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CHA_2DS_2-Vasc score and CHA_2DS_2-Vasc-HS score are poor predictors of in-stent restenosis among patients with coronary drug-eluting stents

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Abstract

Objective: To evaluate the ability of two scoring systems (CHA_2DS_2-VASc score and CHA_2DS_2-VASc+hyperlipidaemia+smoking [CHA_2DS_2-VASc-HS score]) to predict in-stent restenosis (ISR) among patients undergoing drug-eluting stent (DES) implantation.

Methods: This retrospective study enrolled patients who underwent coronary angiography to assess coronary artery disease severity secondary to a diagnosis of stable angina or acute coronary syndrome that subsequently underwent DES implantations. Demographic, clinical, angiographic and biochemical parameters were compared between those patients that experienced ISR and those that did not during the study follow-up period. Univariate and multivariate logistic regression analyses were used to evaluate associations between the baseline parameters, the two scoring systems and ISR risk.

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Results: A total of 358 patients (non-ISR group $n = 316$; ISR group $n = 42$) participated in the study. Compared with the non-ISR group, more patients in the ISR group had diabetes mellitus and received stents with smaller diameters but longer lengths. There were no significant differences with regard the predictive ability for ISR of either the CHA_2DS_2-Vasc or the CHA_2DS_2-Vasc-HS scores. Multivariate logistic regression analyses demonstrated that stent diameter, follow-up duration and glycosylated haemoglobin were independent risk factors for ISR.
Conclusions: The CHA_2DS_2-Vasc and CHA_2DS_2-Vasc-HS scores did not predict ISR in patients after coronary DES placement.

Keywords
CHA_2DS_2-Vasc score, CHA_2DS_2-Vasc-HS score, in-stent restenosis, drug-eluting stent

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Introduction

Percutaneous coronary intervention (PCI) is the most frequently utilized approach to treating individuals suffering from coronary atherosclerotic disease.[1] Several large trials proved that drug-eluting stents (DES) could significantly reduce in-stent restenosis (ISR) rates.[2] In spite of novel drug and revascularization approaches, ISR following PCI continues to represent a substantial hurdle for interventional cardiologists.[1,2]

The definition of ISR is divided into angiographically-defined ISR and clinically-defined ISR.[3] Angiographically-defined ISR is present when more than 50% of the luminal diameter is reduced after arterial PCI as determined on follow-up angiography.[2,3] Clinically-defined ISR is present when greater than 50% of the diameter exhibits restenosis in addition to the presence of one or more of the following: signs of objective ischaemia (changes detectable by electrocardiogram); history of recurrent angina; coronary flow reserve valuation according to a fractional flow reserve (FFR) value < 0.8; minimum cross-sectional vessel area < 4 mm^2 (< 6 mm^2 for left main) by intravascular ultrasonography (IVUS); restenosis ($> 70\%$ stenosis of the lumen diameter), even in the absence of apparent symptoms.[3]

With regard to the first generation of DES, the j-Cypher Registry includes 12 812 patients who received sirolimus-eluting stents for their treatments.[4] Among these patients, the 1-year target lesion revascularization (TLR) rate was 7.3%, reaching 15.9% at 5 years, with a per-year occurrence rate of 2.2%.[4] Relative to first-generation DES, the second-generation stents are linked to reduced instances of death and myocardial infarction (MI).[5] Three-year TLR rates were similar to the rates for target vessel revascularization at 1 and 5 years.[5] There is also a late catchup in neo-intimal hyperplasia in the first and second-generation DESs.[1] Another confounding factor that should be considered is that restenosis rates have grown remarkably in recent years due to their widespread use in patients with complex coronary lesions (high syntax scores).[1,2]

The $CHADS_2$, and more recently CHA_2DS_2-VASc, scores are used as the validating scores among those with non-valvular atrial fibrillation (AF) to predict embolic stroke risk.[6] These scores help

guide antithrombotic therapy in patients with AF patients.[6] Investigators have reported that both $CHADS_2$ and CHA_2DS_2-VASc scores were related to mortality in individuals that had both stable coronary angina and acute coronary syndrome (ACS).[7,8] A previous study used $CHADS_2$ and CHA_2DS_2-VASc scores to predict coronary artery disease (CAD) severity.[7] The authors concluded that $CHADS_2$ and CHA_2DS_2-VASc scores positively correlated with the number of diseased vessels present ($r = 0.406$, $r = 0.308$, respectively), as well as with the Gensini score ($r = 0.383$, $r = 0.300$, respectively).[7] The CHA_2DS_2-VASc+hyperlipidaemia+smoking (CHA_2DS_2-VASc-HS) score was determined to be the optimal method for predicting CAD severity.[7] The CHA_2DS_2-VASc-HS cut-off score for the prediction of severe CAD was greater than 2, with a sensitivity of 85.2% and a specificity of 57.5%.[7]

