Evaluation of relationship between common carotid artery intima-media thickness and coronary in-stent restenosis: A case-control study

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Abstract: *Aim:* The study was intended to evaluate relationship of common carotid artery intima-media thickness (CIMT) with coronary in-stent restenosis (ISR) and to assess clinical profile of patients to determine the predictors of coronary ISR. *Methods:* This was a single-center, case-control study performed between December 2012 and February 2015 in India. The study population consisted of PCI-treated patients with ISR ($n = 32$) and those without any post-PCI symptoms at least 6 months prior to the study period ($n = 40$). Quantitative coronary angiography was performed in patients to determine ISR. *Results:* Average CIMT for cases and controls was 0.96 ± 0.23 and 0.66 ± 0.09 mm (OR = 57, $p < 0.001$), respectively. CIMT was <0.8 mm in 25% of cases and 95% of controls. On multivariate analysis, presence of hypertension (OR = 10.79, $p = 0.026$) and higher stent diameter (OR = 14.87, $p = 0.039$) were independently associated with increased presence of ISR. CIMT <0.8 mm (OR = 0.03, $p = 0.025$), STEMI (OR = 0.03, $p = 0.004$), and estimated glomerular filtration rate >50 ml/min (OR = 0.005, $p = 0.014$) were independently associated with lower presence of ISR. *Conclusions:* Elevated CIMT appears to be an independent risk indicator for increased ISR. As CIMT is a non-invasive parameter, post-PCI follow-up measurements of CIMT in routine clinical practice will provide potential benefits to predict the restenosis rates.

Keywords: percutaneous coronary intervention, in-stent restenosis, carotid artery intima-media thickness, coronary artery disease, revascularization

Introduction

At present, the emergence of the cardiovascular diseases (CVDs) in the developing countries contributes a greater share to the global burden than the developed countries. Most of CVD would occur on account of a conglomerate of conditions that include acute myocardial infarction (MI), angina pectoris, and congestive heart failure, although these are not necessarily mutually exclusive terms. Data also suggest that the prevalence rates of CVD among younger adults (≥40 years) are likely to increase in future [1].

Atherosclerosis serves as a primary pathology that underlies a significant majority of distinct disorders, causes development of flow-limiting lesions, which can ultimately lead to impaired tissue oxygen delivery and results into clinical presentation that can be either as sudden as acute coronary syndrome (ACS) encompassing MI [either

ST-elevation MI (STEMI) or non-STEMI] and unstable angina (UA) or as chronic stable angina (CSA) [2].

Myocardial revascularization has been shown to confer significant benefits in terms of symptom control and improved prognosis. However, the long-term success of revascularization by balloon angioplasty technique has been limited by restenosis [3–5]. To overcome this problem, stents were introduced, which have improved the results of percutaneous coronary revascularization but also introduced in-stent restenosis (ISR) [6].

Hence, there is a need to concentrate on the risk factors and the predictors of ISR. The risk factors can be patient-related and procedure-related, which are known to affect the outcome, survival, morbidity of patients with post-percutaneous coronary intervention (PCI) [7–12]. Recently, there has been increased interest in assessing novel risk factors for CVD risk assessment and one of these is carotid artery intima-media thickness (CIMT). Several published studies showed the evident relationship of CIMT and CVD especially coronary artery disease (CAD) and atherosclerosis [13–17]. However, there are very few studies conducted in past showing association of CIMT and ISR [18–20].

Hence, the present work was postulated to study the relationship of CIMT with coronary ISR and to assess the clinical profile of patients to determine the predictors of coronary ISR.

Materials and Methods

This was a single-centered, prospective, case-control study undertaken at the tertiary care center in India, from December 2012 to February 2015. The study was approved by institutional ethics committee. Informed consent from all the patients was obtained in local language prior to study.

Inclusion criteria include patients of age ≥18 years with ISR (with at least 50% diameter stenosis in-stent or in-segmenton at least two orthogonal projections) as cases. Asymptomatic patients of age ≥18 years who had underwent PCI with stent placement and symptoms free at least 6 months prior to the study were included as controls. Exclusion criteria include patients with age group <18 years, with angiographic evidence of acute/subacute stent thrombosis and with duration of hospital stay <24 h.

