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Risk stratification of cardiovascular complications using CHA₂DS₂-VASC and CHADS₂ scores in chronic atherosclerotic cardiovascular disease

Jonathan Sen^{a,b,*}, Andrew Tonkin^{c,1}, John Varigos^{c,1}, Sylvanus Fonguh^{a,1}, Scott D. Berkowitz^{e,1}, Salim Yusuf^{d,1}, Peter Verhamme^{f,1}, Thomas Vanassche^{f,1}, Sonia S. Anand^{d,1}, Keith A.A. Fox^{g,1}, John W. Eikelboom^{d,1}, John Amerena^{a,1}, on behalf of the COMPASS Trial Investigators

^a Cardiology Research Unit, University Hospital Geelong, Barwon Health, Geelong, Australia

^b Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, Melbourne, Australia

^c School of Public Health and Preventive Medicine, Monash University, Australia

^d Department of Medicine, Population Health Research Institute, McMaster University, Hamilton Health Sciences, Hamilton, Ontario, Canada

^e Research & Development, Pharmaceuticals, Bayer U.S. LLC, Whippany, NJ, United States

^f Department of Cardiovascular Sciences, Center for Molecular and Vascular Biology, University of Leuven, Leuven, Belgium

^g Center for Cardiovascular Science, University of Edinburgh, Edinburgh, United Kingdom

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ABSTRACT

Background

The COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial showed that rivaroxaban plus aspirin reduced major adverse cardiovascular events (MACE) in patients with chronic coronary artery disease (CAD) and/or peripheral artery disease (PAD). We explored whether CHA₂DS₂-VASC or CHADS₂ scores, well-validated tools for assessing risk of thromboembolic events in atrial fibrillation, can identify vascular patients at highest risk of recurrent events who may derive greatest benefits of treatment.

Methods

Predictive accuracies of the CHA₂DS₂-VASC and CHADS₂ scores for MACE, were assessed in this analysis of the COMPASS trial. Kaplan-Meier estimates of cumulative risk were used to compare the effects of rivaroxaban plus aspirin ($n = 9152$) with aspirin alone ($n = 9126$) according to risk scores.

Results

High CHA₂DS₂-VASC (6–9) or CHADS₂ (3–6) scores were associated with over three times greater absolute risk of MACE compared with CHA₂DS₂-VASC score of 1–2 or CHADS₂ score of 0. The effects of rivaroxaban plus aspirin compared with aspirin alone were consistent across CHA₂DS₂-VASC and CHADS₂ score categories for MACE, bleeding and net clinical benefit, with greatest reduction in MACE observed in patients treated for 30 months with highest CHADS₂ score (3–6) (hazard ratio = 0.67, 95% CI: 0.53–0.86, $p = 0.0012$, 25 events per 1000 patients prevented).

Conclusion

The CHA₂DS₂-VASC and CHADS₂ scores can be used in patients with chronic CAD and/or PAD to identify patients who are at highest risk of MACE. Those identified at highest risk by CHADS₂ scores had greatest benefit from dual pathway inhibition with rivaroxaban plus aspirin.

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* Corresponding author at: Cardiology Research Unit, University Hospital Geelong, Barwon Health, PO Box 281, Geelong, Victoria 3220, Australia.

E-mail address: JohnAm@barwonhealth.org.au (J. Sen).

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1. Introduction

Atherosclerosis is a pathological process that leads to progressive hardening of the walls of the coronary and peripheral arteries that manifests clinically as coronary artery disease (CAD), peripheral arterial disease (PAD) and cerebrovascular disease, which are leading causes of morbidity and mortality worldwide [1,2]. Patients with chronic atherosclerotic cardiovascular disease (ASCVD) are at risk of major adverse cardiovascular events (MACE), such as myocardial infarction, stroke,

and cardiovascular death [3]. A simple tool that stratifies patients with established ASCVD into different risk categories could help to identify those who achieve the greatest benefit of secondary prevention therapies to improve outcomes.

Two simple scores, CHADS₂ [4] and CHA₂DS₂-VASc [5] are commonly used to estimate the risk of stroke in patients with atrial fibrillation (AF) and to identify those who are most likely to benefit from anticoagulation [5]. The CHA₂DS₂-VASc score has been shown to have a modestly better discriminative ability than the CHADS₂ score in AF, especially in lower risk groups [6,7]. CHA₂DS₂-VASc scores may also predict MACE in patients with other conditions, such as chronic obstructive pulmonary disease [8], those undergoing isolated coronary artery bypass grafting (CABG) surgery [9] or percutaneous coronary intervention [10], with heart failure [11], or with implantable cardiac defibrillators [12].