In another non-AF population, CHA_2DS_2-VASc scores were also reported to be predictive of adverse cardiovascular events and mortality in patients with Takotsubo syndrome,[9] and for the risks of stroke and death in patients with sick sinus syndrome after pacemaker implantation.[10] In recent years, considerable effort has been made to find a useful scoring system to predict ISR. For example, two previous studies indicated that CHA_2DS_2-VASc scores were significantly greater among those in the ISR group.[11,12] The authors concluded that CHA_2DS_2-VASc scores were optimal for forecasting ISR in patients implanted with bare-metal stents (BMS).[11,12] However, whether clinicians can use the CHA_2DS_2-VASc scores to anticipate ISR in patients after DES implantation has not yet been explored. Thus, the aim of this current study was to assess whether CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores were predictive of ISR in patients undergoing revascularization with DES secondary to CAD or ACS.

Patients and methods

Study population and design

This retrospective study enrolled consecutive patients who underwent coronary angiography to assess CAD severity secondary to a diagnosis of stable angina or ACS. These individuals subsequently underwent DES implantations at the Department of Cardiology, The Second Affiliated Hospital of Jiaxing University, Jiaxing, Zhejiang Province, China between January 2012 and September 2017. The patients that went through repeat angiography to evaluate ISR after stent implantation were retrospectively incorporated into this study. Exclusion criteria comprised infectious diseases, hepatic or haemolytic disorders, severe kidney diseases, rheumatological diseases and thyroid hormone abnormalities.

As this study was an anonymous retrospective analysis, verbal informed consent was provided by participating patients. The study received approval from the Ethics Committee of The Second Affiliated Hospital of Jiaxing University (no. 20181102H02).

Study protocol

Baseline parameters were defined and recorded as follows: age, sex, presence of risk factors that correlate with CAD (diabetes mellitus, hypertension, dyslipidaemia, family history and smoking), fasting blood glucose, thyroid function, blood electrolytes, lipid profile values and left ventricular ejection fraction (LVEF) before PCI. These findings were recorded for all patients included in the research, along with stent size and balloon pressure after PCI.

Two independent blinded cardiologists (S.G.Z. and J.J.X.) interpreted the coronary

angiogram results using a digital subtraction angiography system (Allura Xper FD-20 X-ray system; Philips Healthcare, Best, the Netherlands). The patients' ISR was judged as follows: angiographic ISR was present if there was $\geq 50\%$ narrowing of the stented or peri-stent segment (5 mm proximal and distal to the stent edge in subsequent coronary angiography) luminal diameter. If $< 50\%$ stenosis was evident, then non-ISR status was recorded.

Hypertension was defined by a history of systolic blood pressure (SBP) > 140 mmHg and/or diastolic blood pressure (DBP) > 90 mmHg. Diabetes mellitus was defined by a fasting blood glucose of at least 126 mg/dl and/or a documented use of insulin or other antidiabetic agents. Chronic heart failure was diagnosed based on $< 40\%$ LVEF on transthoracic echocardiography or congestive heart failure. Vascular disease was defined by a history of peripheral arterial disease, MI or complex aortic plaques.[13]

Statistical analyses

A statistical power analysis was performed for sample size estimation based on data from two previously published studies that contained 358 and 1350 patients, respectively.[11,12] The findings of the larger study were selected to conduct the power analysis.[12] The mean $\pm$ SD CHA_2DS_2-VASc scores in the ISR (+) group and the ISR (–) group were 3.7 ± 1.8 and 2.1 ± 1.4, respectively.[12] With an alpha $= 0.05$ and power $= 0.80$, the projected sample size needed with this effect size was approximately $n = 17$ between the two groups. The percentages of ISR in DES was reported to be between 5% and 15% according to previous research.[1,2] Thus, a proposed sample size of 358 was considered to be more than adequate for the main objective of this study and should also allow for unexpected patient loss. It should also facilitate possible subgroup analyses.

All statistical analyses were performed using the SPSS® statistical package, version 22.0 (IBM Corp., Armonk, NY, USA). Distributions were analysed via the Kolmogorov–Smirnov test. Continuous variables are presented as mean $\pm$ SD when conforming to a normal distribution; otherwise, they are presented as median (interquartile range). Unpaired Student's *t*-test, Mann–Whitney *U*-test or Wilcoxon rank sum test were used for these continuous variables. Categorical variables are presented as frequencies (%) and were tested using χ^2-test. Univariate and multivariate logistic regression analyses were used to evaluate associations between the baseline clinical characteristics and risk of ISR. Based on receiver operating characteristic (ROC) curves, the optimal cut-off values for the CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores that could predict ISR risk were determined. The statistical tests were two sided and a P-value < 0.05 was considered statistically significant.