Mehran et al.'s [21] angiographic classification for ISR was used to categorize the types of ISR *(Table I)*. CIMT was measured using carotid ultrasonography system (MyLab50; Esaote SpA, Genoa, Italy) with a 7.5-MHz linear transducer for all patients in accordance with Mannheim CIMT consensus statement [22]. With the longitudinal projection of the common carotid artery, the carotid bulb, and the internal carotid artery, the site of the greatest thickness including a plaque lesion was sought along both near and far walls bilaterally (max-IMT).

Current symptoms, predisposing factors, past history of CAD, previous revascularization, drug history, dietary, and detailed clinical examination including assessment of anthropometric data were collected from all the recruited patients.

Hemogram, random blood glucose, lipid profile, and renal function tests were investigated and estimated glomerular filtration rate (eGFR) was calculated using Cockcroft–Gault's formula [23]. Details of coronary angiography of all cases were recorded and analyzed. The 2D echocardiography was done to assess the left ventricular function.

Student's *t*-test (two-tailed, independent) and χ^2/Fisher's exact test have been used for statistical analysis of continuous and categorical study parameters, respectively, using SPSS (version 15; Chicago, IL, USA).

Results

A total of 72 patients with CAD were studied, out of which 32 (44.4%) patients having angiographically proven ISR were considered as cases and 40 (55.5%) asymptomatic patients studied post-PCI were considered as controls.

The baseline characteristics of patients of both groups are depicted in *Table II*. Both controls and cases prior to PCI are presented with STEMI as the most common diagnosis (60% and 65.6%, respectively).

Table I Angiographic classification of in-stent restenosis (ISR) by Mehran et al.

Class-I	Focal ISR group; lesions are ≤10 mm in length and are further positioned at: IA – the unscaffolded segment (i.e, articulation or gap), IB – the body of the stent, IC – the proximal or distal margin (but not both), or ID – a combination of these sites (multifocal ISR)
Class-II	Diffuse intrastent ISR; lesions are >10 mm in length and are confined to the stent(s), without extending outside the margins of the stent(s)
Class-III	Diffuse proliferative ISR; lesions are >10 mm in length and extend beyond the margin(s) of the stent(s)
Class-IV	ISR with total occlusion; lesions have a TIMI flow grade 0

Table II | Baseline characteristics of patients of case and control group

Variables	Cases	Controls	*P* value
Age (mean ± SD, years)	54.34 ± 8.73	49.13 ± 10.59	0.028
BMI (mean ± SD, kg/m^2)	28.55 ± 4.14	26.17 ± 3.25	0.008
Male, *n* (%)	22 (68.8%)	25 (62.5%)	0.580
Diabetes mellitus, *n* (%)	13 (40.6%)	7 (17.5%)	0.029
Hypertension, *n* (%)	22 (68.8%)	14 (35.0%)	<0.001
Diabetes mellitus and hypertension, *n* (%)	9 (28.1%)	4 (10.0%)	0.04
Smoking, *n* (%)	15 (46.9%)	12 (30.0%)	0.142
Alcohol, *n* (%)	7 (21.9%)	9 (22.5%)	0.949
Pulse (mean ± SD, /min)	79.59 ± 8.51	75.98 ± 11.22	0.136
SBP (mean ± SD, mmHg)	139.75 ± 18.49	133.45 ± 12.84	>0.093
DBP (mean ± SD, mmHg)	88.69 ± 9.71	88.48 ± 9.00	0.924
RBS (mean ± SD, mg/dl)	160.09 ± 64.01	151.53 ± 61.64	0.56
Creatinine (mean ± SD, mg/dl)	1.25 ± 0.21	1.06 ± 0.22	<0.001
eGFR (mean ± SD, ml/min)	69.93 ± 16.04	80.23 ± 21.78	0.029
LDL (mean ± SD, mg/dl)	138.70 ± 29.16	123.37 ± 31.70	0.03
HDL (mean ± SD, mg/dl)	34.34 ± 8.75	38.20 ± 10.86	0.09
Triglycerides (mean ± SD, mg/dl)	134.31 ± 54.12	157.98 ± 46.69	0.06

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; RBS: random blood sugar; eGFR: estimated glomerular filtration rate; LDL: low-density lipoprotein; HDL: high-density lipoprotein; SD: standard deviation

Whereas, 81.3% ($n = 26$) cases at admission (with ISR) had non-ST-elevation (NSTE)–ACS (non-STEMI or UA) as the most common diagnosis. Mean duration of symptom-free period from previous PCI to presentation with ISR was 152.3 ± 80.1 weeks.