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial demonstrated that the combination therapy of rivaroxaban plus aspirin compared with aspirin reduced the risk of MACE with hazard ratio of 0.76 (95% CI: 0.66–0.86) and mortality with hazard ratio of 0.82 (95% CI: 0.71–0.96) in patients with chronic CAD and/or PAD [13]. However, no significant effect on MACE reduction was seen between patients treated with rivaroxaban alone compared with aspirin alone. Therefore, current recommendation is to use rivaroxaban plus aspirin to prevent MACE in patients with chronic CAD or PAD. The objectives of this study were to evaluate whether two simple and almost universally known risk scores, the CHA₂DS₂-VASc and CHADS₂ scores, can be used to identify patients with chronic atherosclerotic disease at highest risk for MACE and to examine the effects of rivaroxaban plus aspirin compared to aspirin alone on clinical outcomes and net clinical benefit according to risk score. We hypothesized that COMPASS patients with chronic CAD or PAD with higher CHA₂DS₂-VASc and CHADS₂ scores would derive the greatest net clinical benefit from combination therapy with rivaroxaban plus aspirin.

2. Methods

2.1. Study design

This was a post hoc analysis of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01776424) number: NCT01776424). Selection, detection and confounding bias were reduced by analysing data from an international, double-blind, double-dummy randomised controlled trial using a 3-by-2 partial factorial. The COMPASS trial compared cardiovascular outcomes (i.e., myocardial infarction, stroke and cardiovascular death) in patients with chronic atherosclerotic vascular disease without known AF. The patients were randomised to one of three treatment regimens: 1) rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily); 2) rivaroxaban (5 mg twice daily) only; and 3) aspirin (100 mg once daily) and followed for an average duration of 23 months. Details of the trial's methodology and main results have been published elsewhere [13]. This study only analysed data from two groups: those randomised to the aspirin only and rivaroxaban plus aspirin groups because combination therapy significantly improved outcomes compared to aspirin alone, while rivaroxaban monotherapy did not [13]. The COMPASS study protocol was approved by locally appointed ethics committee and institutional review boards. Written informed consent was obtained from all participants. The COMPASS trial complied with the Declaration of Helsinki.

2.2. CHA₂DS₂-VASc and CHADS₂ scores

The CHA₂DS₂-VASc (congestive heart failure (CHF), hypertension, age $\geq$ 75 years [doubled], diabetes, stroke/transient ischemic attack (TIA)/thromboembolism [doubled], vascular disease [prior myocardial infarction, peripheral artery disease, or aortic plaque], age 65–75

years, and sex category [female]) and CHADS₂ (CHF, hypertension, age $\geq$ 75 years, diabetes, stroke/TIA [doubled]) scores were calculated based on validated criteria (Online Table S1 and S2) [4,5]. The mean and standard deviation of CHA₂DS₂-VASc and CHADS₂ scores were determined, and distributions of both scores were illustrated graphically. We assessed CHA₂DS₂-VASc scores by individual scores from 1 to 9 and grouped score category: 1–2, 3, 4, 5, and 6–9. Similarly, CHADS₂ scores were calculated as individual scores from 0 to 6 and grouped score category: 0, 1, 2, 3–6.

2.3. Outcomes

The pre-specified primary outcome was MACE, defined as a composite of myocardial infarction, stroke and cardiovascular death. Secondary outcomes in this analysis included all-cause mortality, and an extension of the pre-specified trial outcome, which was the composite of MACE and major adverse limb events (MALE), the latter including other clinically important vascular outcomes such as acute limb ischemia and major amputation. Tertiary efficacy outcomes included individual efficacy components: cardiovascular death, myocardial infarction, ischemic stroke, haemorrhagic stroke, and heart failure hospitalization. Safety outcomes included major bleeding (modified International Society on Thrombosis and Haemostasis criteria, which included fatal bleeding, symptomatic bleeding into critical area or organ, bleeding into surgical site that led to reoperation and/or bleeding that led to presentation to an acute care facility or hospitalization), and serious bleeding (fatal or symptomatic bleeding into critical organ). The net-clinical-benefit outcome was the composite of myocardial infarction, stroke, cardiovascular death, fatal bleeding, or symptomatic bleeding into a critical organ. The incidence of each outcome was calculated in both treatment arms across all strata of CHA₂DS₂-VASc and CHADS₂ scores.

