Original Article

Role of Carotid Intima-Media Thickness and Carotid Plaque in Predicting Significant Coronary Artery Stenosis in Thai Patients with Chronic Coronary Syndrome: A Cross-Sectional Study

Thakorn Pruktanakul MD[1], Thanapon Nilmoje MD[1], Jitpreedee Sungsiri MD[2], Noppadol Kietsiriroje MD[1], Rattana Leelawattana MD[1]

[1] Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

[2] Department of Radiology, Faculty of Medicine, Prince of Songkla University, Songkhla, Thailand

Objective: To evaluate the diagnostic role of carotid artery intima-media thickness and plaque for significant coronary artery disease (CAD) in Thai patients with chronic coronary syndrome (CCS) when coronary angiography (CAG) was indicated.

Material and Methods: The present study cross-sectional study included adult patients diagnosed with CCS admitted for elective CAG. One day prior or on the day of the procedure, carotid ultrasonography was performed, and diagnostic values of this test were calculated.

Results: One hundred patients, including 69 males and 31 females, with a mean age ± standard deviation of 62.6±12.2 years were recruited. Sixty-three patients had significant CAD, of which carotid plaque (CP) was an independent risk factor (adjusted odds ratio 3.63, 95% confidence interval 1.17 to 11.22, p=0.025). From which, CP had a 29% prevalence, and provided a sensitivity, specificity, positive predictive value, and negative predictive value of 38%, 86%, 83%, and 45%, respectively, in predicting the disease. There was a weak correlation between carotid intima-media thickness and a significant disease (r=0.279, p=0.05), in addition to poor diagnostic accuracy of the calculated optimal cut-off value (area under the curve=0.68, p<0.05).

Conclusion: CP was common, and specific for significant CAD in CCS with mild symptoms. This parameter might facilitate discriminating those having significant disease.

Keywords: Carotid plaque; Coronary artery disease; Intima-media thickness; Ultrasonography

Received 24 January 2022 | Revised 23 September 2022 | Accepted 4 October 2022

J Med Assoc Thai 2022;105(11):1061-6

Website: http://www.jmatonline.com

Coronary artery disease (CAD) is one of the major causes of death among Thais, accountable for 12% of total deaths per year[1]. Currently, coronary angiography (CAG) remains the gold standard diagnostic tool for CAD, which is also an effective therapeutic intervention simultaneously. However, the major limitation for having CAG performed in patients with significant CAD is the long waiting list, due to inadequate cardiac catheterization centers in Thailand.

An important reason contributing to the long waiting list is that they usually present with non-specific symptoms, such as, chest pain and dyspnea. Thus, CAG is almost always requested for those who have these symptoms, even though, there has been a large, population-based study documenting the numbers of insignificant coronary stenosis results[2]. In a setting with limited resources, like Thailand, there is a concern regarding to the prioritization of the patients who need CAG. Therefore, carotid intima-media thickness (CIMT) and carotid plaque (CP) may provide additional risk prioritization, thus, enabling better patient selection. Carotid arteries, theoretically, can display atherosclerotic changes similar to coronary arteries, and are easily accessible by non-invasive ultrasonography (US). Studies in patients with CAD have reported significant correlations between both increased CIMT and CP, and significant

Correspondence to:

Pruktanakul T.

Department of Internal Medicine, Faculty of Medicine, Prince of Songkla University, Songkhla 90110, Thailand.

Phone: +66-74-451463

Email: pthakorn@medicine.psu.ac.th

How to cite this article:

Pruktanakul T, Nilmoje T, Sungsiri J, Kietsiriroje N, Leelawattana R. Role of Carotid Intima-Media Thickness and Carotid Plaque in Predicting Significant Coronary Artery Stenosis in Thai Patients with Chronic Coronary Syndrome: A Cross-Sectional Study. J Med Assoc Thai 2022; 105:1061-6.

