

## Predicting Long-Term Cardiovascular Events after Transient Ischemic Attacks: Carotid Artery Intima-Media Thickness or ABCD2 Score or Both?

### Abstract

**Background:** Patients who experienced transient ischemic attack (TIA) are at high-risk for cardiovascular events. This study aims to evaluate diagnostic value of carotid artery intima-media thickness (CIMT) and ABCD2 score for predicting cardiovascular events in long-term follow-up after TIA. We prospectively included sixty patients with TIA who admitted to hospital from March 2016 to August 2016. **Methods:** Duplex ultrasonography of internal carotid arteries was performed. ABCD2 scores were evaluated for each patient. At a median follow-up of 20 months, patients were asked about new cardiovascular events. We used IBM SPSS software version 22.0 with Chi-squared, *t*-test, ANOVA, receiver operating characteristic, and area under the curve (AUC) analysis for our work. **Results:** Sensitivity and negative predictive value of the combined score (ABCD2+CIMT) was the highest (96.3% and 90.9%, respectively), and the specificity and positive predictive value of the CIMT were the highest (57.5% and 63.1%, respectively) to predict cardiovascular events in long-term. **Conclusion:** Compared to ABCD2 score, CIMT proved to be more accurate to predict cardiovascular events in long-term follow-ups (AUC = 0.736 vs. AUC = 0.640). However, adding CIMT value to ABCD2 score was even better (AUC = 0.750). Therefore, CIMT measurement in the ABCD2 score after TIA enables prediction of long-term cardiovascular events.

**Keywords:** Area under curve, carotid intima-media thickness, receiver operating characteristic curve, stroke, transient ischemic attack

### Introduction

Transient ischemic attack (TIA) is a temporary episode of neurologic dysfunction due to ischemia in the absence of any infarction.<sup>[1,2]</sup> TIA and minor ischemic strokes are associated with an early high risk of recurrent stroke.<sup>[3-7]</sup> Approximately, after 3 months, 10% of TIAs will result to stroke attack, half of which will happen in 2 days after TIA. The ABCD2 score was designed to identify patients at high risk of ischemic stroke in a short time. However, its predictive performance is not optimal.<sup>[8-13]</sup>

In most cases, the source of atherosclerosis is diagnosed with internal carotid artery B-mode ultrasonography. An increased cross-sectional carotid intima-media thickness (CIMT) is associated with unfavorable levels of established cardiovascular events. A major application of CIMT is to prognosticate following risks of vascular diseases.<sup>[14,15]</sup>

Applicability of ABCD2 score and CIMT has not been evaluated in long-term

follow-ups, and there is not any evidences of using the combined form and comparing its result separately for predicting long-term cardiovascular, which they are our novelty in this study. Thus, in this study, we aim to evaluate the efficacy of ABCD2 score and CIMT in long-term follow-ups to predict the occurrence of ischemic-associated cardiovascular events in patients with TIA comprehensively.

### Methods

#### Patient selection

We prospectively studied sixty patients diagnosed with TIA by emergency ward neurologist of hospital from March 2016 to August 2016. TIA is transient episode of neurological dysfunction due to an ischemic origin that is completely resolved within 24 h.<sup>[1]</sup>

Inclusion criteria were patients with sudden onset of the following symptoms: hemiparesis, hemianopia, dysarthria, ataxia, dysphagia, vertigo, loss of consciousness, and eye deviation in 24 h or less before their

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visit. Full neurologic and cardiologic examinations were done for all patients followed by electrocardiogram and computed tomography (CT) or magnetic resonance imaging (MRI) scan of the brain. We excluded all patients with history of amaurosis fugax, migraine, epilepsy, functional disorder, peripheral dizziness, head deviation, syncope, hypertensive crises, and malignancies from the study. Patients with >50% carotid stenosis, having any mobile, ulcerative, or hemorrhagic carotid plaques were excluded due to having higher risk for central thrombosis. Mean age was  $63.57 \pm 12.01$  years with 1.72 male to female ratio.

Ethics: Our protocol of this study was approved by the Department of Medical Ethics. Patient filled and signed informed written consent.