2.4. Statistical analysis

Descriptive analyses of patients treated with aspirin or rivaroxaban plus aspirin were used to characterise the central tendency and variability of relevant baseline continuous data (e.g., age), reported as mean, median, standard deviation, and interquartile range, as appropriate. Categorical or dichotomous discrete variables (e.g., sex, history of chronic heart failure, stroke, transient ischemic attack or thromboembolism, hypertension, vascular disease, and diabetes), are presented as numbers and percentages. *p* Values for categorical variables were calculated using Fisher's exact test for counts <5 and Chi-square test for counts >5 , and ANOVA for mean comparison. All reported *p* values are two-sided and a *p* value <0.05 was considered statistically significant.

The statistical approach to risk stratification was similar to previous analyses in patients with atherothrombosis [14–16]. Annualized event rates were determined from number of participants with an outcome per total number of person-years and reported as % per 100 patient-years of follow-up. Hazard ratios (HR) for each outcome according to CHA₂DS₂-VASc and CHADS₂ scores were calculated using Cox regression analyses with the score as the dependent continuous or categorical variable.

The areas under the receiver operating characteristic curves for the two scores were compared to assess how well the cut-off values can distinguish between with and without endpoints at follow-up. The *c*-statistic for each endpoint was used to determine the ability of the CHA₂DS₂-VASc and CHADS₂ scores to discriminate between low and high-risk patients.

The time to first outcome was estimated using Kaplan-Meier curves for all patients in the aspirin-treated and rivaroxaban plus aspirin-treated groups stratified by CHA₂DS₂-VASc or CHADS₂ scores. The log-rank test was used to compare the incidence risk between the treatment groups. The cumulative incidence risk curves between the score categories were compared using a log-rank test with a *p* value <0.05 considered statistically significant. For each CHA₂DS₂-VASc and CHADS₂

score category, the number of events prevented or caused by rivaroxaban plus aspirin compared to aspirin only was determined by absolute risk reduction and reported as events prevented per 1000 patients treated for 30 months. Heterogeneity testing across subgroups of risk score was also conducted. All analyses were conducted using SAS 9.4 (SAS Institute Inc., USA).

2.5. Patient and public involvement

Patients or the public were not involved in the design, conduct or dissemination plans of this study.

3. Results

A total of 18,278 patients were randomised to receive aspirin alone or rivaroxaban plus aspirin in the COMPASS trial. Baseline characteristics were well balanced between these treatment groups (Online Table S3). The mean and distribution of CHA₂DS₂-VASC and CHADS₂ scores were similar between treatment groups (CHA₂DS₂-VASC score of 3.7 ± 1.2 for both groups and CHADS₂ scores with mean 1.7 (standard deviation (SD): 1.0) and 1.7 (SD 1.1) in rivaroxaban plus aspirin group and aspirin alone group, respectively) (Fig. 1). As expected, participants with higher CHA₂DS₂-VASC or CHADS₂ scores were older and had a greater proportion of patients with cardiovascular risk factors, such as hypertension and diabetes, and history of stroke, transient ischemic attack or thromboembolism, heart failure, and renal impairment (Online Table S4 and S5).

3.1. Risk of primary outcome: MACE

A stepwise increase in the primary outcome (MACE) was found with increasing CHA₂DS₂-VASC or CHADS₂ scores (Fig. 1). There was a decrease in proportion of MACE from CHADS₂ score of 4 to 5–6, but this analysis is limited by small sample size in the CHADS₂ score of 5–6 group ($n = 191$) compared to much larger sample size in the CHADS₂ score of 3 ($n = 2643$) and 4 ($n = 660$) and lack of statistical evidence of heterogeneity. When examining annual rate of MACE, the trend is consistently increasing with higher risk scores (Online Fig. S1). CHA₂DS₂-VASC scores were predictive of MACE with HR for each 1-point increase of 1.32 (95% CI 1.23–1.42, $p < 0.0001$). Risk of MACE was 3 times greater in patients with a high CHA₂DS₂-VASC score (6–9) compared to low scores (1–2) (HR = 3.39, 95% CI: 2.54–4.51, $p < 0.0001$). A similar pattern was evident for CHADS₂ scores. CHADS₂ scores were also predictive of MACE with a higher HR of 1.48 for each

1-point increase (95% CI: 1.37–1.59, $p < 0.001$). Risk of MACE was almost 4 times greater in patients with a high CHADS₂ score (3–6) compared to low score (0) (HR = 3.75, 95% CI: 2.96–4.76, $p < 0.0001$).

