

# ความชุกและปัจจัยเสี่ยงของโรคเส้นเลือดหัวใจตีบในผู้ป่วยโรคลิ้นหัวใจรูมาติกและที่ไม่ใช่รูมาติกที่เข้ารับการตรวจฉีดสีสวนหัวใจก่อนผ่าตัด

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ศูนย์หัวใจสิริกิติ์ภาคตะวันออกเฉียงเหนือ ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

## Prevalence and Clinical Risk Factors of Coronary Artery Disease in Rheumatic and Non-Rheumatic Valvular Heart Disease Patients Undergoing Preoperative Coronary Angiography

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**หลักการและวัตถุประสงค์:** การตรวจสวนหัวใจก่อนผ่าตัดถือเป็นการตรวจที่สำคัญก่อนการผ่าตัดลิ้นหัวใจแต่ก็เป็นการตรวจที่ผู้ป่วยต้องเจ็บตัวและอาจเกิดภาวะแทรกซ้อนที่รุนแรงได้ การศึกษาหาความชุกและปัจจัยเสี่ยงของโรคเส้นเลือดหัวใจตีบในผู้ป่วยโรคลิ้นหัวใจรูมาติกและไม่ใช่รูมาติกอาจทำให้สามารถเลือกผู้ป่วยตรวจสวนหัวใจก่อนผ่าตัดได้เหมาะสมขึ้น และลดการตรวจสวนหัวใจที่ไม่จำเป็นลง

**วิธีการศึกษา:** ทำการศึกษาแบบตัดขวางย้อนหลังโดยการเก็บข้อมูลจากเวชระเบียน ในผู้ป่วยโรคลิ้นหัวใจทุกคน ที่ได้รับการตรวจสวนหัวใจก่อนผ่าตัดกับคณะผู้วิจัยที่ศูนย์หัวใจสิริกิติ์ระหว่างเดือนเมษายน พ.ศ. 2558 ถึงเมษายน พ.ศ. 2561

**ผลการศึกษา:** ผู้ป่วยทั้งหมด 238 รายได้เข้าร่วมการศึกษา โดยเป็นโรคหัวใจรูมาติก 110 ราย (ร้อยละ 46.2) และไม่ใช่รูมาติก 128 ราย (ร้อยละ 53.8) มีความชุกโรคเส้นเลือดหัวใจตีบร้อยละ 13.9 ของผู้ป่วยทั้งหมด (ร้อยละ 6.4 ในกลุ่มผู้ป่วยโรคหัวใจรูมาติก และ ร้อยละ 20.3 ในกลุ่มผู้ป่วยชนิดไม่ใช่รูมาติก  $p = 0.002$ ) การวิเคราะห์แบบตัวแปรเดียวพบว่า อายุเกิน 50 ปี เบาหวาน ความดันโลหิตสูง และไตเสื่อมระยะที่ 3 ขึ้นไป เป็นปัจจัยเสี่ยง แต่โรคหัวใจรูมาติกเป็นปัจจัยป้องกันในการพบเส้นเลือดหัวใจตีบ แต่เมื่อวิเคราะห์แบบหลายตัวแปรพบว่า มีเพียงอายุและความดันโลหิตสูงที่ยังคงเป็นปัจจัยเสี่ยง ในทางตรงข้ามเพศหญิงที่เป็นโรคหัวใจรูมาติกที่ไม่มีเบาหวานและความดันโลหิตสูงเป็นกลุ่มที่มีความเสี่ยงต่ำสุด

**สรุป:** ผู้ป่วยโรคหัวใจรูมาติกมีความชุกของโรคเส้นเลือดหัวใจตีบน้อยกว่าผู้ป่วยที่ไม่ใช่รูมาติก อย่างไรก็ตาม ปัจจัยเสี่ยงของโรคเส้นเลือดหัวใจตีบในผู้ป่วยทั้งสองกลุ่มยังคงเป็นปัจจัยเสี่ยงดั้งเดิมของโรคเส้นเลือดหัวใจตีบ ดังนั้น การตรวจเส้นเลือดหัวใจเพื่อเตรียมผ่าตัดโดยวิธีอื่นที่ไม่เจ็บตัว ควรจะเป็นอีกทางเลือก

**Background and Objective:** Preoperative coronary angiography (CAG) is an essential procedure before conducting a valvular operation. However, it is invasive and may cause serious complications. Identification of the prevalence of coronary artery disease (CAD) and its clinical risk factors in patients with rheumatic (RHD) compared to those with non-rheumatic heart disease (NRHD) should result in more appropriate patient selection and reduction of the over-utilization of CAG.