### Baseline clinical variables

Demographic and clinical data were collected for all patients [Table 1]. Furthermore, we collected complete blood analysis and a clinical past medical history with specific attention toward cardiovascular risk factors including hypertension, diabetes, smoking, and hyperlipidemia for each patient.

The ABCD2 score includes five parameters: age, blood pressure, clinical features, duration of symptoms, and presence of diabetes type 2. The result can be between 0 and 7.

The ABCD2 score was calculated retrospectively: age ( $\geq 60$  years, 1 point); blood pressure (systolic blood pressure [SBP]  $\geq 140$  mmHg or diastolic blood pressure [DBP]  $\geq 90$  mmHg, 1 point); clinical presentation of TIA (hemiparesis, 2 points; speech

disturbance, 1 point); TIA duration ( $\geq 60$  min, 2 points; 10–59 min, 1 point); and presence of diabetes (1 point). The ABCD2 score was classified into three subgroups ( $\leq 3$  points, low risk; 4–5 points, moderate risk, and 6–7 points, high risk).<sup>[7]</sup>

Hypertension was defined as SBP  $\geq 140$  mmHg and/or DBP  $\geq 90$  mmHg, or using any antihypertensive drugs; diabetes as fasting blood glucose  $\geq 126$  mg/dL and/or current use of antidiabetic agents and nicotine abuse as current and/or former regular smoking.

### Ultrasonography protocol

Duplex ultrasound of both internal carotid arteries after the bifurcation was performed on all patients mostly when presented by a specialized radiologist. Presence of plaque and CIMT were evaluated using high-resolution ultrasound equipped with a linear transducer at 7.5 MHz in B-mode (ACCUVIX V10; MEDISON) for neuroradiologist to examine.

### Follow-up

At a median follow-up of 20 months (minimum 16 months, maximum 24 months), all of the 60 patients were followed by phone calls and were asked about new cardiovascular diseases. The dataset was completed by family members and previous general physicians. Main concerning questions were about cardiovascular ischemic events (myocardial infarction [MI] or acute coronary syndrome, or any admission to cardiac care unite), cerebral ischemic events (ischemic stroke or TIA or any admission due to these etiologies), and mortality due to cardiovascular events. The interviewers were blinded to the ABCD2 scores and CIMT.

### Statistical analysis

Data were analyzed by our statistical analysis software (IBM SPSS version 22.0, IL, Chicago, USA). All data were expressed as mean  $\pm$  SD. The distributions of nominal variables were compared using Chi-squared test. To compare the mean values of quantitative variables, the independent *t*-test and one-way analysis of variance (ANOVA) were used. For statistical analysis, the ABCD2 score was categorized into three groups ( $\leq 3$  points, low; 4–5 points, moderate; 6–7 points, high). To further evaluate the relationship between score and risk of cardiovascular events, correlation and receiver operating characteristic (ROC) curve analysis were performed. Moreover, we used multivariate analysis to evaluate the independency of significant factors. Associations are presented as hazard ratios (HR) with corresponding 95% confidence intervals (CI) and a two-sided  $P < 0.05$  was considered to be statistically significant.

### Results

Table 1 shows patients' demographic characteristics. Ischemic stroke and new TIA were diagnosed in 12 (20%)

**Table 1: Demographic characteristics and main clinical variables of patients**

Variables	n (%)
$\geq 60$ years	42 (70)
Gender	
Female	22 (36.7)
Male	38 (63.3)
SBP $\geq 140$ mmHg	34 (56.7)
Clinical features	
Unilateral weakness	23 (38.3)
Speech impairment	9 (15)
Sensory impairment	11 (18.3)
Vertigo	17 (28.3)
Duration of symptoms	
$\leq 10$ min	11 (18.3)
10–59 min	14 (23.3)
$\geq 60$ min	35 (58.3)
Diabetes	40 (66.7)
Mean CIMT mm (SD)	0.87 (0.12)
Median duration of symptoms	1.25 h
Mean ABCD2 score (SD)	4.25 (1.63)

SBP=Systolic blood pressure, CIMT=Carotid intima-media thickness, SD=Standard deviation

and seven (11.7%) patients, respectively. Four (6.7%) patients were diagnosed with acute MI at the time of follow-up, and four (6.7%) patients had died due to cardiovascular ischemic events. Distribution of ABCD2 subgroup was as follows: 0–3 points: 16 (26.7%) patients; 4–5 points: 31 (51.7%) patients; and 6–7 points: 13 (21.7%) patients. Four (25%), 16 (51.6%), and 7 (53.8%) events occurred in low-, moderate-, and high-risk groups of ABCD2 score, respectively.