CHA₂DS₂ scores had slightly higher c-statistic for MACE: 0.62 (95% CI: 0.59–0.64) than CHA₂DS₂-VASC with c-statistic of 0.60 (95% CI: 0.57–0.62), but the difference was not statistically significant. The cumulative incidence risk of MACE was highest with a CHA₂DS₂-VASC score of ≥ 6 or CHADS₂ score ≥ 3 (Fig. 2).

3.2. Risk of secondary outcomes

Similarly, the event rate of individual secondary outcomes: myocardial infarction, ischemic stroke, heart failure hospitalization, cardiovascular death, all-cause death, and major bleeding also increased with higher CHA₂DS₂-VASC and CHADS₂ scores ($p < 0.001$, Table 1). Higher CHA₂DS₂-VASC scores (6–9) or CHADS₂ scores (3–6) were also associated with 3.4 or 4 times greater risk of composite of MACE and MALE ($p < 0.0001$, both), and 4.8 or 5.5 times greater risk of all-cause mortality ($p < 0.0001$, both) compared with low CHA₂DS₂-VASC score (1–2) or CHADS₂ score (0). Patients with higher CHA₂DS₂-VASC also had 1.9 times greater risk of major bleeding ($p = 0.002$), which was greater than CHADS₂ scores of 1.7 times greater risk of major bleeding ($p = 0.01$). However, there was no significant difference in risk of serious bleeding between higher and lower risk scores ($p = 0.06$ and 0.08 , respectively for CHA₂DS₂-VASC and CHADS₂ scores). Net-clinical-benefit outcome was 3.4 or 3.7 times greater in higher CHA₂DS₂-VASC or CHADS₂ scores compared with lower scores ($p < 0.0001$, both). The respective c-statistics for CHA₂DS₂-VASC and CHADS₂ scores as predictors of MACE and MALE events were similar: 0.59 (95% CI: 0.57–0.62) and 0.61 (95% CI: 0.59–0.63).

3.3. Effects of rivaroxaban plus aspirin vs. aspirin alone

The incidence of MACE, the composite of MACE and MALE, and net-clinical-benefit were consistently lower in patients treated with rivaroxaban plus aspirin compared to aspirin alone across all risk scores (Online Fig. S1). Incidence of all-cause mortality were lower in majority of risk scores, but this was not consistent. Although incidence of major bleeding events was higher in patients with rivaroxaban plus aspirin across risk scores, the incidence of severe bleeding events was low and not significantly different. Cumulative incidence risk curves for MACE for aspirin alone group and rivaroxaban plus aspirin group stratified by risk scores were also compared and illustrated in Online Figs. S2 and S3. The incidence risk was lower in patients treated with

Fig. 1. Distribution of (A) CHA₂DS₂-VASC or (B) CHADS₂ scores and proportion of patients with a first MACE during follow-up. MACE, major adverse cardiovascular events.

Fig. 2. Cumulative incidence of major adverse cardiovascular events stratified by (A) CHA₂DS₂-VASc scores and (B) CHADS₂ scores.

rivaroxaban plus aspirin compared to aspirin alone, and largest significant risk reduction from rivaroxaban plus aspirin occurred in patients with CHADS₂ score of 3 or above (HR = 0.67, 95% CI: 0.53–0.86, $p = 0.0012$).

Absolute benefit of reduction in MACE and MALE were seen in all score categories with largest risk reduction in highest CHA₂DS₂-VASc or CHADS₂ scores (Table 2). The risks of major bleeding events were consistently higher in rivaroxaban plus aspirin group. However, the incidence of serious bleeding event was low with relatively insignificant risk in each score category. Absolute benefit of reduction in net-clinical-benefit outcome was also seen in all score categories with largest risk reduction in highest CHA₂DS₂-VASc or CHADS₂ scores. The risk reduction of net-clinical-benefit outcomes of rivaroxaban plus aspirin was lowest in patients with lowest CHA₂DS₂-VASc score (1–2)

(HR = 0.85, 95% CI: 0.55–1.32, $p = 0.473$) or CHADS₂ score (0) (HR = 1.08, 95% CI: 0.63–1.84, $p = 0.788$), whereas the risk reduction of net-clinical-benefit outcomes was highest with highest CHADS₂ scores (3–6) (HR = 0.73, 95% CI: 0.58–0.92, $p = 0.006$) followed by CHA₂DS₂-VASc score of 6–9 (HR = 0.78, 95% CI: 0.54–1.13, $p = 0.184$). There were no significant interactions between risk scores and treatment groups for MACE or other secondary outcomes.