Results

This retrospective study enrolled 358 patients (mean $\pm$ SD age, 64.28 ± 9.95 years; 253 [70.67%] males) who underwent repeat coronary angiography. Three types of DES were used in this study: (i) Endeavor Resolute® zotarolimus-eluting coronary stent (Medtronic, Minneapolis, MN, USA); (ii) Partner sirolimus-eluting coronary stent (rapamycin) (Lepu Medical Technology, Beijing, China); (iii) Promus ELITE™ everolimus-eluting platinum chromium coronary stent system (Boston Scientific, Marlborough, MA, USA). These were compared with regard to their risk of ISR during follow-up. A total of 172 patients were treated with an Endeavor Resolute® stent and of these, 23 (13.37%) experienced ISR; 164 patients were treated with a Partner sirolimus-eluting coronary stent (rapamycin) and of

these, 18 (10.98%) experienced ISR; and 22 patients were treated with a Promus ELITE™ everolimus-eluting platinum chromium coronary stent system and of these, one patient (4.55%) experienced ISR. Based on a χ^2-test, there was no significant difference between the three stents with regard to the rate of ISR.

The 358 patients were divided into a non-ISR group ($n = 316$) and an ISR group ($n = 42$) based on angiography characteristics. As presented in Table 1, age, sex, SBP, DBP, smoking history, dyslipidaemia history or the specific location of the coronary artery stent did not differ significantly between the ISR and non-ISR groups. Compared with the non-ISR group, more patients in the ISR group had diabetes mellitus (40.48% [17 of 42 patients] versus 25.00% [79 of 316 patients]; $P = 0.033$).

Table 1. Baseline clinical and angiographic characteristics of patients ($n = 358$) who underwent coronary angiography to assess coronary artery disease severity secondary to a diagnosis of stable angina or acute coronary syndrome stratified according to the occurrence of in-stent restenosis (ISR).

Characteristic	Non-ISR group $n = 316$	ISR group $n = 42$	Statistical significance[a]
Age, years	64.16 ± 9.96	65.21 ± 9.89	NS
Sex, males	224 (70.89%)	29 (69.05%)	NS
Hypertension	239 (75.63%)	24 (57.14%)	$P = 0.015$
SBP, mmHg	137.17 ± 22.69	136.60 ± 22.00	NS
DBP, mmHg	79.34 ± 13.96	77.19 ± 10.50	NS
Diabetes mellitus	79 (25.00%)	17 (40.48%)	$P = 0.033$
Smoking history	160 (50.63%)	42 (100.00%)	NS
Smoking in men	157 (70.09%)	21 (72.41%)	NS
Dyslipidaemia history	93 (29.43%)	14 (33.33%)	NS
Coronary artery stent location			
LAD	179 (56.65%)	24 (57.14%)	NS
RCA	87 (27.53%)	16 (38.10%)	NS
LCX	41 (12.97%)	2 (4.76%)	NS
LM	9 (2.85%)	0 (0.00%)	NS
LVEF, %	61.55 ± 6.71	62.21 ± 6.56	NS
LA, mm	34.71 ± 4.98	34.22 ± 4.64	NS
CHA_2DS_2-Vasc score	2.64 ± 1.48	2.79 ± 1.46	NS
CHA_2DS_2-Vasc-S score	3.14 ± 1.43	3.31 ± 1.46	NS
CHA_2DS_2-Vasc-H score	2.94 ± 1.53	3.12 ± 1.50	NS
CHA_2DS_2-Vasc-HS score	3.44 ± 1.48	3.64 ± 1.46	NS
Stent diameter, mm	3.00 (2.25–4.00)[b]	3.00 (1.50–4.00)	$P = 0.029$
Stent length, mm	24 (12–38)[b]	29 (14–38)	$P = 0.033$
Time between the two catheterizations, months	12 (2–48)	13 (3–77)	$P = 0.017$

Data presented as mean ± SD, median (interquartile range) or *n* of patients (%).

[a]Continuous variables were compared using unpaired Student's *t*-test, Mann–Whitney *U*-test or Wilcoxon rank sum test; and categorical variables were compared using χ^2-test.

[b]Five cases had no specific parameter.

SBP, systolic blood pressure; DBP, diastolic blood pressure; LAD, left anterior descending artery; RCA, right circumflex artery; LCX, left circumflex artery; LM, left main coronary artery; LVEF, left ventricular ejection fraction; LA, left atrium; CHA_2DS_2-Vasc-S, CHA_2DS_2-Vasc and smoking; CHA_2DS_2-Vasc-H, CHA_2DS_2-Vasc and hyperlipidaemia; CHA_2DS_2-Vasc-HS score; CHA_2DS_2-Vasc and smoking and hyperlipidaemia; NS, no significant between-group difference ($P \geq 0.05$).