DOI: 10.35755/jmedassocthai.2022.11.13693

coronary stenosis. However, these studies suggest that CIMT cut-off values can change depending on the study population[3-9]. This necessitates the need for ethnicity-specific research. Hence, the present study aimed to validate the predictive value of CIMT and CP for the diagnosis of significant CAD in Thai patients with chronic coronary syndrome (CCS) requiring CAG.

Materials and Methods

Study design and participants

A cross-sectional study was conducted to investigate the diagnostic performance of CIMT and CP in the prediction of significant CAD among 100 patients admitted for elective CAG at Songklanagarind Hospital between June 2018 and November 2019. The present study was approved by the Office of the Human Research Ethics Committee, Faculty of Medicine, Prince of Songkla University (REC 60-458-14-1). All participants provided both verbal and written informed consents.

Eligible patients were aged 18 or above, diagnosed with CCS and requiring CAG according to the 2019 European Society of Cardiology (ESC) guidelines for the diagnosis and management of CCS, which are 1) non-invasive assessment suggesting high event risk for determination of options for revascularization, 2) high clinical likelihood of CAD and symptoms refractory to medical therapy, or 3) typical angina at a low level of exercise and clinical evaluation, including exercise electrocardiography indicating high-risk of events[10], or diagnosed with acute coronary syndromes (ACS) without any of the very high or high-risk characteristics. Furthermore, patients referred for elective CAG as CCS patients according to the 2020 ESC guidelines for the management of ACS in patients presenting without persistent ST-segment elevation[11] were also eligible.

All eligible patients must not have undergone CAG before. Patients were also excluded from the study if 1) CAG was unsuccessful by any reason, or 2) if they had at least one previous injury or having procedure on their carotid arteries due to any cause apart from CAG.

Demographic data and clinical data, including the Canadian Cardiovascular Society (CCS) grade of angina pectoris scores(10) and the indications for CAG, were reviewed, and recorded before the patients had carotid US and CAG done.

Carotid ultrasonography

One day prior, or on the day of CAG, the authors measured CIMT, and CP using a Samsung UGEO H60 ultrasound system with LF5-13 linear transducer (Quantum Healthcare Co., Thailand). This procedure was performed by the primary investigator, who underwent a supervised hands-on training program on performing CIMT and CP measurements by a radiologist specialist. The inter-observer and intra-observer intraclass correlation coefficient (ICC) value was 0.953 (95% CI 0.902 to 0.978) and 0.967 (95% CI 0.871 to 0.992), respectively.

The measurement was performed in accordance with the instructions from the American Society of Echocardiography CIMT Task Force, 2008[12]. The variables of interest were mean and maximal CIMT, and the occurrence of CP from the left and right common carotid arteries (CCA). In the B-mode system, a mean of the far wall CIMT, which is located one cm distal from the carotid bulb, was automatically measured on a 1-cm length, by the Auto-IMT function application. CP was defined by either a 50% or more focal wall thickening greater than the surrounding walls, or a focal region with CIMT greater than 1.5 mm and having a point of inflection on the surface of the CIMT. Indeterminate results would be reviewed and interpreted by the radiologic specialist.

CAG

CAG was performed by experienced interventional cardiologists blinded from the ultrasonographic results. Following the American College of Cardiology 2017 appropriate use criteria for coronary revascularization in patients with stable ischemic heart disease, significant CAD was diagnosed when the CAG result showed one of the following criteria 1) 70% or more luminal diameter narrowing by visual assessment of epicardial stenosis, measured in the worst view angiographic projection, 2) 50% or more luminal diameter narrowing by visual assessment of the left main stenosis, measured in the worst view angiographic projection, 3) 40% to 70% luminal narrowing by visual assessment of epicardial stenosis, measured in the worst view angiographic projection with an abnormal fractional flow reserve[13].

