFY registry

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ARTICLE INFO

Article history:
Received 18 October 2016
Accepted 16 May 2017
Available online 19 May 2017

Keywords:
Coronary artery disease
Heart rate
Risk factors
India
Registries
Secondary prevention

ABSTRACT

Objectives: We describe the clinical characteristics, prevalence and control of coronary artery disease (CAD) risk factors of the Indian cohort enrolled in the CLARIFY registry and compare them with data from rest of the world (ROW).
Methods: CLARIFY is an international, prospective, observational, longitudinal cohort study in stable CAD outpatients. The baseline data of Indian cohort (n = 709) were compared to ROW (n = 31994).
Results: The CLARIFY India patients were significantly younger than the ROW (59.6 ± 10.9 vs 64.3 ± 10.4). Indian patients were more likely than those in ROW to have diabetes (42.9% vs 28.8%) and angina (27.8% vs 21.9%). Mean heart rate was significantly greater in Indians measured by either palpatory method (76.1 ± 10.4 vs 68.0 ± 10.5) or ECG (74.9 ± 12.9 vs 67.0 ± 11.3). The use of aspirin (85.6% vs 87.8%), β-blockers (69.4% vs 75.4%), and lipid-lowering agents (90% vs 92.4%) was lower in India. A significantly greater proportion of patients in India exhibited low HDL cholesterol (41.6% vs 31.2%), and heart rate ≥70 bpm (82.2% vs 48.5%). The risk factors control was poor in India with heart rate goal of ≤60 bpm achieved in 2.5%; HbA1c <7% in 9.9%; and HbA1c <6.5% in 4.6% patients.
Conclusion: The CLARIFY registry demonstrates a high prevalence and poor control of cardiovascular risk factors in Indian patients. Systematic efforts to improve risk factor control are required.

1. Introduction

Coronary artery disease (CAD) is the leading cause of cardiovascular morbidity and mortality worldwide, contributing to over 7 million deaths annually.[1] Regardless of a recent decline in CAD mortality in the developed countries,[2] the burden of CAD in India is rising remarkably. The national commission on macroeconomics and health estimated about 359 lakh CAD cases in 2005 that has been projected to rise up to 615 lakhs in 2015,[3] with the corresponding loss of the national income of approximately 237 billion USD in India.[4] These estimates draw special attention to the urgent need of aggressive strategies for the prevention and control of CAD in India.

A line of evidence indicates that the Indians are more susceptible to CAD and manifest higher mortality rate than their western counterparts.[5–8] The fact may be attributed to diverse risk factors distribution and control across various geographical locations in India.[9] Therefore, one of the crucial strategies in the primary prevention of CAD could be achieving the risk factors control, which has been emphasised even in recent clinical practice guidelines.[10,11] Although, there are enormous advances in the secondary prevention of CAD as witnessed by numerous clinical trials of antiplatelet therapy, statins, and angiotensin-converting enzyme inhibitors, the data on contemporary clinical practice management of CAD and its impact on clinical outcomes are scarce in India. Moreover, the available epidemiological data are not derived from well-designed high-quality studies, and majorly included patients with acute coronary syndrome with limited information on outpatients with stable CAD.[12,13] Bridging this gap, the Prospective Observational Longitudinal Registry of patients with stable coronary artery disease (CLARIFY) registry was carried out across 45 geographical regions of the world with the objectives to gain information on their demographic characteristics, clinical presentation, and management of CAD. The registry also intends to

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http://dx.doi.org/10.1016/j.ihj.2017.05.014

study clinical outcomes of these patients and identify the long-term prognostic factors determining the clinical outcomes.

This communication describes the clinical characteristics, prevalence and control of risk factors for CAD in India and compares them with the rest of the world (ROW) by analysing data from global CLARIFY registry.