For remaining 33 (55%) patients, no cardiovascular ischemic event was diagnosed within the 2 years after TIA.

The ANOVA analysis revealed no analytical significance between mean CIMT and ABCD2 score subgroups ( $P = 0.081$ ). The individuals with prevalent cardiovascular events had higher mean CIMT ( $0.92 \pm 0.06$  vs.  $0.82 \pm 0.13$ ;  $P < 0.001$ ) [Figure 1].

The cutoff enabling prediction of cardiovascular events was 0.855 mm for CIMT and three score for ABCD2 score.

The evaluations of CIMT for cardiovascular events were 88.8% sensitivity, 57.5% specificity, 63.1% positive predictive value (PPV), and 86.3% negative predictive value (NPV) with overall accuracy of 71.6% and area under the curve (AUC) = 0.736 with 95% CI; 0.611–0.862 [Figure 2].

The evaluations of ABCD2 score for cardiovascular events were 85.1% sensitivity, 36.3% specificity, 52.2% PPV, and 75% NPV with overall accuracy of 58.3% and AUC = 0.640 with 95% CI; 0.501–0.779.

For further evaluating the value of adding CIMT to ABCD2 score in predicting long-term cardiovascular events, we added ABCD2 scorers to their ultrasound CIMT value ( $<0.855$  mm = 0 score,  $0.855$ – $1$  mm = 1 score, and  $>1$  mm = 2 score) and the overall score of  $\geq 4$  was considered positive for analysis. It had 96.29% sensitivity, 30.30% specificity, 53.06% PPV, 90.90% NPV, and overall accuracy of 60% along with AUC = 0.750 and 95% CI; 0.625–0.874 [Figure 3].

Whenever we evaluated each component of all clinical scores (CIMT and ABCD2 score) using logistic regression analyses, higher CIMT and older age were significant factors related to the risk of cardiovascular events. The odds ratio (adjusted for sex and age) for each 0.01 mm increase in CIMT resulted 1.14 for combined vascular events (95% CI; 1.04–1.24,  $P = 0.004$ ).

## Discussion

TIA diagnosis will be made after precise history and physical examination by experienced physicians. Some radiological tests can be performed to evaluate patients who have experienced a TIA, which includes MRI or CT scan of the brain and heart echocardiogram and carotid ultrasonography.

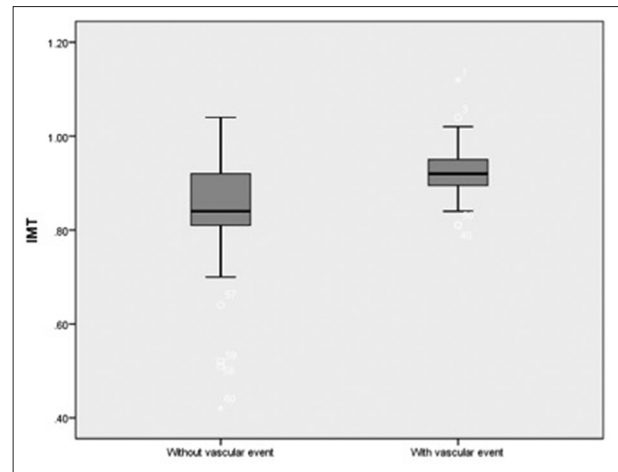


Figure 1: Comparison of mean CIMT between patients with and without combined vascular events