Sample size calculation

A minimum sample size for adequate sensitivity/specificity was estimated by the formula proposed by Hajian-Tilaki[14]. Design assumptions included a prevalence of significant CAD of 60% among patients receiving successful CAG in the authors' institute, and a pre-defined specificity of 95% for mean CIMT at 0.9 mm as recommended by the 2007 European

Society of Hypertension and ESC guidelines for the management of arterial hypertension[15] to detect significant CAD. The precision of the estimate was pre-determined at 7%. Therefore, the expected sample sizes were calculated and resulted in 62 for pre-defined sensitivity and 93 for pre-defined specificity. The mean CIMT was envisaged to be used as a diagnostic test, therefore, the expected sample size required for the optimal test specificity was at least 93 cases.

Statistical analysis

Continuous data were expressed as mean with standard deviation, with frequencies being expressed as a percentage. Significant differences between measurements were tested using t-test for continuous variables and chi-square test for categorical variables. A receiver operating characteristic (ROC) curve was employed to identify the diagnostic performance of CIMT in predicting significant CAD. The optimal mean CIMT cut-off for the diagnosis of significant CAD was determined by the value with highest Youden's index. Multivariate logistic regression analysis was performed to determine independent predictors for significant CAD, if the primary outcome showed a p-value of less than 0.2. Manual double data entry was performed and verified using EpiData software version 3.1 (EpiData Association, Odense, Denmark). All analyses were performed using R software version 3.6.1 (The R Foundation, Vienna, Austria). A p-value of less than 0.05 was considered statistically significant.

Results

One hundred patients who met the eligibility criteria, were recruited into the present study, and included 69 males and 31 females, with a mean age of 62.6±12.2 years. Nearly all patients had a CCS grading of angina pectoris of either I or II. History of ACS accounted for approximately 60% of the CAG indications. Two-thirds of the patients were found to have significant CAD from the CAG. Males had significantly higher incidence of significant CAD (p=0.007) than females. The median waiting time from appointment to CAG was 3.7±1.4 months, and two-thirds of the patients had a waiting time of four months or more. Other parameters were not significantly different between both groups (Table 1). Lipid profile was the only parameter that was not completely available, with a missing rate of 57%. There were no serious adverse effects reported in the present study.

Comparing the two CAG result groups, the median values of the right, left, and mean CIMT in the patients with significant CAD were significantly higher than those with insignificant CAD ($p<0.05$ for each) (Table 2). A weak correlation between the mean CIMT and significant CAD was found ($r=0.279$; $p=0.05$). The optimal cut-off for the mean CIMT, to differentiate patients with significant CAD from those with insignificant CAD, was 0.8 mm with sensitivity, specificity, positive predictive value (PPV), and a negative predictive value (NPV) of 35%, 84%, 79%, and 44%, respectively (AUC=0.68, $p<0.05$).

The prevalence of CP in the present study was 29%. The proportion of patients with CP was significantly higher in the significant CAD group than in those with insignificant CAD at 38% versus 14% (p=0.017), providing a sensitivity, specificity, PPV, and NPV of 38%, 86%, 83%, and 45%, respectively. After adjusting for other risk factors, the only independent predictor for significant CAD was CP (adjusted odds ratio 3.63, 95% CI 1.17 to 11.22, p=0.025) (Table 3).

Discussion

The present study demonstrated that mean CIMT in patients with significant CAD was significantly higher than in those with insignificant CAD, yet, the utility of this parameter to predict significant CAD was inadequate. The presence of CP was the only independent predictor, with a 3.6-fold increased risk of significant coronary stenosis regardless of the number of vessels involved.

To enhance the reproducibility for CIMT measurement, the present study used a semiautomated border detection program, which had been shown to provide lower inter-reader variation compared to manual measurements[16]. The inter-observer and intra-observer ICC of CIMT measurements in the present study had an excellent agreement. It was the same as the report in a recent, large prospective cohort study conducted in Brazil[17].