**Methods:** We conducted a retrospective cross-sectional study by reviewing the records of all consecutive patients with valvular heart disease who underwent preoperative CAG under our care at Queen Sirikit heart center from April 2015 - April 2018.

**Results:** A total of 238 patients were included in this study, 110 (46.2%) of whom suffered from RHD and 128 (53.8%) of whom had NRHD. The overall prevalence of significant CAD was 13.9% (20.3% in NRHD and 6.4% in RHD,  $p = 0.002$ ). Overall, age over 50 years, diabetes mellitus, hypertension, and chronic kidney disease stage 3 or higher were risk factors for CAD and RHD was a protective factor according to univariate analysis. However, only hypertension and age remained significant after multivariate analysis. In contrary, female patients with rheumatic etiology and had no diabetes mellitus and hypertension were the lowest-risk subgroups.

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หนึ่งให้ผู้ป่วยโรคหัวใจรูมาติกที่มีความเสี่ยงดั้งเดิมของโรคเส้นเลือดหัวใจตีบ

**คำสำคัญ:** การฉีดสีสวยหัวใจก่อนผ่าตัด, โรคหัวใจรูมาติก, โรคเส้นเลือดหัวใจตีบ

**Conclusion:** The prevalence of CAD was lower in patients with RHD compared to those with NRHD. However, the clinical risk factors that predicted CAD in both groups were conventional CAD risks. Thus, alternative non-invasive preoperative coronary studies should be an option in RHD patients with low traditional CAD risk factors.

**Keywords:** preoperative coronary angiography, rheumatic heart disease, coronary artery disease

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## Introduction

Rheumatic heart disease (RHD) is still an essential medical problem in developing countries including Thailand.<sup>1</sup> Patients usually present with severe valvular stenosis or regurgitation that requires treatment with open-heart surgery, similar to patients with non-rheumatic valvular heart disease (NRHD), which is more common in developed countries. The current valvular heart disease guidelines<sup>2, 3</sup> recommended preoperative coronary angiography (CAG) as the gold standard for evaluating coronary arteries before conducting a valvular operation in patients suspected of having myocardial ischemia based on the presence of chest pain or non-invasive testing, patients with left ventricular systolic dysfunction, men over 40 years of age, postmenopausal woman, and patients with one or more cardiovascular risk factors. However, it is an invasive procedure that may cause severe complications, including stroke and mortality. In addition, the preoperative CAG is more likely to detect normal coronary arteries in patients with RHD than in those with NRHD.<sup>4</sup> The explanatory reasons for this finding are still uncertain - from the lower prevalence of coronary artery disease (CAD) in RHD or rheumatic etiology may be a protective factor for CAD or higher CAD traditional risk factors in NRHD population. Thus, identification of the prevalence of CAD and its clinical risk factors in patients with RHD compared to those with NRHD may be the first step to explain this finding and help physicians choosing safer and less invasive methods of evaluating coronary arteries before open heart surgery according to the regional prevalence of CAD and individual risk factors. Furthermore, It should also reduce the over-utilization of coronary angiography. This study aimed to identify the prevalence of and clinical risk factors that predict CAD in patients undergoing preoperative CAG with RHD compared to those with NRHD.

## Materials and Methods

### Study design

We conducted a retrospective cross-sectional study, including all consecutive patients with valvular heart disease who underwent preoperative CAG under our care at Khon Kaen university's Queen Sirikit heart center of the Northeast from April 2015- April 2018. Patients with non-valvular heart diseases or for whom complete CAG data were not available, were excluded from the study.