The median stent diameters were significantly smaller in the ISR group compared with the non-ISR group (3.00 mm [1.50–4.00 mm] versus 3.00mm [2.25–4.00 mm], respectively; $P = 0.029$), but the median stent lengths were significantly longer (29 mm [14–38 mm] versus 24 mm [12–38 mm], respectively; $P = 0.033$) in the ISR group compared with the non-ISR group. The median time period between the two catheterizations in the ISR group was significantly greater than that in the non-ISR group (13 [3–77 months] versus 12 [2–48 months], respectively; $P = 0.017$). Both the CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores were comparable between the two groups.

The laboratory parameters for the study population are listed in Table 2 including: total cholesterol, triglycerides, high- and low-density lipoprotein cholesterol, creatinine, calcium, inorganic phosphorus, magnesium and estimated glomerular filtration rate. There were no significant differences in these values between the two groups. Triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone, free T3 and free T4 did not differ significantly between the two groups. The ISR group had significantly elevated median interim glycosylated haemoglobin ($HbA1_c$) levels compared with the non-ISR group (6.50 [4.80–10.50] versus 5.90 [4.90–13.40], respectively; $P = 0.006$).

As illustrated in Figure 1a, the incidence of ISR slowly increased as the CHA_2DS_2-VASc score increased. Figure 1b shows that the rates of ISR in the first year were the highest and increased gradually until the third year after stent implantation.

Table 2. Laboratory characteristics of patients ($n = 358$) who underwent coronary angiography to assess coronary artery disease severity secondary to a diagnosis of stable angina or acute coronary syndrome stratified according to the occurrence of in-stent restenosis (ISR).

Laboratory characteristics	Non-ISR group $n = 316$	ISR group $n = 42$
TC, mol/l	4.06 (1.72–12.91)	3.81 (2.54–6.40)
TG, mmol/l	1.35 (0.35–20.49)	1.41 (0.56–7.93)
HDL-C, mmol/l	1.02 (0.54–2.08)	1.06 (0.62–2.85)
LDL-C, mmol/l	2.42 (0.58–6.85)	2.10 (1.04–4.91)
Creatinine, μmol/l	79.02 (8.00–200.00)	74.41 (5.75–154)
Calcium, mmol/l	2.24 ± 0.14	2.23 ± 0.11
Calcium*Phosphorus, mg^2/dl^2	30.07 ± 7.21	29.88 ± 6.85
Inorganic phosphorus, mmol/l	1.08 ± 0.25	2.08 ± 0.23
Magnesium, mmol/l	0.86 ± 0.11	0.83 ± 0.11
eGFR	114.02 ± 20.92	114.85 ± 13.80
$HbA1_c$, %	5.90 (4.90–13.40)	6.50 (4.80–10.50)*
T3, ng/ml	0.89 ± 0.16	0.89 ± 0.16
T4, μg/ml	5.94 ± 1.17	5.87 ± 1.29
FT3, pg/ml	2.51 ± 0.44	2.41 ± 0.53
FT4, ng/ml	0.98 (0.63–7.42)	1.00 (0.63–4.89)
TSH, μU/ml	1.36 (0.03–8.03)	1.39 (0.42–3.59)

Data presented as mean ± SD or median (interquartile range).

*$P = 0.006$ compared with non-ISR group; Mann–Whitney *U*-test.

TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; $HbA1_c$, glycosylated haemoglobin; T3, triiodothyronine; T4, thyroxine; FT3, free T3; FT4, free T4; TSH, thyroid stimulating hormone.