The previous studies had shown that a higher mean CIMT was significantly associated with significant CAD, using various cut-off values[3-6]. The CIMT cut-off value for the diagnosis of CAD concluded from the recent meta-analyses was 1 mm[18,19], which was thicker than 0.8 mm reported by the present study. This may be explained by a different criteria of significant CAD adopted among studies[13,19] or a higher number in Caucasian population included in these meta-analyses compared with Asian population, which has been known to have

Table 1. Baseline characteristics

Parameter	All patients (n=100)	Significant CAD (n=63)	Insignificant CAD (n=37)	p-value
Age (years); mean±SD	62.6±12.2	62.5±12.2	62.8±12.5	0.882
Male; n (%)	69 (69.0)	50 (79.4)	19 (51.4)	0.007
CCS grading; n (%)				
I	62 (62.0)	37 (58.7)	25 (67.6)	0.506
II	31 (31.0)	21 (33.3)	10 (27.0)	0.664
III	6 (6.0)	4 (6.3)	2 (5.4)	1.000
IV	1 (1.0)	1 (1.6)	0 (0.0)	1.000
Co-morbidities; n (%)				
Diabetes	25 (25.0)	17 (27.0)	8 (21.6)	0.720
Hypertension	67 (67.0)	40 (59.7)	27 (40.3)	0.451
Dyslipidemia	62 (62.0)	40 (63.5)	22 (59.5)	0.851
Smoking	39 (39.0)	29 (46.0)	10 (27.0)	0.096
Family history of premature CAD	5 (5.0)	4 (6.3)	1 (2.7)	0.739
SBP (mmHg); mean±SD	132.0±17.8	132.4±18.4	130.8±17.0	0.650
DBP (mmHg); mean±SD	74.0±11.9	74.8±12.2	72.4±11.2	0.323
TC (mg/dL); mean±SD	168.6±42.1	171.1±44.3	163.4±37.9	0.578
TG (mg/dL); median (IQR)	113 (90, 153)	121 (86, 152)	106 (96, 149)	0.731
HDL-C (mg/dL); median (IQR)	43 (39, 54)	42 (39, 51)	52.5 (43, 57)	0.126
LDL-C (mg/dL); mean±SD	118.5±38.2	122.8±39.1	108.9 ± 35.6	0.261
eGFR (mL/minute); mean±SD	73.8±19.9	72.8±20.8	75.5±18.3	0.513
Time to CAG (months); median (IQR)	4 (3, 4)	4 (3, 4)	4 (2, 4)	0.174
Time to CAG group; n (%)				
<4 months	34 (34.0)	19 (30.2)	15 (40.5)	0.290
≥4 months	66 (66.0)	44 (69.8)	22 (59.5)	0.290
Indication for CAG; n (%)				
History of ACS	59 (59.0)	43 (68.2)	16 (43.2)	0.025
Exercise stress ECG	6 (6.0)	3 (4.8)	3 (8.1)	0.807
Ischemia imaging	2 (2.0)	2 (3.2)	0 (0.0)	0.723
Coronary CTA	13 (13.0)	8 (12.7)	5 (13.5)	1.000
Medication failure	20 (20.0)	7 (11.1)	13 (35.1)	0.008

CAD=coronary artery disease; SD=standard deviation; CCS=Canadian Cardiovascular Society; SBP=systolic blood pressure; DBP=diastolic blood pressure; TC=total cholesterol; TG=triglyceride; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; eGFR=estimated glomerular filtration rate; CAG=coronary angiography; ACS=acute coronary artery syndrome; ECG=electrocardiography; CTA=computed tomography angiography; IQR=interquartile range; ns=not significant

Table 2. Common carotid artery ultrasonographic results

Parameter	All patients (n=100)	Significant CAD (n=63)	Insignificant CAD (n=37)	p-value
Right CIMT (mm); median (IQR)	0.70 (0.60, 0.82)	0.75 (0.63, 0.87)	0.64 (0.56, 0.74)	0.004
Left CIMT (mm); median (IQR)	0.73 (0.64, 0.84)	0.75 (0.67, 0.85)	0.66 (0.55, 0.79)	0.015
Mean CIMT (mm); median (IQR)	0.72 (0.63, 0.83)	0.75 (0.67, 0.87)	0.67 (0.58, 0.74)	0.003
Thickest CIMT (mm); median (IQR)	0.79 (0.68, 0.90)	0.82 (0.70, 0.92)	0.71 (0.61, 0.80)	0.007
Carotid plaque; n (%)	29 (29.0)	24 (38.0)	5 (14.0)	0.017