Higher prevalence of the single vessel disease (SVD) in cases (75% vs. 52.5%, $p = 0.05$) and double vessel disease (DVD) in controls (25% vs. 47.5%, $p = 0.02$) was observed. Left anterior descending artery (52.5% vs. 50.8%, $p = 0.8$) was the most common diseased vessel followed by right coronary artery (RCA; 25% vs. 27.1%, $p = 0.8$) and left circumflex artery (17.5% vs. 10.2%, $p = 0.3$) with proximal site (52.5% vs. 50.8%, $p = 0.8$) as the most common lesion site in both cases and controls.

Out of 32 ISR patients (cases), 19 (59.5%) had incidence of new lesions (25 lesions), i.e., location different from previous coronary stent and most common location was RCA (36%, $n = 9$).

All the patients in study population had bare-metal stent deployment. The most common stents deployed in case and control groups were Coronnium® (16.2%, $n = 6$ vs. 45.8%, $n = 27$), Flexinnium® (13.5%, $n = 5$ vs. 42.8%, $n = 25$), both cobalt–chromium alloy stents (Sahajanand Medical Technologies Ltd., India), Clearflex® (16.2%, $n = 6$ vs. 11.9%, $n = 7$), stainless steel alloy stent (ClearStream Technologies Ltd., Ireland), respectively. The stainless steel alloy stents use was significantly higher in cases, whereas cobalt–chromium alloy stents use was significantly higher in controls.

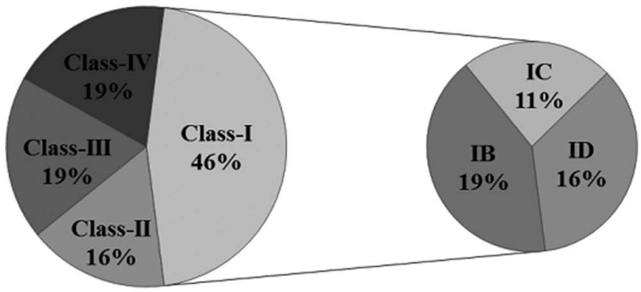

Fig. 1. | Chart showing type of in-stent restenosis

The ISR was classified, according to Mehran et al.'s classification, into four classes. The most common type was class-I 45.9% ($n = 17$), followed by class-III and class-IV each 18.9% ($n = 7$) and least common was class-II 16.2% ($n = 6$) (*Fig. 1*).

All the study patients were receiving beta blockers, of which metaprolol (31.3% vs. 77.5%) intake was higher in controls. Nitrate intake was higher in cases than controls (93.8% vs. 5%). A total of 78.1% patients of case group were taking clopidogrel, whereas all the control group patients were taking it. All the study patients were also receiving either angiotensin converting enzyme inhibitors or angiotensin receptor

Table III Diagnostic and procedure variables of associated with in-stent restenosis

Variables	Cases	Controls	*P* value
Diagnosis, *n* (%)			
STEMI	5 (15.6%)	21 (65.6%)	<0.001
NSTE–ACS	26 (81.3%)	10 (31.3%)	<0.001
CSA	1 (3.1%)	1 (3.1%)	<0.001
Single vessel disease, *n* (%)	24 (75%)	21 (52.5%)	0.05
Double vessel disease, *n* (%)	8 (25%)	19 (47.5%)	0.02
Mean stent length (mean ± SD, mm)	20.1 ± 8.3	19.1 ± 5.0	0.55
Mean stent diameter (mean ± SD, mm)	3.1 ± 0.3	2.9 ± 0.2	0.01
Inflation pressure (mean ± SD, atm)	12.1 ± 1.4	12.0 ± 1.6	0.60
Inflation time (mean ± SD, s)	12.8 ± 1.9	13.1 ± 1.6	0.30
Predilation, *n* (%)	5 (15.6%)	21 (52.5%)	0.001
CIMT			
Average >0.8 mm	24 (75%)	02 (5%)	–
Average <0.8 mm	08 (25%)	38 (95%)	–
Mean ± SD (mm)	0.96 ± 0.23	0.66 ± 0.09	<0.001

STEMI: ST-elevation myocardial infarction; NSTE–ACS: non-ST elevation acute coronary syndrome; CSA: chronic stable angina; CIMT: carotid artery intima-media thickness

blockers (ARB), statins (either atorvastatin or rosuvastatin) and aspirin, whereas 9.4% cases and 2.5% controls were receiving amlodipine but had no association with ISR. The non-compliance with prescribed medication was significantly associated with ISR (OR = 26.7, CI = 3.24–219.35, $p < 0.001$).