### Study protocol

The medical records were retrospectively reviewed. Rheumatic valvular heart disease was diagnosed using standard echocardiographic criteria,<sup>5</sup> other types of valvular heart disease were defined as non-rheumatic valvular heart disease. All echocardiograms were performed by cardiologists who were unaware of the coronary angiogram results. Significant CAD was defined as over 70% luminal narrowing of one or more major epicardial arteries or over 50% luminal narrowing of the left main coronary artery according to the visual estimation of the interventionists who performed the CAG.<sup>6</sup>

The study variables included in univariate analysis were age over 50 years, male sex, diabetes mellitus, hypertension, dyslipidemia (defined as cholesterol over 200 mg/dl), smoking, family history of CAD, body mass index greater than 25 kg/m<sup>2</sup>, history of chest pain, chronic kidney disease stage 3 or higher, RHD, left ventricular ejection fraction, and presence of at least moderate aortic stenosis.

### Study endpoint

Prevalence of CAD will be identified in the overall study population and compared between patients with RHD and those with NRHD. Then, clinical

variables will be analyzed using univariate and multivariate analyzes for three different categories; overall population, RHD patients, and NRHD patients. After that, all significant clinical risk factors for CAD will be integrated to reveal the true low-risk population.

### Statistical analysis

The required sample size for this study was calculated to be 196 patients. The prevalence of CAD was estimated to be 0.15, the desired precision was 0.05, and the confidence level was 0.95. All categorical variables were compared using a chi-square test, and all continuous variables were compared with the use of a two-tailed unpaired t-test. All designated clinical variables were initially entered univariate analyzes. Predictors of obstructive CAD according to the univariate analyzes were then analyzed using multivariate logistic regression. Only independent predictors ( $p < 0.05$ ) were considered significant in the multivariate model. SPSS software version 23 was used in all statistical analyzes.

The Ethics Committee of Khon Kaen University approved this study protocol on 15 May 2018 (reference number: HE611251).

### Results

A total of 250 patients were included in the study, 12 of whom were excluded because of their having been diagnosed with non-valvular heart disease. One hundred ten (46.2%) had RHD, and the remaining 128 (53.8%) had NRHD. Patients' baseline characteristics are shown in Table 1.

In terms of clinical characteristics, patients with NRHD were more likely to be older, male, heavier, have hypertension, suffer from aortic stenosis, and have higher left ventricular ejection fractions, whereas those with RHD were more likely to have mitral stenosis, tricuspid regurgitation, and a history of stroke. The overall prevalence of significant CAD was 13.9% in this series, a figure that was significantly higher in patients with NRHD (20.3%) than those with RHD (6.4%;  $p=0.002$ ).

The clinical risk factors that predicted CAD were subjected to univariate analysis (Table 2) and multivariate analysis (Table 3). In the overall study population, we found that age over 50 years, diabetes mellitus, hypertension, and chronic kidney disease stage 3 or higher were the significant risk factors for CAD and that rheumatic heart disease was the only

protective factor according to univariate analysis. After performing multivariate analysis, only hypertension and age were still significant (odds ratio (OR) = 3.82; 95% confident interval (95% CI) = 1.50-9.73;  $p = 0.005$  and OR = 1.09; 95% CI = 1.02-1.15;  $p = 0.007$ , respectively).

In patients with RHD, diabetes mellitus, hypertension, and high BMI were the significant risk factors for CAD according to univariate analysis and only hypertension was still significant (OR = 13.02; 95% CI = 1.52-111.42;  $p = 0.02$ ) after multivariate analysis. In patients with NRHD, diabetes mellitus and hypertension were significant risk factors according to univariate analysis and age was the only significant risk factor (OR = 1.11; 95% CI = 1.04-1.19;  $p = 0.001$ ) according to multivariate analysis.

To identify the true low-risk patients, the prevalence of CAD in patients with RHD and those with NRHD was further reclassified by age, gender, and the presentation of diabetes mellitus or hypertension (Table 4). We found that a subgroup of female patients with rheumatic etiology and had no diabetes mellitus and hypertension was the lowest-risk subgroup which preoperative CAG detected no significant CAD in these study population.