CAD=coronary artery disease; CIMT=carotid artery intima-media thickness; IQR=interquartile range

Table 3. Multiple logistic regression model for statistically significant risk factors in predicting significant CAD

Variable	Crude OR (95% CI)	Adjusted OR* (95% CI)	p-value
Male	3.64 (1.50 to 8.85)	2.16 (0.68 to 6.87)	0.190
Smoking	2.30 (0.96 to 5.54)	1.25 (0.41 to 3.80)	0.696
History of NSTE-ACS	2.82 (1.22 to 6.53)	1.39 (0.46 to 4.26)	0.559
Medication failure	0.23 (0.08 to 0.65)	0.36 (0.09 to 1.47)	0.154
Carotid plaque	3.94 (1.35 to 11.49)	3.63 (1.18 to 11.22)	0.025

CAD=coronary artery disease; OR=odds ratio; NSTE-ACS=non-ST-segment elevation acute coronary syndrome

* Adjusted for male gender, smoking status, history of NSTE-ACS, medication failure, and carotid plaque

lower pooled mean CIMT[20]. In addition, of all the studies included in the meta-analysis by Liu et al, almost half showed that CIMT had poor accuracy in diagnosing CAD[18], as was also found in the present study. The diagnostic role of CIMT for CAD may not be convincing.

CP has been known as a strong predictor for cardiovascular disease as demonstrated in studies[8,9,21], including the present study. Although, the detection of CP was not superior to CIMT measurement in terms of diagnostic accuracy for CAD, it provided a significant higher diagnostic accuracy for the prediction of future CAD events[22]. Additionally, the reproducibility for CP detection was also very good in this report[17]. Therefore, this parameter is more pragmatic and less time-consuming than the mean CIMT measurement. Thus, it might be one of the useful parameters that medical personnel can consider using to timely allocate the CAG for patients with mild symptoms who require this procedure more urgently.

Revascularization therapy for patients with angiographically significant stenoses was associated with significant angina relief[23]. Moreover, patients with an established, high-risk CCS had a cardiac mortality rate of more than 3% per year[10]. In the present study, albeit only 30% of all patients had CAG done before the median waiting time, this proportion would correspond to 29% of patients whose CP was present, since they were at higher risk to develop significant CAD events than those with absent CP. Therefore, the physicians are able to better stratify patients with CCS who are at higher risk for significant CAD by incorporating a CP evaluation as one of the scheduling processes for CAG.

The strengths in the present study included using a semi-automated border detection program to facilitate CIMT measurement, and the very good ICC. In addition, all patients underwent CAG, which is the gold standard for diagnosing CAD. There were limitations in the present study. Firstly, this study was conducted in a single center, with a small sample size. Therefore, the results may not be generalizable. Secondly, missing data of lipid profile in most patients led to an inconclusive association between these parameters and CAG results. Thirdly, the results of the present study cannot be applied for patients with the CCS class III and IV since there was a lack of these population in this study. A larger multicenter study is needed to evaluate the validity of the presence of CP as a marker to better facilitate CAG to the patients with CCS who urgently need it the most.

Conclusion

CP was common and demonstrated good prediction for significant CAD in patients with established CCS who have mild symptoms and meet indications for CAG. This parameter might be useful to help prioritizing among patients with less symptoms for CAG in a situation of long waiting times.

What is already known on this topic?

CIMT has been known to positively correlate with CVD events, whereas, it is becoming more evident that CP is a strong predictor for future CVD.

What this study adds?