4. Discussion

The CHA₂DS₂-VASc and CHADS₂ scores, well-validated tools for assessing risk of thromboembolic events in patient with AF [5], predicted outcomes such as MACE and MACE/MALE in this large trial of 18,278 included patients with chronic atherosclerotic vascular disease.

Table 1Univariate proportional hazards analyses of cardiovascular outcomes by CHA₂DS₂-VASC and CHADS₂ scores as continuous variables.

Outcomes	CHA ₂ DS ₂ -VASC		CHADS ₂	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Primary outcome: MACE	1.323 (1.235–1.417)	<0.001	1.477 (1.368–1.594)	<0.001
Secondary and tertiary outcomes:				
MACE and major adverse limb events	1.32 (1.26–1.39)	<0.0001	1.46 (1.38–1.54)	<0.0001
All-cause mortality	1.397 (1.293–1.509)	<0.001	1.542 (1.415–1.681)	<0.001
Cardiovascular death	1.478 (1.332–1.641)	<0.001	1.701 (1.517–1.907)	<0.001
Myocardial infarction	1.123 (1.006–1.254)	0.039	1.233 (1.090–1.396)	<0.001
Ischemic stroke	1.608 (1.415–1.827)	<0.001	1.748 (1.517–2.014)	<0.001
Haemorrhagic stroke	0.971 (0.575–1.639)	0.912	1.052 (0.584–1.894)	0.867
Heart failure hospitalization	1.673 (1.507–1.857)	<0.001	1.872 (1.669–2.101)	<0.001
Major bleeding	1.108 (0.980–1.251)	0.101	1.132 (0.984–1.301)	0.082
Net-clinical-benefit outcomes	1.34 (1.27–1.42)	<0.0001	1.56 (1.45–1.67)	<0.0001

Cox proportional hazards model were used to determine the hazard ratios and 95% confidence intervals per 1-point increase in CHA₂DS₂-VASC or CHADS₂ scores. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events.

CHADS₂ scores appeared to predict composite outcomes slightly better than CHA₂DS₂-VASC scores with higher c-statistics and lower risk of bleeding. The treatment effects of rivaroxaban plus aspirin appeared similar across CHA₂DS₂-VASC and CHADS₂ scores with largest absolute benefits in patients with highest CHADS₂ scores.

Based on annual event rates, the pattern of reduced MACE and increased major bleeding with rivaroxaban plus aspirin was consistent across the spectrum of CHA₂DS₂-VASC and CHADS₂ scores. There was less consistency for less common outcomes including individual components of the primary outcome and all-cause mortality. This might be attributed to smaller sample sizes in each group stratified by the risk score to have adequate power to analyze the outcomes, especially the higher risk scores: CHADS₂ score of 5–6 group had 191 patients and CHA₂DS₂-VASC score of 6–9 had 1280 patients.

Several earlier studies have reported that CHADS₂ and CHA₂DS₂-VASC scores predicted vascular events in patients with no known AF [10,17,18]. The SHINANO registry in Japan demonstrated that in 1714 patients with coronary heart disease without AF undergoing percutaneous coronary intervention, both CHADS₂ and CHA₂DS₂-VASC score were independent predictors for MACE [10]. However, in contrast to our findings, discrimination was lower for CHADS₂ scores than CHA₂DS₂-VASC score (0.59 [95% CI: 0.54–0.64] vs. 0.64 [95% CI: 0.59–0.69], respectively, $p < 0.05$). Similarly, in a Caucasian community population with arterial hypertension in Trieste, Italy, the CHA₂DS₂-VASC score was able to predict thromboembolic events, cardiovascular hospitalization and all-cause mortality in both those with sinus rhythm ($n = 11,159$) and AF ($n = 1440$) [17].