2. Methods

2.1. Study design

CLARIFY is an international, prospective, observational, longitudinal cohort study in stable CAD outpatients with 5 years of follow-up. Detailed methods have been published previously.[14–16]

2.2. Patient selection

Stable CAD patients with at least one of the following: coronary stenosis >50% on coronary angiography; documented myocardial infarction (MI, >3months ago); chest pain with myocardial ischemia proven using stress electrocardiogram stress echocardiography, or myocardial imaging; history of coronary artery bypass graft surgery (CABG) or percutaneous coronary intervention (PCI; performed >3 months ago), were enrolled in the registry. Patients with planned revascularisation, patients hospitalised for cardiovascular disease (CVD) (included revascularisation) 3 months prior to enrolment, patients with conditions anticipated to impede 5-year follow-up (e.g. serious non-cardiovascular disease, conditions limiting life expectancy, limited cooperation or legal capacity, or severe CVD [advanced heart failure, severe valve disease, history of valve repair/replacement, etc]), were excluded from the study.

2.3. Data collection and selection of patients for India sub-study

The information collected included demographic characteristics; risk factors and lifestyle; medical history included present symptoms; physical examination; cardiac evaluation included measuring the heart rate (HR) by pulse palpation and the resting electrocardiogram within the previous 6 months. Blood pressure both systolic and diastolic was recorded. All patients had an ECG taken and a record of rhythm documented. Blood tests recorded included haemoglobin, fasting blood glucose, HbA_1c, serum triglycerides and cholesterol, and serum creatinine, if available. A note was made of current medications taken regularly by the patient for ≥7 days before entry in the registry.

In the current paper, only the patients recruited from India (709) were compared with rest of the world.

2.4. Ethics

The registry was conducted in line with the principles outlined in the Declaration of Helsinki and was approved by the National Research Ethics Service, Isle of Wight, Portsmouth, and Southeast Hampshire Research Ethics Committee, UK. Approval was also obtained in all participating centres in accordance with local regulations. All patients provided written informed consent. The ISRCTN registration number of CLARIFY is ISRCTN43070564.

2.5. Statistical analysis

Data are summarised as mean with standard deviation or median with interquartile range. Categorical data are presented as counts and percentages. Data were analysed by $\chi 2$ tests or Fisher's exact test for categorical and *t*-test or Mann–Whitney *U* test for continuous variables using 2-sided tests at a significance level of 5% using Statistical Analysis Software (version 9.2).

3. Results

The global CLARIFY registry included a total of 32703 analysable patients, of these, Indian cohort comprised of 709 (2.2%) stable CAD patients.

3.1. Patient characteristics

A majority of baseline characteristics and lifestyle practices of CLARIFY India cohort were similar to the ROW population (Table 1). The CLARIFY India patients were significantly younger than the ROW (59.6 ± 10.9 vs 64.3 ± 10.4). Indian patients were more likely than those in the ROW to have diabetes (42.9% vs 28.8%), but less likely to have a family history of premature CAD (21.3% vs 28.7%), dyslipidaemia (63% vs 75.2%), peripheral arterial disease (4.8% vs 10%), aortic abdominal aneurysm (0.1% vs 1.6%), and carotid disease (1.8% vs 7.7%) (Table 2). Indian participants had less frequent history of MI (55.3% vs 60%), PCI (42.5% vs 59%) and CABG (20.7% vs 23.6%) than the ROW patients. The mean HR (bpm) of CLARIFY

Table 1
Baseline demographic characteristics and lifestyle of patients.

Clinical characteristics	India (N = 709)	Rest of the world (N = 31994)	p value
Demographic characteristics			
Age (years), mean(SD)	59.6 (10.9)	64.3 (10.4)	<0.0001
Male	564 (79.5)	24801 (77.5)	0.2223
BMI (kg/m^2), mean(SD)	25.7 (4)	27.9 (4.6)	<0.0001
Ethnicity			<0.00001
Caucasian	13 (1.8)	21099 (65.9)	
South Asian	696 (98.2)	1748 (5.5)	
Lifestyle			
Living Alone	21 (3)	3665 (11.5)	<0.0001
Smoking status			<0.00001
Current	62 (8.7)	4015 (12.6)	
Former	171 (24.1)	14938 (46.7)	
Never	476 (67.1)	13037 (40.8)	
Alcohol Intake	124 (17.4)	16955 (53)	<0.0001
Weekly Physical Activity			<0.00001
None	88 (12.4)	5199 (16.3)	
Only Light	449 (63.3)	16361 (51.2)	
Vigorous at least once or twice	98 (13.8)	5372 (16.8)	
Vigorous 3 or more times	74 (10.4)	5047 (15.8)	
Value represents n (%) unless specified			

Table 2
Medical history of patients.