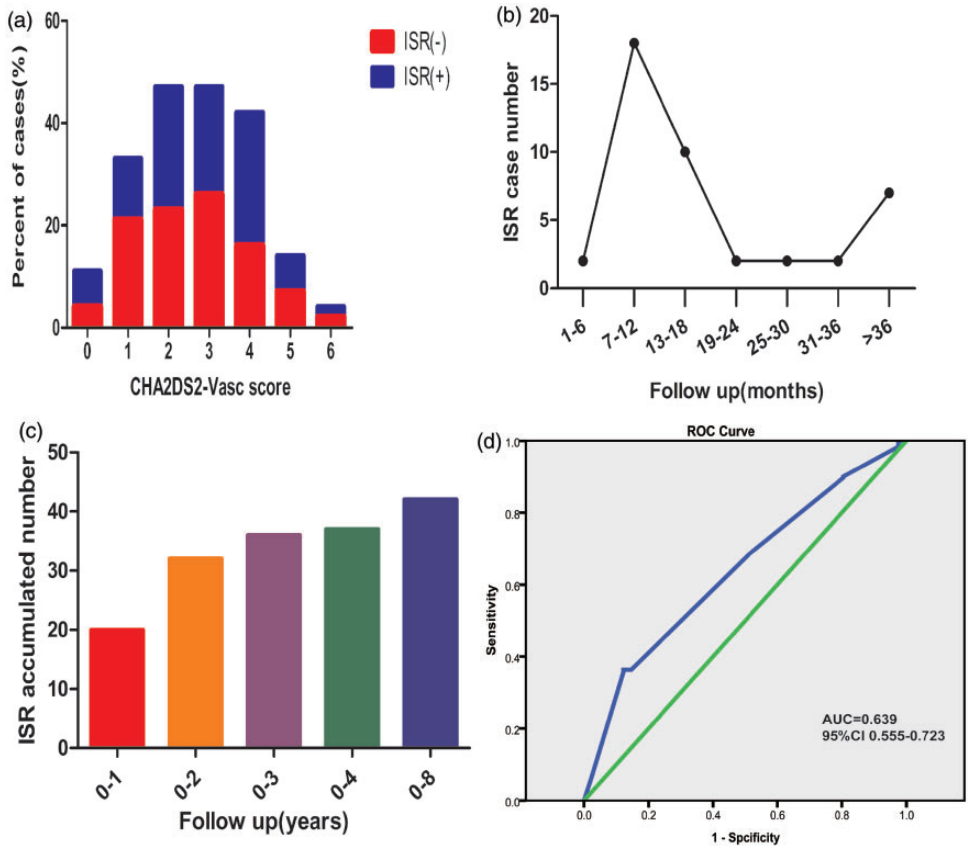

Figure 1. Analysis of predictors of in-stent restenosis (ISR) in patients ($n = 358$) who underwent coronary angiography to assess coronary artery disease severity secondary to a diagnosis of stable angina or acute coronary syndrome. (A) Comparison of the rates of ISR stratified according to the CHA_2DS_2-Vasc score. (B) The ISR case number according to the follow-up duration in months. (C) The cumulative ISR number from year 0 to year 8. (D) The receiver operating characteristic (ROC) curve analysis of stent diameter for predicting ISR.

The first-year ISR rate was 5.59% (20 of 358 patients), the second-year rate was 8.94% (32 of 358 patients), and the 5-year rate was 10.34% (37 of 358 patients). ISR occurred most frequently between 3 and 24 months after stent placement (32 of 42 patients). There was also a late catch-up phase at 4+ years after implantation (Figure 1c). According to the multivariate logistic regression analyses, stent diameter (odds ratio [OR] 0.175; 95% confidence interval [CI] 0.055, 0.562; $P = 0.003$), follow-up duration (OR 1.071; 95% CI 1.028, 1.116; $P = 0.001$) and $HbA1_c$ (OR 1.295; 95% CI 1.023, 1.638; $P = 0.031$) were all demonstrated to be independent ISR risk factors in patients who had undergone previous DES implantation (Table 3).

In the ROC curve analysis of stent diameter (area under the curve = 0.639, 95% CI 0.555, 0.723), a stent diameter ≤ 3 mm was determined to be an effective predictive cut-off point for ISR (Figure 1d). There were 35 patients in the ISR group and 198 patients in the non-ISR group with stent diameters ≤ 3 mm. There were seven patients in the

Table 3. Univariate and multivariate logistic regression analyses of the predictors of in-stent restenosis in patients ($n = 358$) who underwent coronary angiography to assess coronary artery disease severity secondary to a diagnosis of stable angina or acute coronary syndrome.

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	Statistical significance	OR (95% CI)	Statistical significance
Hypertension	0.430 (0.221, 0.833)	$P = 0.012$	0.485 (0.200, 1.175)	NS
Diabetes mellitus	2.040 (1.048, 3.973)	$P = 0.036$	1.646 (0.569, 4.742)	NS
Stent diameter	0.235 (0.096, 0.574)	$P = 0.001$	0.175 (0.055, 0.562)	$P = 0.003$
Stent length	1.064 (1.009, 1.122)	$P = 0.023$	1.054 (0.984, 1.208)	NS
Follow-up duration	1.067 (1.036, 1.099)	$P < 0.001$	1.071 (1.028, 1.116)	$P = 0.001$
HbA_{1c}	1.324 (1.07, 1.64)	$P = 0.010$	1.295 (1.023, 1.638)	$P = 0.031$

OR, odds ratio; CI, confidence interval; $HbA1_c$, glycosylated haemoglobin; NS, no significant association ($P \geq 0.05$).