The mean left ventricular ejection fraction was lower in cases (52.2% ± 12.3%) than the controls (55.6% ± 10.1%) ($p = 0.19$).

The various procedural variables, such as stent length, stent diameter, inflation pressure, inflation time, and predilation, were obtained in both cases and controls *(Table III)*.

The mean values of right (0.95 ± 0.26 mm vs. 0.65 ± 0.11 mm), left (0.97 ± 0.28 mm vs. 0.67 ± 0.11 mm), and average (0.96 ± 0.23 mm vs. 0.66 ± 0.09 mm) CIMT were increased in the cases than the controls *(Table III)*.

On multivariate analysis, hypertension, use of stainless steel stent, mean stent diameter, use of nitrates, poor drug compliance, and CIMT (>0.8 mm) were found to be positively associated with risk of ISR. On the other hand, presence of STEMI, use of cobalt–chromium stent, use of metaprolol and clopidogrel, and eGFR (50 ml/min) were found to have negative predictive value for ISR *(Table IV)*.

Table IV Multivariate predictors of in-stent restenosis

Variables	Odds ratio	*P* value
Age >40 years	17.22	0.121
STEMI	0.03	0.004
Cobalt–chromium	0.064	<0.001
Stainless steel	3.14	0.01
Diabetes	1.83	0.564
Hypertension	10.79	0.026
Metaprolol	0.17	<0.001
Nitrate	285	<0.001
Clopidogrel	0.09	0.002
Drug compliance	26.7	<0.001
eGFR >50 ml/min	0.005	0.029
Mean stent diameter (mm)	14.87	0.01
Predilation	0.167	<0.001
Average CIMT (>0.8 mm)	57	<0.001

STEMI: ST-elevation myocardial infarction; eGFR: estimated glomerular filtration rate; CIMT: carotid artery intima-media thickness

Discussion

Several published studies have evaluated the predictors of ISR post-PCI [8, 12, 24–28], but only limited data are available, which show association of CIMT and ISR [18–20]. Hence, in this study, the correlation of CIMT and ISR has been studied.

In this study, age was found to be higher in cases, which was statistically significant ($p = 0.028$) *(Table I)*. The majority of ISR patients were in 4th–6th decade. Similar distribution of age was observed by Mohan et al.

[24] and Kwon et al. [19], whereas on the other hand, Macdonald et al. [26] showed that age and sex had no association with restenosis.

In this study, the most common presentation in ISR patients was NSTE–ACS (UA or NSTEMI, 81.3%) followed by STEMI (15.6%) and the CSA was the least. Mohan et al. [24] also found that patients who were presented with UA had a higher rate of restenosis on follow-up similar to this study.

The ISR patients had higher prevalence of SVD and controls had higher DVD, but in the study of Jones et al. [18], higher number vessels were diseased in ISR group than controls. From the present finding and from similar findings of Mohan et al. [24], Bauters et al. [25], and Hermans et al. [29], it can be stated that restenosis has found to be an ubiquitous phenomenon without any predilection for a particular site in the coronary tree as no significant difference in vessel and site of lesion in coronary tree was observed.

Many studies have demonstrated that the stent design rather than material had effect on restenosis rates [25, 30]. But in this study, the cobalt–chromium stent had negative association and stainless steel stent had a positive association with restenosis ($p < 0.001$), which was similar to the finding of Bauters et al. [25] in which Palmaz Schatz® stent (stainless steel) usage was independent predictor of restenosis.

The prevalence of class-I lesion (45.9%) was more in ISR patients than other types. These findings were consistent with original study of Mehran et al. [21] in which they also found about 42% class-I lesion. In this study, diabetes and hypertension were strongly associated with ISR ($p = 0.029$ and <0.001) and both were demonstrated as the important predictors of restenosis similar to the previous findings [24, 25, 30, 31]. Smoking and alcohol consumption were not associated with restenosis and this finding was equivalent with previous studies [7, 25]. In a previous study, Mohan et al. [24] stated that smokers were found to be having fewer incidences of restenosis than non-smokers as smoking slows down the proliferation of vascular smooth muscle cells, but this needs further evaluation and evidence.