### Discussion

The current valvular heart disease guidelines<sup>2, 3</sup> recommended performing a preoperative CAG as a gold standard before valvular surgery despite the prevalence of CAD in these patients was relatively low, the procedure itself was invasive and could end up with some serious complications. In this study, 13.9% of patients had significant coronary artery stenosis. This finding was comparable to those of other studies. They found the rate of significant CAD was 10-20%.<sup>7, 8</sup> In addition, the prevalence of significant CAD was lower in patients with RHD (6.4%) than those with NRHD (20.3%), which was similar to the results of a previous study.<sup>4</sup> However, the prevalence of significant CAD in patients with RHD in this study was lower than in studies by Shu-Chun Li et al. (10.2%)<sup>7</sup> and Tao Yan et al. (13.2%)<sup>9</sup> but higher than in studies conducted by Dany David Kruczan et al. (4%)<sup>4</sup> and Chu PH et al. (1.7%).<sup>10</sup> The difference in CAD prevalence might reflect the diversity of risk factors in each population. The local data should be needed to guide management specifically in each location.

To understand the reasons that significant CAD

**Table 1** Baseline characteristics of the overall study population and in patients with rheumatic valvular heart disease (RHD) compared to those in patients with non-rheumatic valvular heart disease (NRHD)

	Overall population (N = 238)	RHD (N = 110)	NRHD (N = 128)	P-value between RHD and NRHD
Age (years; mean ± SD)	59.8 ± 9.6	56.25 ± 8.6	62.97 ± 9.4	<0.001
Male sex – no. (%)	134 (56.3)	42 (38.2)	92 (71.9)	<0.001
Weight (kilograms; mean ± SD)	57.7 ± 11.4	55 ± 11.3	60 ± 11	0.001
Height (centimeters; mean ± SD)	160.4 ± 7.8	159 ± 7.8	161 ± 7.7	0.061
Body mass index (kg/m <sup>2</sup> ; mean ± SD)	22.4 ± 4.1	21.6 ± 4.2	23.0 ± 4.0	0.008
Diabetes mellitus – no. (%)	13 (5.5)	5 (4.5)	8 (6.2)	0.56
Hypertension – no (%)	39 (16.4)	9 (8.2)	30 (23.4)	0.002
Cholesterol (mg/dl; mean ± SD)	164.9 ± 37.2	165 ± 40	164 ± 33	0.948
Triglyceride (mg/dl; mean ± SD)	128.1 ± 63.8	125.6 ± 63	130.6 ± 64	0.637
High density lipoprotein (HDL; mg/dl; mean ± SD)	45.1 ± 14.4	43.9 ± 15.9	46.4 ± 12.8	0.305
Low density lipoprotein (LDL; mg/dl; mean ± SD)	105.1 ± 36.6	107.2 ± 39.4	102.9 ± 33.7	0.479
Dyslipidemia (Cholesterol > 200 mg/dl) – no. (%)	39 (16.2)	15 (13.7)	24 (18.7)	0.412
The family history of CAD – no. (%)	23 (9.7)	12 (10.9)	11 (8.6)	0.547
Current smoking – no. (%)	34 (14.3)	13 (11.8)	21 (16.4)	0.313
History of chest pain – no. (%)	73 (30.7)	29 (26.4)	44 (34.4)	0.181
Previous stroke – no. (%)	3 (1.3)	3 (2.7)	0 (0)	0.06
Chronic kidney disease ≥ stage 3 – no. (%)	105 (44.1)	47 (42.7)	58 (45.2)	0.70
Moderate and severe mitral stenosis – no (%)	95 (39.9)	93 (84.5)	2 (1.6)	<0.001
Moderate and severe mitral regurgitation – no. (%)	100 (42.0)	44 (40)	56 (43.8)	0.559
Moderate and severe aortic stenosis – no. (%)	66 (27.7)	17 (15.5)	49 (38.3)	<0.001
Moderate and severe aortic regurgitation – no. (%)	67 (28.2)	27 (24.5)	40 (31.2)	0.252
Moderate and severe tricuspid regurgitation – no. (%)	87 (36.6)	61 (55.5)	26 (20.3)	<0.001
Left ventricular ejection fraction (%; mean ± SD)	61.7 ± 13.3	59.4 ± 11.5	63.7 ± 14.5	0.014
Significant CAD – no. (%)	33 (13.9)	7 (6.4)	26 (20.3)	0.002
- Single vessel disease – no. (%)	17 (51.5)	5 (71.4)	12 (46.2)	0.23
- Multi vessel disease – no. (%)	16 (48.5)	2 (28.6)	14 (53.8)	0.23
- Significant LM involvement – no. (%)	9 (27.3)	1 (14.3)	8 (30.8)	0.38