Table 2

Treatment effects of combination therapy with rivaroxaban plus aspirin compared with aspirin alone over mean follow-up of 30 months.

	Number of events prevented per 1000 patients treated with rivaroxaban plus aspirin (95% confidence interval)		
	MACE	MACE/MALE	Net-clinical-benefit
CHA ₂ DS ₂ -VASC score group			
1–2	6 (–5.4 to 16.8)	8 (–3.6 to 20.1)	4 (–7.7 to 16)
3	15 (5.4 to 24.5)	19 (9.1 to 29.2)	10 (0.1 to 20.5)
4	13 (0.9 to 25.6)	12 (–0.5 to 25.2)	14 (1.4 to 26.9)
5	11 (–6.7 to 29.7)	17 (–2.1 to 36.1)	13 (–6.3 to 31.8)
6–9	23 (–7.3 to 53)	27 (–3.7 to 58.5)	20 (–11.4 to 50.6)
CHADS ₂ score group			
0	3 (–9.2 to 14.6)	3 (–10 to 15.3)	–2 (–14.9 to 11.1)
1	16 (7 to 24.8)	21 (11.7 to 30.5)	14 (4.5 to 23.5)
2	7 (–4.1 to 18)	6 (–5.5 to 17.8)	6 (–5.1 to 18)
3–6	25 (6.6 to 42.5)	31 (12.1 to 49.2)	24 (5.3 to 42.3)

MACE, major adverse cardiovascular events; MALE, major adverse limb events.

Several components of the CHADS₂ and CHA₂DS₂-VASC scores are also included in the REACH risk score which was used in an earlier publication to identify patients at highest risk of vascular events in the COMPASS cohort [19]. Furthermore, the Classification and Regression Trees (CART) survival analysis used in this same publication identified patients with heart failure or diabetes as being at high risk. This overlap between the CHADS₂ and CHA₂DS₂-VASC scores and the REACH and CART analyses supports the conclusion that any of these approaches can be used to identify patients who will derive the greatest net clinical benefit from treatment with the COMPASS regimen. The CHADS₂ and CHA₂DS₂-VASC scores are simpler and almost universally known risk scores; therefore, we believe that our evaluation of these scores will be more directly applicable to patients with CAD and/or PAD being considered for treatment with rivaroxaban plus aspirin.

Guidelines from the American College of Cardiology and American Heart Association [20], European Society of Cardiology [21], and National Institute for Health and Care Excellence [22] recommend anticoagulation in patients with AF and CHA₂DS₂-VASC score of 2 or greater for men and 3 or greater for women. However, these risk scores are usually not calculated in patients with ASCVD without AF. Our data shows that patients without AF with CHADS₂ score of 3 or more points had an estimated 4-fold higher risk of MACE compared to patients with low scores of 2 or less and derive the greatest benefit from the addition of rivaroxaban 2.5 mg twice daily. The CHADS₂ score appeared to be more discriminating compared with CHA₂DS₂-VASC score. This may be because CHA₂DS₂-VASC score assigns a point for female sex, yet outside of AF population, males may have comparable or higher rate of MACE [23–25]. Furthermore, an additional advantage of the CHADS₂ score over CHA₂DS₂-VASC score is that CHADS₂ score is simpler and can be easily applied at the bedside.

Combined therapy with rivaroxaban plus aspirin was beneficial across the spectrum of CHADS₂ and CHA₂DS₂-VASC scores, with consistent relative reductions in the risk of MACE, major adverse limb events, and mortality, and improved net clinical benefit. Although there was also a consistent increase in major bleeding, the absolute rates of severe bleeding were low, even in those with the highest risk scores, and there was no overall increase in intracerebral haemorrhage and fatal bleeding.

4.1. Study strengths

The strengths of this study consist of using comprehensive, prospective data available from the large randomised controlled trial, COMPASS which included patients with chronic CAD and/or PAD who were representative of those that are commonly encountered in general clinical practice, with follow-up with a mean duration of 23 months, and testing clinician-friendly validated risk scores.

