Atherosclerosis 237 (2014) 504–513

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

The $CHADS_2$ and CHA_2DS_2-VASc scores predict adverse vascular function, ischemic stroke and cardiovascular death in high-risk patients without atrial fibrillation: Role of incorporating PR prolongation

Yap-Hang Chan [a, b], Kai-Hang Yiu [a], Kui-Kai Lau [c], Yuen-Fung Yiu [a], Sheung-Wai Li [d], Tai-Hing Lam [b], Chu-Pak Lau [a], Chung-Wah Siu [a, e, 1], Hung-Fat Tse [a, e, *, 1]

[a] Division of Cardiology, Queen Mary Hospital, The University of Hong Kong, China
[b] School of Public Health, The University of Hong Kong, China
[c] Division of Neurology, Queen Mary Hospital, The University of Hong Kong, China
[d] Department of Medicine, Tung Wah Hospital, China
[e] Research Center of Heart, Brain, Hormone and Healthy Ageing, University of Hong Kong, China

ARTICLE INFO

Article history:
Received 15 October 2013
Received in revised form
9 August 2014
Accepted 11 August 2014
Available online 30 August 2014

Keywords:
$CHADS_2$ and CHA_2DS_2-VASc scores
PR prolongation
Vascular dysfunction
Cardiovascular continuum
Adverse cardiovascular events
Risk prediction

ABSTRACT

Objectives: To investigate whether the $CHADS_2$ and CHA_2DS_2-VASc scores have clinical utility for prediction of adverse vascular function and vascular dysfunction-mediated incident cardiovascular (CV) events among high-risk patients without atrial fibrillation (AF), and the additional value of incorporating PR prolongation to the scores.

Methods: We analyzed 579 high-risk CV outpatients without clinical AF in a prospective cohort for new-onset ischemic stroke, myocardial infarction (MI), congestive heart failure (CHF), and CV death. Brachial flow-mediated dilation (FMD) and nitroglycerin-mediated dilatation (NMD), carotid intima-media thickness (IMT) and pulse wave velocity (PWV) were determined.

Results: Baseline $CHADS_2$ score was associated with lower FMD (Pearson $r = -0.16$, $P < 0.001$) and NMD ($r = -0.17$, $P < 0.001$), higher carotid IMT ($r = 0.30$, $P < 0.001$) and PWV ($r = 0.35$, $P < 0.001$; similar for CHA_2DS_2-VASc score: All $P < 0.05$). After follow-up of 63 ± 11 months, 82 patients (14.2%) developed combined CV endpoint. ROC curve analysis showed that both $CHADS_2$ and CHA_2DS_2-VASc scores were predictors for ischemic stroke (C-Statistic: $CHADS_2$ 0.70, $P = 0.004$; CHA_2DS_2-VASc 0.68, $P = 0.010$), MI ($CHADS_2$ 0.63, $P = 0.030$; CHA_2DS_2-VASc 0.70, $P = 0.001$), and CV death ($CHADS_2$ 0.63, $P = 0.022$; CHA_2DS_2-VASc 0.65, $P = 0.011$). Higher $CHADS_2$ score was associated with reduced event-free survival from combined CV endpoints (log-rank = 16.7, $P < 0.001$) with differences potentiated if stratified by CHA_2DS_2-VASc score (log-rank = 29.2, $P < 0.001$). Incorporating PR prolongation, the CHA_2DS_2-VASc-PR score achieved the highest C-Statistic for CV death prediction (0.70, $P < 0.001$) superior to the $CHADS_2$ score (chi-square: 12.1, $P = 0.0005$).

Conclusions: The $CHADS_2$ and CHA_2DS_2-VASc predict vascular dysfunction and cardiovascular events in high-risk CV patients without clinical AF, with further improved performance incorporating PR prolongation.

1. Introduction

AF as the commonest sustained cardiac arrhythmia, contributes to substantial morbidities and mortalities predominantly from thromboembolism and stroke which occur at an increased risk of five-fold, further escalating in the presence of risk factors [1]. The $CHADS_2$ and CHA_2DS_2-VASc scores have shown promising values in early risk stratification of patients with non-valvular AF in terms of

* Corresponding author. Cardiology Division, Department of Medicine, The University of Hong Kong, Rm 1928, Block K, Queen Mary Hospital, Hong Kong, China. Tel.: +852 28553598; fax: +852 28186304.
E-mail address: hftse@hkucc.hku.hk (H.-F. Tse).
[1] Co-supervising authors contributed equally to this work.

http://dx.doi.org/10.1016/j.atherosclerosis.2014.08.026
0021-9150/

Glossary of abbreviations

ACEI	angiotensin-converting enzyme inhibitors
AF	atrial fibrillation
ARB	angiotensin receptor blockers
BMI	body-mass index
CAD	Coronary Artery Disease
CCB	calcium-channel blockers
$CHADS_2$ score	see Appendix
CHA_2DS_2-VASc score	see Appendix
CHF	congestive heart failure
CV	cardiovascular
ECG	electrocardiogram
FMD	flow-mediated dilation
HbA1c	glycosylated hemoglobin A1c
hs-CRP	high-sensitivity C-reactive protein
HDL	high-density lipoprotein
IMT	carotid intima-media thickness
LDL	low-density lipoprotein
MI	myocardial infarction
NMD	nitroglycerin-mediated dilatation
PWV	Pulse Wave Velocity

intracardiac thrombogenesis and cardioembolism [2], thus allowing discriminatory and tailored initiation of antithrombotic treatments for effective risk reduction, balancing against the risks from treatment-related complications [1,3].