Higher mean BMI was found in ISR patients and it was statistically associated with restenosis. But it was not an independent predictor after multivariate regression analysis and this was consistent with the previous findings [18, 24, 28]. Blood pressure (both systolic and diastolic), pulse rate, and blood glucose level were not associated with restenosis, which was homogeneous with the findings of Bourassa et al. [27]. Lower mean eGFR was associated with restenosis in study patients, and this was equivalent to the study of Matsuo et al. [32] as chronic kidney disease creates an inflammatory milieu, which increases the incidence of restenosis and repeat revascularizations.

Although hypercholesterolemia has been an established risk factor for atherosclerosis [27, 33, 34], lipid profile of patients in this study showed that no other component except higher mean LDL cholesterol level has association with restenosis.

When the effects of individual drugs, such as antiplatelet, statins, ACE inhibitor, ARB, calcium channel blockers, and beta-blockers were analyzed on restenosis, except for nitrates, clopidogrel, and metaprolol, none of them provided a statistically significant clinical benefit. Similar findings of higher usage of nitrates in ISR patients were seen in previous studies, which may be due to the ischemia [18]. Metaprolol and clopidogrel intake was negatively associated with restenosis. But there was no link between restenosis and anti-platelet therapy in other studies [24, 28, 35]. The poor drug compliance was statistically associated with restenosis in the study patients, which was reported in previous studies too [24].

The relationship between procedural variable like mean stent length, diameter, inflation pressure, inflation time, and predilation of lesion with restenosis was studied and higher mean stent diameter was found to be associated with ISR in this study. This finding in contrast to previous studies, where the lower diameter of stents was associated with restenosis [9, 10, 25, 26, 28, 36], whereas study by Mohan et al. [24] had shown no relation of restenosis with stent diameter, there are conflicting data on this variable, but it is difficult to draw any conclusion from the small sample of study patients. In this study, restenosis was higher in directly stented segments compared with predilation, which was also contrary to the study stating that no difference in restenosis rates was found in patients with or without predilation [28].

In this study, the mean value of both left and right carotid arteries and average CIMT were increased in ISR patients. When analyzed as a categorical variable with average CIMT >0.8 mm, it was strongly associated with restenosis and this was also an independent predictor in multivariate logistic regression. We established the relationship of ISR and CIMT (>0.8 mm) and the results (OR = 57, CI: 11.15–291.4, $p < 0.001$) found were parallel to the various previous studies. Jones et al. [18] found that CIMT (>1 mm) was independently associated with ISR (OR = 2.7, CI: 1.5–4.7, $p < 0.0006$). In their study, the mean CIMT value of ISR-free group was 0.9 ± 0.4 mm and of ISR group was 1.1 ± 0.9 mm. Kwon et al. [19] had distributed patients with ISR into two groups: thin CIMT (<0.84 mm) and thick CIMT (>0.84 mm) and estimated clinical events at 12 months post-PCI. They observed that major adverse cardiovascular events were not different between the thick CIMT and thin CIMT groups, except for restenosis (OR = 1.754, CI: 1.129–2.726, $p = 0.012$). However, on contrary to the findings of Kwon et al. [19], Lacroix et al. [37] performed univariate analysis and demonstrated that CIMT >0.7 mm was allied with an increased risk of cardiac events after coronary angioplasty compared with those with CIMT <0.7 mm

($p = 0.03$). Thus, they indicated that CIMT may be linked to post-interventional events. Therefore, studies with inclusion of larger number of patients need to be conducted to validate the meticulous association and effect of CIMT on ISR. Further research is now needed to examine role of treatments targeting in reduction of CIMT in reducing long-term restenosis rates, morbidity, and mortality in patients with post-PCI.

Limitations of the study

Main limitation of the study was small number of patients. With this study, prognostic information could not be provided due to the limited sample size and lack of follow-up data after discharge. As our hospital is a multispecialty tertiary care center receiving more severe and complicated cases, there may be referral bias due to which the study may not reflect the true prevalence. Another limitation is the observational nature of the study for measurement of ISR, which considered asymptomatic status as surrogate marker of absence of ISR. Use of invasive coronary angiography would have even detected asymptomatic ISR.

Conclusions

It was found that CIMT is an independent predictor and is strongly associated with ISR. Hence, the non-invasive nature and ease of estimation are positive correlates to recommend measurement of CIMT in routine clinical practice in both pre- and post-PCI patients.

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