Ultrasound-detected CP may facilitate risk stratification of high-risk CCS patients for having significant CAD.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Tantirat P, Thitichai P. Coronary artery disease: CAD. In: Chaifoo W, Yingyong T, editors. Annual epidemiological surveillance report. Bangkok: Canna Graphic; 2018. p. 230-2.
2. Patel MR, Peterson ED, Dai D, Brennan JM, Redberg RF, Anderson HV, et al. Low diagnostic yield of elective coronary angiography. N Engl J Med 2010;362:886-95.
3. Chang CC, Chang ML, Huang CH, Chou PC, Ong ET, Chin CH. Carotid intima-media thickness and plaque occurrence in predicting stable angiographic coronary artery disease. Clin Interv Aging 2013;8:1283-8.
4. Azarkish K, Mahmoudi K, Mohammadifar M, Ghajarzadeh M. Mean right and left carotid intima-media thickness measures in cases with/without coronary artery disease. Acta Med Iran 2014;52:884-8.
5. Holland Z, Ntyintyane L, Gill G, Raal F. Carotid intima-media thickness is a predictor of coronary artery disease in South African black patients. Cardiovasc J Afr 2009;20:237-9.
6. Coskun U, Yildiz A, Esen OB, Baskurt M, Cakar MA, Kilickesmez KO, et al. Relationship between carotid intima-media thickness and coronary angiographic findings: a prospective study. Cardiovasc Ultrasound 2009;7:59.
7. Johri AM, Nambi V, Naqvi TZ, Feinstein SB, Kim ESH, Park MM, et al. Recommendations for the assessment of carotid arterial plaque by ultrasound for the characterization of atherosclerosis and evaluation of cardiovascular risk: from the American Society of Echocardiography. J Am Soc Echocardiogr 2020;33:917-33.

8. Johri AM, Calnan CM, Matangi MF, MacHaalany J, Hétu MF. Focused vascular ultrasound for the assessment of atherosclerosis: A proof-of-concept study. J Am Soc Echocardiogr 2016;29:842-9.
9. Kwon TG, Kim KW, Park HW, Jeong JH, Kim KY, Bae JH. Prevalence and significance of carotid plaques in patients with coronary atherosclerosis. Korean Circ J 2009;39:317-21.
10. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41:407-77.
11. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2021;42:1289-367.
12. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr 2008;21:93-111.
13. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119-77.
14. Hajian-Tilaki K. Sample size estimation in diagnostic test studies of biomedical informatics. J Biomed Inform 2014;48:193-204.
15. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC Task Force on the management of arterial hypertension. J Hypertens 2007;25:1751-62.
16. Mac Ananey O, Mellotte G, Maher V. Comparison of semi-automated and manual measurements of carotid intima-media thickening. Biomed Res Int 2014;2014:531389.
17. Santos-Neto PJ, Sena-Santos EH, Meireles DP, Santos IS, Bensenor IM, Lotufo PA. Reproducibility of carotid ultrasound measurements in the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) at baseline. Braz J Med Biol Res 2019;52:e8711.
18. Liu D, Du C, Shao W, Ma G. Diagnostic role of carotid intima-media thickness for coronary artery disease: A meta-analysis. Biomed Res Int 2020;2020:9879463.
19. Bytyçi I, Shenouda R, Wester P, Henein MY. Carotid atherosclerosis in predicting coronary artery disease: A systematic review and meta-analysis. Arterioscler Thromb Vasc Biol 2021;41:e224-37.
20. Abeysuriya V, Perera BPR, Wickremasinghe AR. Regional and demographic variations of Carotid artery Intima and Media Thickness (CIMT): A Systematic review and meta-analysis. PLoS One 2022;17:e0268716.
21. Johri AM, Behl P, Hétu MF, Haqqi M, Ewart P, Day AG, et al. Carotid ultrasound maximum plaque height-A sensitive imaging biomarker for the assessment of significant coronary artery disease. Echocardiography 2016;33:281-9.
22. Inaba Y, Chen JA, Bergmann SR. Carotid plaque, compared with carotid intima-media thickness, more accurately predicts coronary artery disease events: a meta-analysis. Atherosclerosis 2012;220:128-33.
23. Xaplanteris P, Fournier S, Pijls NHJ, Fearon WF, Barbato E, Tonino PAL, et al. Five-year outcomes with PCI guided by fractional flow reserve. N Engl J Med 2018;379:250-9.