ISR group and 113 patients in the non-ISR group with stent diameters > 3 mm (35/233 versus 7/120; $P = 0.012$).

Discussion

This current retrospective study demonstrated that the CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores were neither independently nor positively correlated with ISR incidence in patients who underwent revascularization with DES. This finding was in opposition to the findings of two earlier studies on ISR of BMS.[11,12] This current study also found that higher $HbA1_c$ values and smaller stent sizes were positively associated with a higher risk of ISR. In our opinion, patients with higher $HbA1_c$ values and/or smaller stent size undergoing stent implantation should be considered for repeat coronary angiography, rather than having only one test performed in the first year after stent placement.

In-stent restenosis, defined as a gradual re-narrowing of the inner stent wall after coronary artery stent placement, is a pathophysiological injury response due to negative vascular remodelling or neo-intimal vascular smooth muscle cell proliferation.[14] Endothelial denudation and disruption of atherosclerotic plaques are potential immediate effects of balloon angioplasty or coronary stenting.[2] This trauma could consequently induce any of the following events: inflammatory cell infiltration, platelet aggregation, growth factor release, proliferation of medial layer smooth muscle cells, proteoglycan deposition and/or extracellular matrix remodeling.[2]

In-stent restenosis is divided into angiographically-defined ISR and clinically-defined ISR.[1,3,14] Angiographically-defined ISR occurs when there is more than a 50% reduction in the luminal diameter identified on follow-up angiography after an arterial PCI.[3] Clinically-defined ISR is present when the restenosis diameter exceeds 50%, in addition to at least one of the following: objective signs of ischaemia (electrocardiogram changes); history of recurrent angina; IVUS showing a minimum cross-sectional vessel area $< 4\,mm^2$ ($< 6\,mm^2$ for left main); coronary flow reserve assessment with FFR < 0.8; restenosis (> 70% reduction in lumen diameter), even in the absence of clinical symptoms.[3]

Generally, ISR occurs 3–20 months after stent placement.[1] The mean length of time was 12 months, but BMS restenosis

occurred 6–9 months after implantation.[1,2] The incidence of ISR ranged from 16–40% with BMS and from 3–20% with DES;[1,2] however, the exact incidence of restenosis is difficult to determine.[14] This current study showed that ISR occurred 3–24 months following stent placement (32 of 42 patients) and reached a maximum after 7–12 months. There was also a late catch-up beyond 4 years after stent placement. The first-year ISR rate was 5.59%, the second-year rate was 8.94%, and the 5-year rate was 10.34%. These results were consistent with those of other studies.[14–16]

The Mehran system, which is used predictively in DES-ISR patients, is a morphological classification system used for BMS-ISR lesions: pattern I (focal) is an ISR (< 10 mm in length) lesion located in the inner segment of the stent; pattern II (diffuse) is ISR (> 10 mm in length) occurring within the stent; pattern III (proliferative) is ISR (> 10 mm in length) extending beyond the stent; and pattern IV is total vessel re-occlusion.[1,2]

Currently, the main ISR predictors can be divided into three categories: (i) patient and comorbidity-related characteristics; (ii) lesion characteristics; and (iii) procedural characteristics. Patient and comorbidity-related characteristics include the following: female sex, age, and the presence of diabetes, multi-vessel CAD, chronic kidney disease, metal allergy and local immunological and inflammatory hypersensitivity reactions.[1] Lesion characteristics related to ISR include the following: smaller reference artery diameter, lesion length, ostial lesion, initial plaque burden and residual plaque following revascularization with stent implantation.[14,16] Procedural characteristics include the following: longer stents, excessive vessel straightening by the stent, stent under-expansion, strut fracture, incomplete lesion coverage and overlapping stents.[1,16] The CHA_2DS_2-VASc score is a stroke risk assessment tool that was derived from and validated in patients with AF.[7,8] This score has been proved to be more sensitive than the $CHADS_2$ score.[17] Several recent studies have shown that the CHA_2DS_2-VASc score can predict undesirable events in those with stable CAD,[18] ACS,[17,19,20] sick sinus syndrome,[21] heart failure,[22] and patients with Takotsubo syndrome,[9] in whom the stent has extended beyond its initial use. A previous study concluded that $CHADS_2$ scores were linked to long-term mortality (hazard ratio [HR] 1.38) and stroke (HR 1.46) in 2335 patients with ACS.[23] Another retrospective analysis of patients after acute MI showed that the CHA_2DS_2-VASc score could also predict long-term cardiac events.[24] Interestingly, the authors found that the CHA_2DS_2-VASc score was more prognostic among patients after ST-elevation MI (STEMI) than among those after non-ST-elevation MI (NSTEMI).[24] Another study concluded that the CHA_2DS_2-VASc score was beneficial in predicting long-term mortality and stroke in patients with diabetes mellitus after STEMI, but could not predict the long-term risk of MI.[20] Recent studies showed that the CHA_2DS_2-VASc score may be used to predict acute stent thrombosis in patients with an STEMI[25] and prosthetic valve thrombosis in patients with a mechanical prosthetic valve.[26]

