International Journal of Cardiology 292 (2019) 126–130

Contents lists available at ScienceDirect

International Journal of Cardiology

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

Atrial high-rate episodes and thromboembolism in patients without atrial fibrillation: The West Birmingham Atrial Fibrillation Project

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ARTICLE INFO

Article history:
Received 14 March 2019
Accepted 16 April 2019
Available online 17 April 2019

Keywords:
Atrial high-rate episode
CHA_2DS_2-VASc score
Cardiac implantable electronic device
Risk factor

ABSTRACT

Background: Patients with cardiac implantable electronic device (CIED) developing atrial high-rate episodes (AHRE) have a significant risk of thromboembolic events (TEs), but risk factors have been scarcely investigated.
Objectives: To analyze risk factors for TEs in a contemporary cohort of patients with CIED.
Methods: Consecutive non-AF patients without anticoagulation at baseline were followed up after the CIED implantation. The role of newly-developed AHRE and other risk factors for TEs were analyzed using a time-dependent Cox regression model and Kaplan-Meier analysis with log-rank tests.
Results: A total of 594 CIED patients were followed up for a mean of 4.2 years: 175 developed AHRE (29.5%; incident rate [IR] 8.80% per patient-year). Of those, 33 experienced TEs (5.5%; IR 1.38% per patient-year). Incidence of TEs was low in patients with a CHA_2DS_2-VASc score < 2 (male)/<3 (female) (AHRE vs. no-AHRE, 0.60% vs. 0.00% per patient-year, $p = 0.469$) and high in those with score ≥ 2 (male)/≥3 (female) (AHRE vs. no-AHRE, 2.12% vs. 1.36% per patient-year, $p = 0.209$), regardless of the AHRE presence. AHRE was not significantly associated with TEs (hazard ratio [HR], 1.46 [0.64–3.33]). There was no temporal relationship between AHRE and TEs. Baseline CHA_2DS_2-VASc score was *independently associated* with TEs (HR, 1.41 [1.13–1.75]) on multivariate analysis, but not AHRE.
Conclusions: Thromboembolic risk in patients with CIED is mainly driven by comorbidity burden, i.e., CHA_2DS_2-VASc score, rather than AHRE per se. Decision-making on stroke prevention needs to focus on comorbidity burden and not merely on the presence or absence of AHRE in CIED patients.

1. Introduction

Atrial high-rate episode (AHRE) is commonly seen in patients with a cardiac implantable electronic device (CIED) [1], whereby approximately 30% to 70% of patients with CIED developed AHRE at follow-up, depending on the clinical profile of the population studies, the definition and duration of AHRE [2,3]. AHRE has been associated with thromboembolic risk in CIED patients without atrial fibrillation (AF) [4,5].

Detection of AHRE with a duration of over 5 to 6 min was associated with a risk of subsequent development of clinical AF [2]. In AHRE patients, the risk of thromboembolic events (TEs) appears to be lower than clinical AF [4,6,7]. In addition, AHRE does not seem to be a direct cause for the increased risk, given the lack of a temporal connection between AHRE and TEs [4,8]. Indeed, a substantial proportion of patients had no AHRE before thromboembolic events [9]. Furthermore, there were no AHREs detected among patients in the thirty days before their TEs [9]. Whether AHRE and TE have a causality therefore remains unclear.

Accumulating clinical risk factors, such as previous stroke, heart failure (HF), vascular disease and age, are the major drivers of thromboembolic risk in AF and non-AF population. In a large cohort study (n = 42,987), the CHA_2DS_2-VASc score, a composite of clinical thromboembolic risk factors, was associated with thromboembolic risk even in non-AF population [10]. In patients with high CHA_2DS_2-VASc score (≥4), the absolute risk of TE was high regardless of the presence of AF (e.g., for a score of 4, 8.2% vs 9.7% for patients with and without AF) [10]. In other studies, the CHA_2DS_2-VASc score has also been associated with thromboembolic risk in non-AF subjects [11–13].

In the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) study [4], only patients with a high stroke risk were included (CHA_2DS_2-VASc ≥ 2, for aged over 65 and hypertensive); hence, this study did not include low stroke risk patients, among whom the role of AHRE remains unclear. In a Japanese cohort, the association between

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https://doi.org/10.1016/j.ijcard.2019.04.055
0167-5273/

AHRE and TEs was only shown in high-risk patients ($CHADS_2$ score > 2), but not in low-risk patients ($CHADS_2$ score 0–2) [8], suggesting that AHRE is perhaps more like a stroke risk modulator rather than an independent risk factor.