Clinical characteristics	India (N = 709)	Rest of the world (N = 31994)	p value
Medical history			
Family history of premature CAD	151 (21.3)	9175 (28.7)	<0.0001
Treated Hypertension	493 (69.5)	22717 (71)	0.2050
Diabetes	304 (42.9)	9198 (28.8)	<0.0001
Dyslipidemia	447 (63)	24057 (75.2)	<0.0001
Peripheral Arterial Disease	34 (4.8)	3205 (10)	<0.0001
Myocardial Infarction	392 (55.3)	19203 (60)	0.0060
PCI	301 (42.5)	18861 (59)	<0.0001
CABG	147 (20.7)	7556 (23.6)	0.0402
Aortic abdominal aneurysm	1 (0.1)	503 (1.6)	0.0018
Carotid Disease	13 (1.8)	2461 (7.7)	<0.0001
Internal Cardiac Defibrillator,	2 (0.3)	416 (1.3)	0.0133
Pacemaker	7 (1)	781 (2.4)	0.0088
Stroke	11 (1.6)	1303 (4.1)	0.0005
TIA	17 (2.4)	984 (3.1)	0.1770
Hospitalization for CHF	17 (2.4)	1514 (4.7)	0.0024
Atrial fibrillation/Flutter	9 (1.3)	2304 (7.2)	<0.0001
Asthma/COPD	46 (6.5)	2373 (7.4)	0.1940
Current or previous trial participation	5 (0.7)	1130 (3.5)	<0.0001
Current symptoms and measurements			
Angina	197 (27.8)	7015 (21.9)	0.0002
CHF	63 (8.9)	4862 (15.2)	<0.0001
SBP (mmHg), mean(SD)	131.6 (18.6)	131.0 (16.6)	0.3425
DBP (mmHg), mean(SD)	80.8 (9.3)	77.2 (10)	<0.0001
HR by pulse palpation (bpm), mean (SD)	76.1 (10.4)	68.0 (10.5)	<0.0001
HR on ECG (bpm), mean (SD)	74.9 (12.9)	67.0 (11.3)	<0.0001
LBBB if ECG available	23 (5.4)	1178 (4.9)	0.7512
Value represents n (%) unless specified			

Indian cohort was significantly higher when compared to the ROW; measured by both palpation (76.1 ± 10.4 vs 68.0 ± 10.5) and ECG (74.9 ± 12.9 vs 67.0 ± 11.3). Angina was significantly more prevalent in India (27.8% vs 21.9%).

3.2. Medical therapies

The use of selected chronic cardiovascular medications at enrolment is presented in Table 3. Overall, a major proportion of the India and the ROW cohorts were taking guideline-recommended therapy. The use of anti-platelets was high with aspirin being the most commonly used (85.6% vs 87.8%) in India vs ROW. Thienopyridine (54.9% vs 26.6%) and dual anti-platelets (53.3% vs 27.4%) were prescribed to significantly higher proportion of patients in India than the ROW. The use of β-blockers (69.4% vs 75.4%) and ivabradine (5.4% vs 9.9%) was significantly lower in India compared to the ROW. Though a total of 90% and 92.4% patients in India and the ROW, respectively, used lipid lowering agents, there was less frequent use of statin in India (77.9% vs 90%).

3.3. Risk factors and their control

In general, the prevalence of cardiovascular risk factors was very high in CLARIFY India cohort compared to the ROW (Figs. 1

Table 3
Medical therapy at baseline.