Based on the CHA_2DS_2-VASc score system, there have been some more recently developed novel scoring systems. For example, the CHA_2DS_2-VASc-CF, which incorporates family history and smoking habits; and the CHA_2DS_2-VASc-HS score, which incorporates hyperlipidaemia and smoking.[13,19] When compared with the CHA_2DS_2-VASc score, the CHA_2DS_2-VASc-CF score was better at predicting long-term cardiovascular death in patients who have had an acute MI.[13] Likewise, the CHA_2DS_2-VASc-HS score was proven to positively correlate with the complexity and severity of CAD.[12,19]

The CHA_2DS_2-VASc score represents the potential risk factors for ISR as discussed above. Two previous studies reported elevations in the CHA_2DS_2-VASc scores in patients in the ISR groups compared with the non-ISR groups.[11,12] Their multivariate logistic regression analyses showed that the CHA_2DS_2-VASc score was an independent risk factor for ISR in patients after BMS implantation, and they concluded that the CHA_2DS_2-VASc score was a simple effective means of predicting ISR in those patients.[11,12]

Several prior studies have demonstrated that DES can reduce the incidence of ISR after BMS implantation.[1,2] To the best of our knowledge, the present study is the first to have focused on the predictive role of CHA_2DS_2-VASc scores in patients with ACS or angina after DES implantation. This current study demonstrated that the CHA_2DS_2-VASc score and the CHA2DS2-Vasc-HS score were not associated with an increased risk of ISR in individuals undergoing revascularization with DES, which is in contrast with the findings of two earlier BMS studies.[11,12]

This current study had a number of limitations, including the lack of randomization, the retrospective observational design and the inclusion of patients from a single centre after DES implantation. The current study included 358 patients, all of whose CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores were greater in the ISR group than the non-ISR group, but the differences did not reach statistical significance. Due to the retrospective study design, it was only possible to identify associations between clinical risk factors and restenosis, but not assess causal relationships. The definition of ISR used in this current study was not quantitative but was based on the independent assessment of two interventional cardiologists. As a result, diminished intravascular lumens may have been managed in routine clinical practice. Additionally, the study did not use intravascular ultrasound or optical computed tomography to assess the degree of in-stent re-narrowing. Despite these limitations, the present study adds to our understanding of the predictive role of the CHA_2DS_2-VASc score in patients with ISR after DES implantation. To the best of our knowledge, this is the first study focusing on this clinical question.

In conclusion, CHA_2DS_2-VASc-Vasc and CHA_2DS_2-VASc-HS scores do not appear to be good predictive tools for ISR in patients with ACS or angina who underwent DES implantation. Higher $HbA1_c$ values and smaller stent size were positively associated with a greater risk of ISR. In our opinion, patients with higher $HbA1_c$ values and/or smaller stent sizes who undergo stent implantations should be considered for repeated coronary angiography examinations, as opposed to only one examination in the first year after stent placement.

Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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References

1. Lee MS and Banka G. In-stent restenosis. *Interv Cardiol Clin* 2016; 5: 211–220.
2. Dangas GD, Claessen BE, Caixeta A, et al. In-stent restenosis in the drug-eluting stent era. *J Am Coll Cardiol* 2010; 56: 1897–1907.