However, the role of AHRE and other risk factors has never been compared and investigated simultaneously in patients without AF. This study therefore was aimed at analyzing independent predictors of TEs in non-AF patients with CIED.

2. Material and methods

We included consecutive patients receiving a permanent pacemaker, implantable cardioverter defibrillator (ICD), or cardiac resynchronization therapy (CRT), who attended the cardiology department of Sandwell and West Birmingham Hospitals between January 1999 and January 2017. All these patients received a structured follow-up with 3–9 months of interval. The follow-up duration was defined as the time period from the date of device implantation to last date of hospital visit (including device clinic visit and specialist clinic visit). Information with regard to stroke, transient ischemic attack (TIA), systematic embolism and device recordings were ascertained at these visits. We retrospectively collected the data from the Clinical Data Archive of the National Health System (NHS). Patients were not involved in its conduct, and there was no impact on their care. Ethical review was therefore not required. Patient consent was not sought. AHRE was defined as an episode lasting at least 5 min with atrial rate ≥ 175 bpm, which criteria was similar to that used in the ASSERT study, enabling the exclusion of most noise from non-cardiac origin [4]. The accurate diagnosis of AHRE was reviewed by experts from cardiac electrophysiology team. Baseline demographic characteristics and medical conditions including comorbidities and medications were retrospectively collected. Data collection and secondary verification were performed independently by Y.G.L, K.M and D.P to guarantee data accuracy and quality. Patients with known AF and those on anticoagulation therapy were excluded from this study, considering they were demonstrated to have a significant impact on thromboembolic events.

The concomitant thromboembolic risk factors were grouped into the CHA_2DS_2-VASc score, which was retrospectively calculated using the baseline patient profile as follows: heart failure (HF), hypertension, age ≥ 75 (2 points), diabetes mellitus, previous stroke/TIA (2 points), vascular disease, age 65–75, female sex.

2.1. Definition of outcomes

The primary endpoint of this study was thromboembolic event including ischemic stroke (IS), TIA and systemic embolism (SE) (IS/TIA/SE), which were determined through reviewing medical records issued by experienced physicians or specialists. Computed tomography or magnetic resonance imaging was used to confirm in all patients who were suspected to have IS. TIA was defined as a sudden, focal neurological deficit of presumed vascular origin lasting <24 h. SE was defined as sudden loss of end-organ perfusion as documented by the use of imaging, surgery or autopsy.

This study was conducted in accordance with the EU Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki. Since our project was a review of anonymized data from patients under the care of the cardiology department of Sandwell and West Birmingham Hospitals NHS Trust as part of ongoing clinical audits, there was no requirement for the study to be approved by NHS Research Ethics Committee.

2.2. Statistical analysis

Continuous variables were expressed as the mean ± standard deviation (SD). Categorical variables were expressed as numbers and percentages. Student's *t*-test was used for comparison between continuous variables. Pearson chi-square test was used for analysis of categorical variables. The cumulative hazard of AHRE was illustrated using standard Kaplan-Meier analysis, and differences between groups were assessed using the log-rank test. Considering some AHREs were developed during follow-up, we created a time-dependent covariate to track the development of AHRE. The detection of AHRE > 5 min triggered a time-dependent variable that remained positive for the remainder of the follow-up period. Follow-up was censored when patients suffered endpoint events. All tests were two-tailed. A *p*-value < 0.05 was considered as statistically significant. Analyses were performed using SPSS Statistics, version 23.0 (IBM, SPSS Inc.) and STATA Software, version 14.0 (Stata Corp., College Station, TX).

3. Results

We studied 594 patients (60.6% male; mean age 69 years, SD = 14). During a mean of 4.2 years of follow-up (2393 patient-years) (SD = 2.7), 175 (29.5%) developed at least one episode of AHRE > 5 min, with an annual incidence of 8.8 per 100 patient-years. Median time from CIED implantation to detection of first AHRE > 5 min was 16 months (IQR 7–42 months).

Patients with AHRE were older, had a higher percentage of paced rhythm. Patients without AHRE had a higher implantable cardiac defibrillator (ICD) use and higher prevalence of HF and cardiomyopathy. The CHA_2DS_2-VASc and $CHADS_2$ scores were numerically higher in patients with AHRE compared to those without AHRE. A higher percentage of patients with the CHA_2DS_2-VASc score ≥ 2 (male)/≥3 (female) were found in patients with AHRE (Table 1).