CAD denoted coronary artery disease, and LM denoted left-main. All categorical variables were compared using a chi-square test, and all continuous variables were compared with the use of a two-tailed unpaired t-test. p < 0.05 was considered statistically significant.

was less prevalent in patients with RHD than those with NRHD, we first looked for differences in terms of patients' clinical characteristics. Patients with NRHD were more likely to be older, male, heavier, have hypertension, and suffer from aortic stenosis, all of which are conventional risk factors for CAD. We then conducted a univariate analysis of the clinical risk factors in the overall study population and found that

age over 50 years, diabetes mellitus, and hypertension were risk factors for CAD, whereas rheumatic heart disease was a protective factor. However, after multivariate analysis, the protective benefit of rheumatic heart disease did not exist, and only advanced age and hypertension were significant risk factors for CAD. We, thus, deduced that rheumatic etiology did not have a beneficial effect on the

**Table 2** Univariate analysis of CAD predictors in the overall study population, patients with RHD, and patients with NRHD

Variables	Overall population			RHD			NRHD		
	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Age (> 50)	8.49	1.13-63.94	0.014	2.70	0.31-23.39	0.35	6.66	0.38-116.81	0.08
Male sex	1.23	0.58-2.60	0.59	2.28	0.48-10.74	0.28	0.55	0.22-1.36	0.19
Diabetes mellitus	6.28	1.97-20.09	0.001	13.33	1.80-98.72	0.002	4.45	1.03-19.20	0.031
Hypertension	7.45	3.32-16.72	<0.001	26.13	4.56-149.78	<0.001	4.00	1.59-10.08	0.002
Dyslipidemia (Cholesterol > 200 mg/dl)	1.18	0.36-3.85	0.79	0		0.30	1.63	0.44-6.12	0.46
Current smoking	1.41	0.53-3.71	0.49	1.26	0.14-11.42	0.83	1.28	0.42-3.89	0.66
Family history of CAD	0.93	0.26-3.31	0.90	1.39	0.15-12.67	0.77	0.86	0.17-4.25	0.85
Body mass index > 25 kg/m <sup>2</sup>	1.46	0.66-3.22	0.34	4.39	0.92-20.99	0.047	0.96	0.36-2.53	0.94
History of chest pain	1.82	0.86-3.87	0.12	0.44	0.05-3.87	0.45	2.29	0.95-5.50	0.06
Chronic kidney disease ≥ stage 3	2.53	1.18-5.42	0.015	2.69	0.28-26.13	0.37	2.09	0.58-7.57	0.25
Left ventricular ejection fraction < 50%	1.28	0.49-3.37	0.61	2.15	0.38-12.06	0.37	1.23	0.52-2.96	0.64
Moderate and severe aortic stenosis	1.86	0.87-4.01	0.11	2.35	0.42-13.22	0.32	2.29	0.95-5.50	0.06
Rheumatic heart disease	0.27	0.11-0.64	0.002						

CAD denoted coronary artery disease. All variables were entered univariate analysis. p < 0.05 was considered statistically significant.