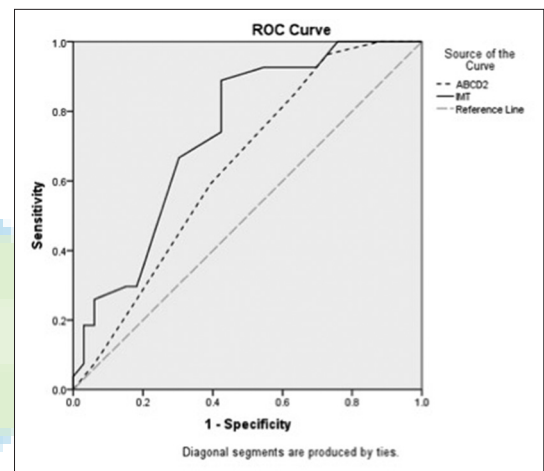


Figure 2. Comparison of the receiver operator characteristic curve between CIMT and ABCD2 score

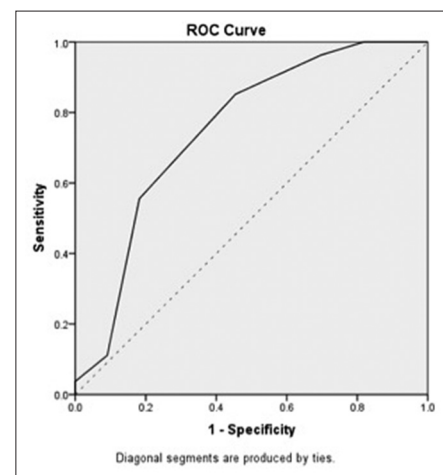


Figure 3: ROC analysis for combined score (ABCD2+CIMT)

TIA and stroke have the same trigger, which is disruption of blood flow to the brain that is commonly described as ministrokes.<sup>[10]</sup>

One-third of the patients will experience recurrent TIA, and stroke will occur to the other third because of losing too many nerve cells.<sup>[11-13]</sup>

Some studies have indicated that the ABCD2 score is useful for predicting stroke after TIA,<sup>[16-18]</sup> whereas other studies have suggested controversial results.<sup>[7,19-21]</sup>

Possible explanation for this discrepancy may be due to the benefit of this; score may differ among study populations, i.e., population-based study or hospital-based study, TIA diagnosed by nonexpert physicians or by stroke specialists, inpatients or outpatients, and definite TIA or possible TIA.<sup>[21,22]</sup>

The ABCD2 score was planned for general physicians and emergency department doctors with the purpose of precise patients' categorization and better define patients at low risk (can be managed in an outpatient setting) and who are at high risk (may benefit most from hospitalization).<sup>[16]</sup> Ideally, prediction scores for TIA patients include high sensitivity and high specificity. We assessed its validity for long-term period instead.

Recent studies have also examined the predictive ability of CIMT. CIMT using ultrasound is a widely available, safe, and reproducible measurement when performed by trained and certified radiologist with standardized equipment. Assessing plaque characteristics and measuring CIMT have prognostic value for cardiovascular events.<sup>[14,15]</sup>

It can be drawn from this study that CIMT was more sensitive, more specific, and had higher AUC in ROC analysis than ABCD2 score for predicting cardiovascular events in 2-year follow-ups [Table 2]. However, if these two scores combine, AUC become higher. As demonstrated in Table 2, the joined score has the highest AUC, sensitivity, and NPV which suggest that the negative result is worthy, and if the overall score becomes <4, it can be predicted that the risk of getting any cardiovascular events in long-term periods is <10%.

In this study, 27 patients (45%) were diagnosed with cardiovascular events within 2 years. They did not receive any medical treatment in hospital during the follow-ups. We hypothesized that due to presenting a source for embolization, they did not receive a complete workup to find thrombus (like transesophageal echocardiogram). It

should be mentioned that TIA is an ischemic event with a chance of recurrence; therefore, these patients prefer to be under anticoagulant regimen like coumarins.

In a meta-analysis of 11 independent TIA cohorts, the validity of the ABCD2 score has been evaluated. By ROC analysis, the overall AUC for 7-day stroke was 0.69 with 95% CI; 0.64–0.74,<sup>[21]</sup> in which our study showed AUC = 0.640 for 2-year follow-up prediction.