3.1. Outcomes of thromboembolic events

A total of 33 patients experienced IS/TIA/SE with an incidence of 1.38 per 100 patient-years. Patients with TEs were older (73 ± 10 years vs. 69 ± 15 years, $p = 0.038$), and had higher CHA_2DS_2-VASc score (4.0 ±

Table 1
Baseline characteristics of subjects divided by AHRE and non-AHRE.

Characteristics	Total (n = 594)	No AHRE (n = 419)	AHRE (n = 175)	*p* value
Demographics				
Female	234 (39.4)	165 (39.4)	69 (39.4)	0.991
Age	69 ± 14	68 ± 15	72 ± 13	**0.001**
Age ≥ 65	402 (67.7)	268 (64.0)	134 (76.6)	**0.003**
Age ≥ 75	255 (42.9)	164 (39.1)	91 (52.0)	**0.004**
Device type				
PM	457 (76.9)	310 (74.0)	147 (84.0)	**0.008**
ICD	65 (10.9)	53 (12.7)	12 (6.9)	**0.039**
CRT	72 (12.1)	56 (13.4)	16 (9.1)	0.151
Comorbidities				
Hypertension	411 (69.2)	283 (67.5)	128 (73.1)	0.178
DM	167 (28.1)	118 (28.2)	49 (28.0)	0.968
Hyperlipidemia	375 (67.2)	261 (66.4)	114 (69.1)	0.539
Vascular disease	210 (35.4)	151 (36.0)	59 (33.7)	0.589
CAD	205 (34.6)	148 (35.3)	57 (32.9)	0.581
Stroke/TIA	59 (9.9)	40 (9.5)	19 (10.9)	0.627
HF	126 (21.2)	98 (23.4)	28 (16.0)	**0.045**
COPD	32 (6.6)	22 (5.4)	10 (5.9)	0.815
Cardiomyopathy	128 (22.0)	105 (25.5)	23 (13.5)	**0.001**
Stroke risk assessment				
$CHADS_2$	1.8 ± 1.2	1.8 ± 1.2	1.9 ± 1.2	0.218
CHA_2DS_2-VASc	3.2 ± 1.7	3.2 ± 1.8	3.4 ± 1.6	0.105
CHA_2DS_2-VASc ≥ 2 (male)/≥3 (female)	461 (77.6)	315 (75.2)	146 (83.4)	0.075

Values are mean ± SD or n (%). Bold emphasis represents P value < 0.05. AHRE = atrial high rate episode; PM = pacemaker; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; CRT = cardiac synchronization treatment; DM = diabetes mellitus; HF = heart failure; ICD = implantable cardiac defibrillator; TIA = transient ischemic attack.

Table 2
Cox regression analysis of risk factors for thromboembolic events.

Risk factors	Univariable analysis		Multivariable analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Atrial high-rate episodes	1.46 (0.64–3.33)	0.373	1.31 (0.51–3.38)	0.582
Age ≥ 65	2.91 (1.12–7.54)	0.028	2.67 (0.87–8.20)	0.086
Female	0.89 (0.44–1.82)	0.757	0.70 (0.30–1.65)	0.418
Heart failure	1.60 (0.71–3.57)	0.255	**7.40 (1.61–34.0)**	**0.010**
Vascular disease	1.32 (0.66–2.63)	0.434	0.63 (0.26–1.55)	0.316
Previous stroke/TIA	3.27 (1.47–7.29)	0.004	**3.76 (1.53–9.22)**	**0.004**
Hypertension	2.03 (0.84–4.92)	0.117	1.09 (0.39–3.05)	0.872
Diabetes mellitus	1.69 (0.83–3.44)	0.150	1.65 (0.75–3.60)	0.212
Hyperlipidemia	2.17 (0.89–5.29)	0.089	0.62 (0.19–1.99)	0.422
Cardiomyopathy	1.04 (0.43–2.53)	0.938	0.62 (0.19–1.99)	0.621

TIA = transient ischemic attach, HR = hazard ratio, CI = confidence interval.

1.5 vs. 3.2 ± 1.7, $p = 0.008$) compared with patients without TEs (see Supplementary Table S1). HF and previous stroke/TIA were independently associated with TE events (Table 2).