**Table 3** Multivariate analysis of CAD predictors in the overall study population, patients with RHD, and patients with NRHD

Variables	Overall population		RHD		NRHD	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.09 (1.02-1.15)	0.007			1.11 (1.04-1.19)	0.001
Diabetes mellitus	2.29 (0.54-9.78)	0.26	8.48 (0.60-120.15)	0.11	1.68 (0.31-9.23)	0.55
Hypertension	3.82 (1.50-9.73)	0.005	13.02 (1.52-111.42)	0.02	2.93 (0.98-8.72)	0.053
Rheumatic heart disease	0.52 (0.19-1.39)	0.19				

Predictors of obstructive coronary artery disease according to the univariate analysis were then analyzed using multivariate logistic regression. p < 0.05 was considered statistically significant.

prevalence of CAD after being adjusted with other traditional coronary risk factors.

Although the prevalence of CAD was lower in patients with RHD than those with NRHD, the clinical risk factors predicting significant CAD in both groups were similar. We found that diabetes mellitus, hypertension, and high BMI were the significant risk factors for CAD according to univariate analysis and that only hypertension was still significant after multivariate analysis in patients with RHD. In patients with NRHD, diabetes mellitus and hypertension were the significant risk factors according to univariate

analysis, but advanced age was the only significant risk factor according to multivariate analysis. These findings showed that traditional risk factors play a role in CAD prevalence, both in patients with RHD and those with NRHD. Appropriate management of modifiable conventional CAD risk factors such as blood pressure control in hypertensive patients should be beneficial in both RHD and NRHD.

This study contained other interesting findings. After integrating few, simple and memorable essential variables including age, gender, and the presentation of diabetes mellitus or hypertension, We found that

**Table 4** The prevalence of coronary artery disease shown in percentage, classified by age and clinical risk factors of rheumatic and non-rheumatic valvular heart disease, genders and the presentation of diabetes mellitus and hypertension

Age (years)			< 50	< 60	< 70	< 80	< 90
RHD	Male	DM or HT	No data	No data	50	66.7	66.7
		No DM and HT	7.1	3.8	5.6	5.3	5.1
	Female	DM or HT	0	50	42.9	33.3	33.3
		No DM and HT	0	0	0	0	0
NRHD	Male	DM or HT	0	33.3	30.8	36.8	35
		No DM and HT	0	2.9	3.8	12.5	12.5
	Female	DM or HT	No data	0	33.3	45.5	45.5
		No DM and HT	0	0	11.8	20.8	20

RHD denoted rheumatic valvular heart disease, NRHD non-rheumatic valvular heart disease, DM diabetes mellitus and HT hypertension.

the female patients with rheumatic etiology and had no diabetes mellitus and hypertension were the lowest-risk subgroups to have CAD. The policy in our region of conducting preoperative CAG in this group of patients should be revised. It might be safer and more appropriate for patients in this group to perform alternative non-invasive diagnostic modalities such as coronary CT angiogram.<sup>11</sup>

There were limitations in our study. First, this was a retrospective cross-sectional study in a single center which may have led to recall bias or missing data. It, thus, requires verification using a larger population. Second, the number of patients included in this study might have been too small to determine all the significant clinical risk factors in each group. However, Hypertension and advanced age were significant risk factors according to multivariate analysis in patients with RHD and NRHD, respectively. This finding suggests that conventional coronary risk factors may predict significant CAD in both patients with RHD and those with NRHD.

The results of this study also have a clinical application. The prevalence of significant CAD in patients with RHD was low, and it was even lower in female patients who had no diabetes mellitus and hypertension. This finding challenges the current guidelines that suggest routine preoperative CAG in men over 40 years old and menopausal women without other coronary risk factors. In this group of patients, coronary CTA should be the first line for evaluating coronary arteries before valvular surgery because it was safer and less invasive.

Further studies to compare clinical benefits,

cost-effectiveness and risk of coronary CTA versus invasive CAG should also be conducted in this group of patients.

### Conclusion

The prevalence of CAD was lower in patients with RHD compared to those with NRHD. However, the clinical risk factors that predicted CAD in both groups were conventional CAD risks. Thus, alternative non-invasive preoperative coronary studies should be an option in RHD patients with low traditional CAD risk factors.

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