Medication	India (N = 709)	Rest of the world (N = 31994)	p value
Aspirin	607 (85.6)	28080 (87.8)	0.0443
Thienopyridine	389 (54.9)	8492 (26.6)	<0.0001
Other antiplatelet agents	69 (9.7)	2954 (9.2)	0.3534
Aspirin and another antiplatelet agent	378 (53.3)	8767 (27.4)	<0.0001
Oral anticoagulant	65 (9.2)	2605 (8.2)	0.1820
Antiplatelet agent and anticoagulant	53 (7.5)	1641 (5.1)	0.0035
β-Blockers	492 (69.4)	24119 (75.4)	<0.0001
Ivabradine	38 (5.4)	3180 (9.9)	<0.0001
Calcium antagonists	183 (25.8)	8726 (27.3)	0.2032
Verapamil or Dilitiazem	41 (5.8)	1855 (5.8)	0.4920
ACE Inhibitors	280 (39.5)	16615 (52)	<0.0001
Angiotensin II receptor blockers	211 (29.8)	8463 (26.5)	0.0274
Lipid-lowering drugs	638 (90)	29553 (92.4)	0.0101
Statins if on lipid lowering agents	497 (77.9)	26602 (90)	0.0001
Other antianginal agents	140 (19.7)	4401 (13.8)	<0.0001
Trimetazidine	68 (9.6)	3388 (10.6)	0.2120
Ranolazine	38 (5.4)	98 (0.3)	<0.0001
Diuretics	214 (30.2)	9371 (29.3)	0.3204
Other antihypertensive agents	72 (10.2)	2179 (6.8)	0.0003
Digoxin and derivatives	28 (3.9)	800 (2.5)	0.0106
Amiodarone/Dronedarone	17 (2.4)	945 (3)	0.2245
Other Antiarrhythmics	2 (0.3)	304 (1)	0.0514
Anti-diabetes agents	254 (35.8)	7762 (24.3)	<0.0001
Value represents n (%) unless specified			

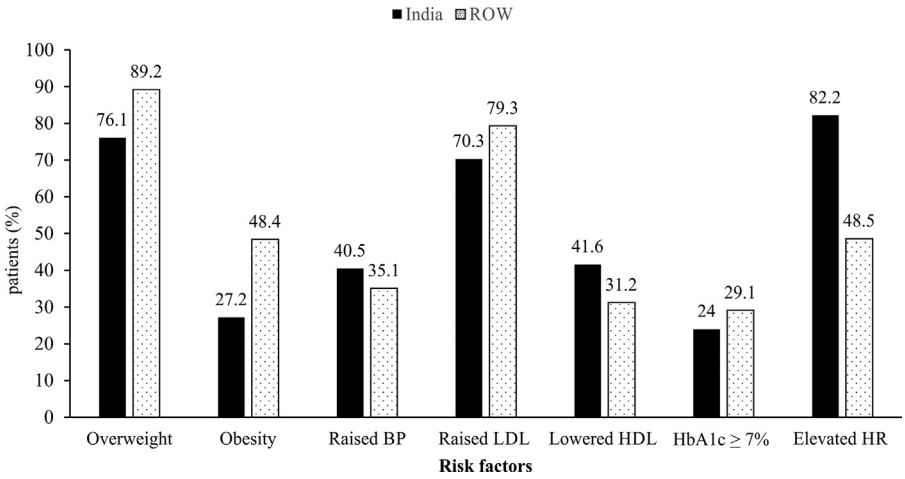

Fig. 1. Distribution of risk factors in India and the rest of the world (all $p < 0.05$). Overweight: BMI ≥23 kg/m2; Obesity: BMI of ≥27.0 kg/m2; Raised BP: SBP ≥140 mmHg and/or DBP ≥90 mmHg; Raised LDL (≥0.7 g/L, 1.8 mmol/L); Lowered HDL (≤40 mg/dL, 1.0 mmol/L); $HbA_1c \geq 7\%$ in diabetic patients; Elevated HR on palpation ≥70 in angina patients BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; HR, heart rate; ROW, rest of the world.