4.2. Study limitations

However, this study was limited by being a post hoc subgroup analysis. Concerning translation of the findings to usual practice, both the CHA₂DS₂-VASC and CHADS₂ scores had only modest predictive abilities based on c-statistics, but similar to that seen in prediction of stroke in AF. A history of AF was not recorded at baseline, but patients who required anticoagulation (which includes most patients with AF) were not eligible for inclusion in COMPASS. Only a minority of COMPASS patients had CHA₂DS₂-VASC of 6–9 (7%) and CHADS₂ of 3–6 (19%), which limits the analysis comparing outcomes between risk scores, but patients with lower scores also derive a net benefit. Furthermore, CHA₂DS₂-VASC and CHADS₂ scores were only collected at baseline, therefore we could not analyze changes in risk scores during follow-up. Other risk factors (e.g., polyvascular disease, chronic kidney disease) not included in these scores also identify patients at higher risk of MACE. The analysis cannot assess whether CHA₂DS₂-VASC or CHADS₂ score would be discriminating among patients with atherosclerosis who were prescribed one of the P2Y₁₂ antagonist that are commonly prescribed in this population.

5. Conclusions

Overall, we demonstrated that the CHA₂DS₂-VASC and CHADS₂ scores, common tools already in widespread clinical use, predicted MACE in patients with chronic atherosclerotic vascular disease in sinus rhythm treated with aspirin +/- rivaroxaban. CHADS₂ scores had slightly better predictive performance than CHA₂DS₂-VASC scores. Patients with CHADS₂ scores of 3 or more showed greatest benefit from rivaroxaban plus aspirin compared to aspirin alone. Higher CHADS₂ and CHA₂DS₂-VASC scores were associated with higher bleeding risk in both treatment groups, but the incidence was low and net clinical benefit of dual pathway inhibition was maintained across all risk scores, particularly in the highest risk categories. Thus, calculating the CHADS₂ score in patients with ASCVD without AF may help identify patients most likely to benefit from dual pathway inhibition.

Conflicts of interest

J.S. and S.F. have no relationships relevant to the contents of this paper to disclose. A.T. reports research support, honoraria for Advisory Board participation or lectures, or travel grants from Amgen, Bayer, Boehringer Ingelheim, and Merck. J.V. reports grants from Bayer AG during the conduct of the study. S.B. conducted this work within the scope of his employment as a clinical research physician by Bayer U.S., LLC. S.Y. is supported by grants, speaker fees and travel expenses to meetings from Bayer AG for the COMPASS trial and other research studies, but no stocks or other interests in the company or its products. P.V. reports research grants from Bayer, Boehringer Ingelheim, Pfizer and BMS and personal fees from Bayer AG, Boehringer Ingelheim, Daiichi Sankyo, and Portola. T.V. reports personal fees from Bayer AG, Boehringer Ingelheim, Daiichi Sankyo, Sanofi, and Servier. S.S.A. is supported by a Tier 1 Canada Research Chair in Ethnicity and Cardiovascular Disease and the Michael G. DeGroot Heart and Stroke Foundation Chair in Population Health; and has received speaking honoraria and consulting fees from Bayer AG and Janssen. K.A.A.F. reports grants and personal fees from Bayer/Janssen during the conduct of the study; grants from AstraZeneca, personal fees from Sanofi/Regeneron, personal fees from Verseon, outside the submitted work. J.W.E. is supported by the Jack Hirsh Population Health Research Institute in Thrombosis and Atherosclerosis Mid-career award from the Heart and Stroke Foundation; and has received grants and personal fees from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Janssen, AstraZeneca, Eli Lilly, GlaxoSmithKline, and Sanofi. J.A. was an investigator in the COMPASS trial and has received personal fees for advising

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CRediT authorship contribution statement

Jonathan Sen: Conceptualization, Methodology, Software, Validation, Investigation, Formal analysis, Writing - original draft, Visualization. **Andrew Tonkin:** Investigation, Writing - review & editing. **John Varigos:** Investigation, Writing - review & editing. **Sylvanus Fonguh:** Software, Formal analysis, Visualization. **Scott D. Berkowitz:** Investigation, Writing - review & editing. **Salim Yusuf:** Investigation, Writing - review & editing. **Peter Verhamme:** Investigation, Writing - review & editing. **Thomas Vanassche:** Investigation, Writing - review & editing. **Sonia S. Anand:** Investigation, Writing - review & editing. **Keith A.A. Fox:** Investigation, Writing - review & editing. **John W. Eikelboom:** Supervision, Methodology, Investigation, Data curation, Writing - review & editing. **John Amerena:** Supervision, Conceptualization, Methodology, Investigation, Writing - review & editing, Project administration.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcard.2021.04.067>.

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