Our study also had parallel results with a systematic review of the discriminative accuracy of the ABCD2 score at 7 days (AUC = 0.72, 95% CI; 0.63–0.82).<sup>[21]</sup>

Our results are comparable to other studies that have examined the short-term prognostic value of the ABCD2 score.<sup>[23,24]</sup> In our results, 20% of the patients had strokes within a 2-year follow-up period. German multicenter hospital-based validation of the ABCD2 score suggested that the stroke risk in a year was 6.5% in a cohort study of 1448 patients.<sup>[25]</sup> Thus, patients with higher ABCD2 scores (>3 points) experienced higher stroke risk.

Silvestrini *et al.* studied on 162 consecutive individuals with asymptomatic 60% stenosis of internal carotid artery, each 0.1 mm increase in IMT resulted HR = 1.30 (95% CI; 1.14–1.18) for combined vascular events, 1.47 for cerebrovascular events (95% CI; 1.16–1.87), and 1.24 (95% CI; 1.09–1.42) for cardiovascular events. IMT value above 1.15 mm increased the risk of stroke and MI 19 and 2 times, respectively.<sup>[26]</sup> Some studies have shown association between CIMT and stroke besides similar relationship with MI. On the other hand, carotid atherosclerosis progression study revealed CIMT did not improve risk prediction significantly in their cohort. They suggested CIMT is not useful to predict the risk of cardiovascular events despite its association with incident vascular disease.<sup>[27]</sup>

Another study suggested that CIMT >0.84 mm was a good prediction for stroke and remained so after adjustment for conventional risk factors (risk ratio = 2.23 unadjusted; 2.42 adjusted). The relevance of CIMT to stroke was found to be stronger than the relationship between plaque and stroke.<sup>[28-30]</sup>

Similarly, in our study, odds ratio (adjusted for age and sex) for each 0.01 mm increase in CIMT resulted 1.14 (95% CI; 1.04–1.24) for combined vascular incidents (*P* = 0.004).

**Table 2: Each score in predicting cardiovascular events after transient ischemic attack in long-term periods**

	ABCD2 score	CIMT*	ABCD2 score + CIMT#
Sensitivity (%)	85.1	88.8	96.3
Specificity (%)	36.3	57.5	30.3
Positive predictive value (%)	52.2	63.1	53.0
Negative predictive value (%)	75	86.3	90.9
Area under the curve (95% CI)	0.640 (0.501-0.779)	0.736 (0.611-0.862)	0.750 (0.625-0.874)

\*The cutoff point in ROC analysis was 0.855, #ABCD2 score combined with CIMT value (<0.855 mm=0 score, 0.855-1 mm=1 score, and >1 mm=2 score) and the test considered positive for the overall score ≥4. CIMT=Carotid intima-media thickness, CI=Confidence interval, ROC=Receiver operating characteristic

CIMT was related to combine vascular events in a univariate analysis. It can be concluded from this study that individuals with vascular events had significantly higher CIMT and higher abnormal CIMT proportion. This study confirmed CIMT single measurement as independent predictors of vascular outcomes. Therefore, its clinical use in risk prediction should be further considered. However, for long-term prediction of cardiovascular event after TIA, additional research is needed. Subsequently, CIMT is more accurate than ABCD2 score to predict cardiovascular events (AUC = 0.736 vs. AUC = 0.640) and the combined form is even better (AUC = 0.750).

## Conclusions

The ABCD2 score alone was not very reliable to predict stroke and other vascular events after TIA in long-term periods. Therefore, adding CIMT measurement to the ABCD2 score enables prediction of long-term vascular events after TIA. A single unified protocol for measuring the CIMT could allow wider application of CIMT in clinical practice. Furthermore, evidence that measuring CIMT in a clinical setting changes physician management, and patient motivation can add considerable power to the value of CIMT as a risk predictor. We suggest further studies with larger patient cohorts and longer follow-ups.

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## Conflicts of interest

There are no conflicts of interest.

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