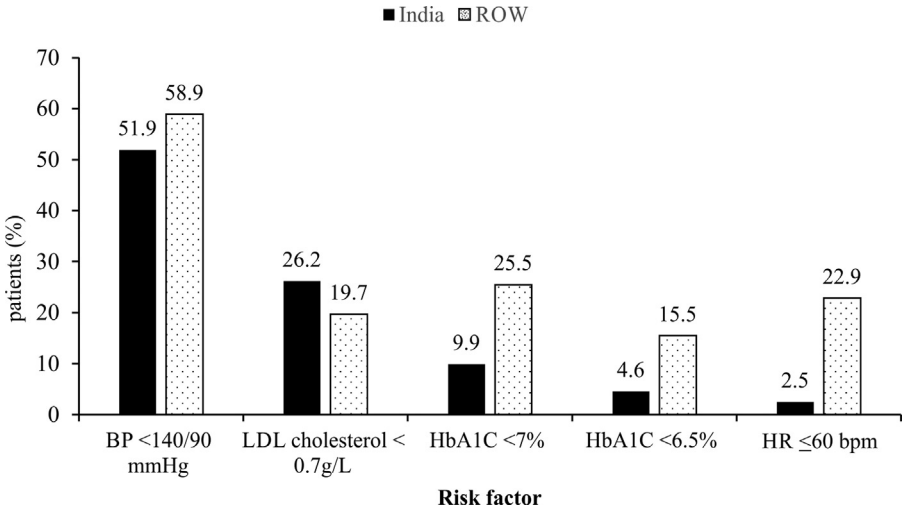

Fig. 2. Control of risk factors in India and the rest of the world (all $p < 0.05$). BP <140/90 mm Hg in patients with hypertension; LDL cholesterol <0.7 g/L in patients with dyslipidaemia; HbA_1c <7% in patients with diabetes; HbA_1c <6.5% in patients with diabetes; Heart rate ≤60 bpm in patients with symptoms of angina BP, blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; HR, heart rate; ROW, rest of the world.

and 2). The Indian cohort was less likely to be overweight (76.1% vs 89.2%) and obese (27.2% vs 48.4%) than the ROW. A significantly greater proportion of patients in India displayed dyslipidaemia, notably raised LDL cholesterol (70.3% vs 79.3%) and low HDL cholesterol (41.6% vs 31.2%). The remarkably high proportion of Indian patients exhibited elevated HR (≥70 bpm) than the ROW (82.2% vs 48.5, $p < 0.0001$), and only 2.5% in India vs 22.9% in the ROW achieved the HR goal of ≤60 bpm when presented with symptoms of angina. About 9.9% and 4.6% patients achieved HbA_1c <7% and HbA_1c <6.5%, respectively, in India.

4. Discussion

The CLARIFY registry is an international, prospective, observational longitudinal registry focused on outpatients with stable CAD.

Similar to the previous epidemiological studies,[17,18] the prevalence of cardiovascular risk factors was higher in CLARIFY India cohort. CLARIFY India results witnessed lower prevalence of overweight and obesity than the ROW. These findings are consistent with the WHO estimates that show a relatively low rate of overweight and obesity in India.[19] However, there is a strong evidence that the metabolic consequences of obesity, dyslipidaemia (particularly hypertriglyceridemia, low HDL and increased numbers of small dense LDL particles) and dysglycaemia (insulin resistance and type 2 diabetes), are apparent at lower absolute levels of total body fat in South Asians than in whites. In agreement with these facts, the proportion of patients with raised LDL-C, reduced HDL-C, and diabetes (with poor glycaemic control) were greater in CLARIFY India cohort. Moreover, one of the remarkable characteristics was younger age of the Indian cohort than the ROW. The results are in agreement with the results of the INTERHEART study, an international case-control study carried out in 52 countries, including India, involving 15152 cases of acute MI.[20] The study has shown a high prevalence of cardiovascular risk factors even among controls who were less than sixty years of age.