3.2. Atrial high-rate episode and thromboembolic risk

Patients with AHRE had a higher annual incidence of thromboembolic event (1.85% vs. 1.14%, $p = 0.373$). AHRE was not significantly associated with TEs (Table 3). After adjustment for risk factors, including HF, hypertension, age, diabetes mellitus, previous stroke/TIA, vascular disease and sex category, the association between AHRE and thromboembolic events remained non-significant (HR, 1.31 [0.51–3.38]; $p = 0.582$).

Among the 33 patients with TEs, 18 patients (54.5%) had no AHRE during follow-up, 7 (21.2%) had AHRE after events, and only 8 (24.2%) had AHRE prior to thromboembolic events. For the 8 patients, the mean time from first AHRE to thromboembolism was 20.8 ± 18.7 months.

3.3. CHA_2DS_2-VASc score and thromboembolic risk

A significant difference of accumulative hazard regarding CHA_2DS_2-VASc score groups was shown in Kaplan-Meir curves analysis (log-rank test *p* value = 0.036 (Fig. 1). The CHA_2DS_2-VASc score was significantly associated with thromboembolic risk, as a continuous variable (HR, 1.41 [1.13–1.75]) and as a dichotomous variable (HR, 3.32 [1.01–10.90], score ≥ 2 [male]/≥3 [female] vs. <2 [male]/<3 [female]).

Patients with CHA_2DS_2-VASc score < 2 (male)/<3 (female) had a low incidence of TEs regardless of the presence and absence of AHRE (AHRE vs. no-AHRE, 0.60% vs. 0.00% per patient-year, $p = 0.469$). In patients with a CHA_2DS_2-VASc score ≥ 2 (male)/≥3 (female), the incidence of TE events was high (AHRE vs. no-AHRE, 2.12% vs. 1.36% per patient-year, $p = 0.209$) (see Supplementary Fig. S1). In this high-risk group, AHRE patients were at numerically higher risk, but the difference was non-significant (HR, 1.45 [0.62–3.37], for AHRE vs. Non-AHRE).

4. Discussion

The major findings of this study are as follows: i) AHRE were non-significantly associated with increasing thromboembolic risk among CIED patients without AF; ii) incidence of TE increased according to the CHA_2DS_2-VASc score regardless of the presence of AHRE; and iii) the risk of TE was mainly driven by comorbidity burden, as is reflected by higher CHA_2DS_2-VASc score.

The extensive use of CIED and availability of long-term monitoring has made it easier to pick up AHRE in patients with CIED. AHRE has been associated with a higher risk of thromboembolic events in non-AF subjects [4]. However, AHRE and TE appear to have temporal disconnection with very few patients had AHRE in the month prior to their events [14]. The precise mechanism(s) of increased thromboembolic risk in patients with CIED and AHRE is yet to be determined.

Evidence of the association between AHRE and TE risk has been shown by several trials including ASSERT [4], TRENDS (A Prospective Study of the Clinical Significance of Atrial Arrhythmia Detected by Implanted Device Diagnostics) [9], and MOST (Atrial Diagnostics Ancillary Study of the MOde Selection Trial) [15]. In the ASSERT study, all the

Table 3
Hazard ratio of atrial high-rate episode on thromboembolic events.

Clinical outcomes	No-AHRE (n = 419)		AHRE (n = 175)		HR* (95% CI)	*p* value
	No. of events	%/year	No. of events	%/year		
IS/TIA/SE	18	1.14	15	1.85	1.46 (0.64–3.33)	0.373
IS	5	0.32	6	0.74	1.34 (0.35–5.16)	0.675
SE	2	0.13	3	0.37	2.55 (0.34–18.9)	0.361
TIA	11	0.70	7	0.87	1.37 (0.43–4.41)	0.599

* Adjusted with heart failure and previous stroke/transient ischemic attack. HR, hazard ratio. Other abbreviations see Table 1.