Interestingly, since the entry scoring criteria of the $CHADS_2$ and CHA_2DS_2-VASc scores [4] are also important fundamental risk factors of atherosclerotic disease independent of the cardioembolic pathway, it is possible that such scores may have important applications for the prediction of a wider array of pathophysiologically-related vascular events beyond the conventional scope of AF. Indeed, a recent study showed that the $CHADS_2$ score predicted subsequent stroke and death in patients with acute coronary syndrome who had no AF, at a performance level that was superior than when applied to patients with AF [5]. Furthermore, the $CHADS_2$ score was found associated with intracerebral atherosclerosis in stroke patients with nonvalvular AF [6], suggesting that it may be a useful clinical composite marker to reflect the stage of vascular phenotype along the cardiovascular (CV) continuum progression [7]. Furthermore, adverse CV events as stroke [8], myocardial infarction (MI) [9] and congestive heart failure (CHF) [10] are pathophysiologically commonly characterized by abnormal vascular function. The potential role of the $CHADS_2$ and CHA_2DS_2-VASc scores in predicting the level of vascular dysfunction and new-onset CV events in high-risk patients without AF may open up important opportunities in optimizing their individualized care for risk-reduction managements.

Moreover, PR prolongation, or first-degree atrioventricular block on electrocardiogram (ECG), has recently been recognized a precursor to AF and is associated with adverse CV outcomes in the population [11,12] as well as in patients with established Coronary Artery Disease (CAD) [13]. It is thus of interest to know whether incorporating this novel marker into assessment in CV patients without AF may result in overall improved risk prediction.

The purpose of this study is therefore three-fold: (1) to investigate the prediction utility of the $CHADS_2$ and CHA_2DS_2-VASc scores among high-risk patients without clinical AF for new-onset vascular events; (2) to examine the relations between $CHADS_2$ and CHA_2DS_2-VASc scores and surrogate indicators of vascular function to elucidate the pathophysiological basis; (3) to explore whether incorporating PR prolongation to the $CHADS_2$ and CHA_2DS_2-VASc scores will improve the overall risk prediction for vascular events among high-risk patients without AF.

2. Subjects and methods

2.1. Study population and design

In this prospective cohort study, we included 597 consecutive high-risk patients with CAD or risk equivalent (prior CAD: 328 [55%]; ischemic stroke: 131 [22%]; diabetes mellitus: 310 [52%]) from internal medicine outpatient clinics during the period from Sep 2005 to Apr 2008. Patients with the following conditions were excluded: recent MI, unstable angina, coronary revascularization, stroke or acute heart failure within the past 6 months; dilated cardiomyopathy, significant valvular heart disease, chronic AF, cardioembolic stroke, New York Heart Association class III or IV heart failure, significant renal impairment with creatinine >220 mmol/L, liver failure and clinical/biochemical evidence for concomitant inflammatory disease. All participants had stable diet pattern and CV medications for at least 3 months prior to recruitment. As the objective of the study is to investigate the role of the $CHADS_2$ and CHA_2DS_2-VASc scores in atherosclerotic vascular events commonly characterized by adverse vascular function, as opposed to the conventional use of the scores in stroke prediction in AF presumably secondary to cardioembolism, we preemptively included patients with established atherosclerotic diseases; and diabetes which is a well established cause of atherosclerosis and a recognized coronary disease risk equivalent, as part of the advanced cardiovascular continuum [7]. Conditions which may impact on cardiovascular risks through predominantly non-atherosclerotic mechanistic pathways were not included to enhance the homogeneity of the study sample. Recent cardiovascular events in the past 6 months were excluded to avoid transient fluctuations in vascular function parameters. Written informed consent was obtained for all patients. The study was approved by Ethics Committee of University of Hong Kong.

During the prospective follow-up (Dec 2007 to May 2012), occurrence of new-onset ischemic stroke, MI, CHF and CV death were retrieved and ascertained from the medical records and discharge summaries of the Clinical Management System (CMS), the territory-wide computerized clinical data network of all public hospitals in Hong Kong. Primary endpoints of the study were ischemic stroke, CV death and new-onset MI. Secondary endpoints were vascular function parameters and combined CV endpoints which included occurrences of any primary endpoints or CHF. We defined CV death as death directly resulting from circulatory disturbances as acute MI, acute/acute-on-chronic heart failure, cardiac arrhythmias, or ischemic/ haemorrhagic stroke. CAD was diagnosed in the presence of any of the following: history of MI [14]; history suggestive of angina pectoris objectively evidenced by inducible ischemia on exercise treadmill or single photon emission computed tomography (SPECT); and the presence of coronary atherosclerosis was defined by coronary angiography, computed tomography or magnetic resonance imaging. Diagnosis of ischemic stroke was made on the basis of clinical examinations and computed tomography or magnetic resonance brain imaging [15]. As a result, at the end of study 579 patients with complete data on $CHADS_2$ and CHA_2DS_2-VASc scores and CV outcomes were available for analysis.

2.2. Baseline demographic, clinical and laboratory assessments

Baseline demographic data, CV risk factors and medications were documented. Hypertension was defined as either resting systolic/diastolic blood pressure ≥140/90 mmHg at two different