One of the crucial strategies for prevention of CAD universally recommended by evidence-based guidelines includes comprehensive management of modifiable risk factors, which includes weekly physical activity, weight management, smoking/tobacco cessation,

and dietary modification.[21] The findings from this sub-set analysis (Table 1) show that the majority of patients in the CLARIFY Indian cohort were not practicing healthy lifestyle for managing modifiable risk factors. Therefore, the current pattern of CAD characterised by the high prevalence of inadequately controlled risk factors, as revealed by CLARIFY registry, suggest that the increased cardiovascular risk in India may be preventable through lifestyle interventions and the judicious use of drugs to attain optimal levels of blood pressure, lipids and glucose.

Medical therapy is an important component of secondary prevention that includes aspirin, statins, and β-blockers. In addition, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers are recommended for concomitant heart failure, hypertension, or diabetes. Several prospective registries such as WHO-PREMISE and PURE studies report underutilization of evidence-based medicine in India[22,23]; however, it is noteworthy that the majority of CLARIFY India patients received the recommended medical care. Like ROW CLARIFY cohort (92.4%), the majority of CLARIFY India patients (90%) received lipid lowering agents with a noticeable difference in the proportion of patients receiving a statin. Although the majority of patients received recommended therapy, yet there are significant gaps in secondary prevention of CVD in urban and rural communities despite the availability of medications at an affordable cost as demonstrated in Andhra Pradesh Rural Health Initiative (APRHI) in India.[24] Moreover, underused treatments, lack of awareness among patients and the physician, and non-adherence to medications are some of the factors responsible for poor management, despite the sheer scale of CVD prevalence in India.[25–27] All these factors mandate systematic interventions to improve the long-term use of basic, inexpensive, and effective drugs.

Determining the long-term prognostic value of HR remains the imperative objective of the CLARIFY. The data on clinical outcomes after 5 year follow-up of these Indian CAD patients is intended to be published separately. Taking into account the increased cardiovascular risk with elevated HR,[28] several recent clinical practice guidelines have emphasised HR reduction as a substantial cardiovascular risk management strategy.[11] In the similar context, the mean HR and proportion of patients having HR $\geq$70 bpm of CLARIFY India cohort were higher than ROW. In addition, only 2.5% and 22.9% patients in the present cohort of CLARIFY India and the ROW, respectively, achieved goal HR $\leq$60 bpm. Similar results were revealed in BEAUTIFUL trial enrolling stable CAD patients; more than half of patients demonstrated a baseline resting HR $\geq$70 bpm, which was associated with significantly higher risk of myocardial infarction, coronary revascularization, and death, even with ß-blockers.[29] An important finding of the trial was that ivabradine added to optimal preventive therapy further reduced the risk of coronary events such as MI by −36% and revascularization by −30%.[29] Ivabradine is a pure HR-lowering agent having a selective action on the sinus node and is thus devoid of the usual side effects of β-blockers. In light of the above data, taking a step forward in the management of coronary patients, recent guidelines now recommend ivabradine for heart rate reduction as a second line treatment in the management of coronary patients.[11]

Voluntary enrolment of patients by physicians contributed inherent selection bias. In particular, the CLARIFY India cohort included patients attending outpatient clinics/hospitals only in major city areas indicating urban bias. Despite these limitations, the registry has several strengths, including a large number of participating countries, making the results more generalizable.

5. Conclusion

The baseline results of the Indian cohort from CLARIFY registry indicate that there is a high prevalence and poor control of cardiovascular risk factors. Systematic approaches to improve control of modifiable risk factors and increase the long-term use of essential primary and secondary prevention medications are required to fulfil the lacuna in the management of stable CAD in current clinical practice.

Disclosure

The authors have no conflict of interest.

Acknowledgement

This study was supported by a research grant from Servier, France, manufacturers of original ivabradine (Coralan®). Servier did not participate in study design, data collection and analysis, decision to publish and preparation of the manuscript. Authors would like to thank all CLARIFY investigators.

Appendix A.

List of the CLARIFY India Investigators (other than authors)

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