3. Mehran R, Dangas G, Abizaid AS, et al. Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation* 1999; 100: 1872–1878.
4. Kimura T, Morimoto T, Nakagawa Y, et al. Very late stent thrombosis and late target lesion revascularization after sirolimus-eluting stent implantation: Five-year outcome of the j-Cypher Registry. *Circulation* 2012; 125: 584–591.
5. Leon MB, Nikolsky E, Cutlip DE, et al. Improved late clinical safety with zotarolimus-eluting stents compared with paclitaxel-eluting stents in patients with de novo coronary lesions: 3-year follow-up from the ENDEAVOR IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) trial. *JACC Cardiovasc Interv* 2010; 3: 1043–1050.
6. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 2012; 33: 2719–2747.
7. Cetin M, Cakici M, Zencir C, et al. Prediction of coronary artery disease severity using $CHADS_2$ and CHA_2DS_2-VASc scores and a newly defined CHA_2DS_2-HS score. *Am J Cardiol* 2014; 113: 950–956.
8. Uysal OK, Turkoglu C, Duran M, et al. Predictive value of newly defined CHA_2DS_2-VASc-HSF score for severity of coronary artery disease in ST segment elevation myocardial infarction. *Kardiol Pol* 2016; 74: 954–960.
9. Parodi G, Scudiero F, Citro R, et al. Risk stratification using the CHA_2DS_2-VASc score in Takotsubo syndrome: Data from the Takotsubo Italian Network. *J Am Heart Assoc* 2017; 6: e006065.
10. Mo BF, Lu QF, Lu SB, et al. Value of combining left atrial diameter and amino-terminal pro-brain natriuretic peptide to the CHA_2DS_2-VASc score for predicting stroke and death in patients with sick sinus syndrome after pacemaker implantation. *Chin Med J (Engl)* 2017; 130: 1902–1908.
11. Kurtul A. Usefulness of the CHA_2DS_2-VASc score in predicting in-stent restenosis among patients undergoing revascularization with bare-metal stents. *Clin Appl Thromb Hemost* 2018; 24: 589–595.
12. Yilmaz S, Akboga MK, Aras D, et al. Evaluation of the predictive value of CHA_2DS_2-VASc score for in-stent restenosis. *Angiology* 2018; 69: 38–42.
13. Kundi H, Kiziltunc E, Korkmaz A, et al. A novel risk scoring system to predict cardiovascular death in patients with acute myocardial infarction: CHA_2DS_2-VASc-CF score. *Clin Appl Thromb Hemost* 2018; 24: 273–278.
14. Elmore JB, Mehanna E, Parikh SA, et al. Restenosis of the coronary arteries: past, present, future directions. *Interv Cardiol Clin* 2016; 5: 281–293.
15. Alfonso F, Byrne RA, Rivero F, et al. Current treatment of in-stent restenosis. *J Am Coll Cardiol* 2014; 63: 2659–2673.
16. Alraies MC, Darmoch F, Tummala R, et al. Diagnosis and management challenges of in-stent restenosis in coronary arteries. *World J Cardiol* 2017; 9: 640–651.
17. Pang H, Han B, Fu Q, et al. Predictive value of $CHADS_2$ and CHA_2DS_2-VASc scores for acute myocardial infarction in patients with atrial fibrillation. *Sci Rep* 2017; 7: 4730.
18. Huang FY, Huang BT, Pu XB, et al. $CHADS_2$, CHA_2DS_2-VASc and R_2CHADS_2 scores predict mortality in patients with coronary artery disease. *Intern Emerg Med* 2017; 12: 479–486.
19. Taşolar H, Çetin M, Balli M, et al. CHA_2DS_2-VASc-HS score in non-ST elevation acute coronary syndrome patients: assessment of coronary artery disease severity and complexity and comparison to other scoring systems in the prediction of in-hospital major adverse cardiovascular events. *Anatol J Cardiol* 2016; 16: 742–748.
20. Hudzik B, Szkodzinski J, Hawranek M, et al. CHA_2DS_2-VASc score is useful in predicting poor 12-month outcomes following myocardial infarction in diabetic patients without atrial fibrillation. *Acta Diabetol* 2016; 53: 807–815.
21. Svendsen JH, Nielsen JC, Darkner S, et al. $CHADS_2$ and CHA_2DS_2-VASc score to

assess risk of stroke and death in patients paced for sick sinus syndrome. *Heart* 2013; 99: 843–848.
22. Yoshihisa A, Watanabe S, Kanno Y, et al. The CHA_2DS_2-VASc score as a predictor of high mortality in hospitalized heart failure patients. *ESC Heart Fail* 2016; 3: 261–269.
23. Poci D, Hartford M, Karlsson T, et al. Role of the $CHADS_2$ score in acute coronary syndromes: Risk of subsequent death or stroke in patients with and without atrial fibrillation. *Chest* 2012; 141: 1431–1440.
24. Kim KH, Kim W, Hwang SH, et al. The CHA_2DS_2-VASc score can be used to stratify the prognosis of acute myocardial infarction patients irrespective of presence of atrial fibrillation. *J Cardiol* 2015; 65: 121–127.
25. Tanik V, Arugaslan E, Cinar T, et al. The Association of the CHA2DS2VASc score with acute stent thrombosis in patients with an ST elevation myocardial infarction who underwent a primary percutaneous coronary intervention. *Med Princ Pract* 2018. doi: 10.1159/000495526 [Epub ahead of print].
26. Çinar T, Hayiroğlu MI, Tanik VO, et al. The predictive value of the CHA2DS2-VASc score in patients with mechanical mitral valve thrombosis. *J Thromb Thrombolysis* 2018; 45: 571–577.