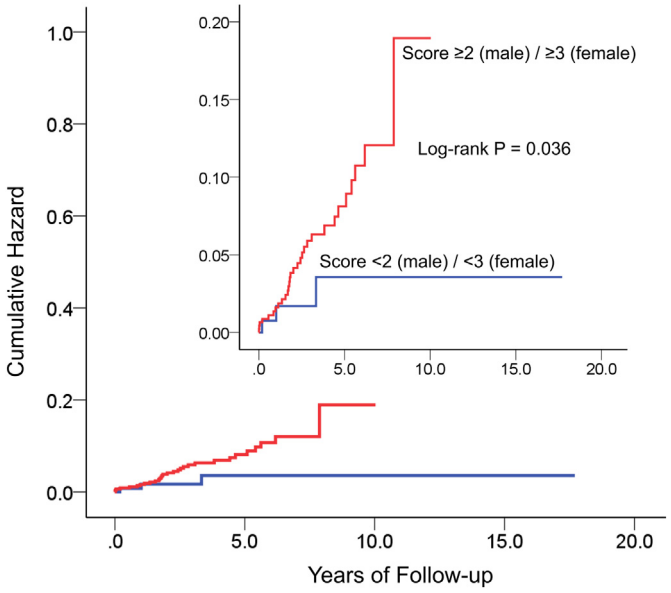

Fig. 1. Accumulated hazard curves of thromboembolic events according to the CHA_2DS_2-VASc score.

patients had high stroke risk (CHA_2DS_2-VASc score ≥ 2, or hypertensive and age ≥ 65 years) and AHREs were associated with thromboembolic risk (HR, 2.49; 95% CI, 1.28–4.85) [4]. In the MOST study, the presence of any AHRE was an independent predictor for death or nonfatal stroke (HR, 2.79; 95% CI, 1.51–5.15); while the association between AHRE and stroke events was not independently reported [15].

In these trials, AHRE and TEs were temporally disconnected. For example, in the ASSERT study, using a time-dependent multivariable analysis, the association between AHRE and thromboembolic risk was marginally significant (HR 1.77 [1.01–3.10], $p = 0.047$) [4]. Further, only 4 of 51 patients (8%) who experienced IS/SE had AHRE within 30 days before the events [4]. Also, the increased thromboembolic risk for AHRE was only shown among patients with $CHADS_2$ score > 2, suggesting that AHRE was be a TE modulator rather than risk factor per se [4]. Similarly, in the TRENDS study, TE events were not preceded by AHRE or AF, but the arrhythmia usually occurred after TE events [9]. Indeed, in the present study, 20 of the 40 patients had TE after AT/AF, 9 of whom did not show any AT/AF in the 30 days prior to the event [9]. Thus, although AHRE was demonstrated to increase thromboembolic risk in previous studies, causality remains weak in patients without AF.

In our study, we found a numerically higher incidence of TEs in patients with AHRE compared with non-AHRE patients (1.85% vs. 1.14% per patient-year), whilst the difference was not significant at multivariable analysis. A temporal disconnection between AHRE and TE events was also seen in this 'real world' study, similar to the previous trials. In our study, among the 33 patients with TE events, only 8 (24.2%) had AHRE prior to thromboembolic events. These findings confirmed that AHRE and TE events do not always occur in the pathophysiological time course, suggesting that AHRE might not be an immediate cause for thromboembolic events.

Whilst, we found that the thromboembolic risk was intimately related with the CHA_2DS_2-VASc score, which suggests that the development of TE events is driven by clinical risk factors. Indeed, in the low-risk group (CHA_2DS_2-VASc score < 2 [male]/<3 [female]), the incidence of TE was low, regardless of AHRE presence; while in the high-risk group (CHA_2DS_2-VASc score ≥ 2 [male]/≥3 [female]), both patients with and without AHRE had a high risk of TE. Although in the high-risk group, patients with AHRE had a higher incident rate compared with non-AHRE patients (2.03% per 100 patient-years vs. 1.38% per 100 patient-years), the difference was not significant. The different results between our study and previous studies may come from the relatively small population in the present study. We might hypothesize that underlying mechanisms of the increased (but not directly connected) thromboembolic risk may include the possibility that AHRE (including AF and other atrial tachycardia arrhythmias) simply embodies left atrial disease [16] or systemic disorders (e.g. inflammation, hypoxia and hypercoagulation) [17], which could contribute to thrombogenesis [18].

Duration of AHRE may also be another factor for thromboembolic risk as was demonstrated in a subgroup study of the ASSERT study [19]. In ASSERT, AHRE between 6 min to 24 h was not significantly different from patients without AHRE [19]. AHRE > 24 h was associated with a significantly higher risk of thromboembolism (HR 5.73 [2.41–13.64]) [19]. In general, an AHRE lasting for >24 h would be considered as clinical AF to a great extent [20], although not demonstrated in this subgroup study per se. As was demonstrated in the subgroup analysis of the ASSERT study, patients with longer subclinical AF were more likely to have other stroke risk factors, suggesting that confounders other than AHRE duration may be responsible for thromboembolic events. In the ASSERT study, all subjects were at high thromboembolic risk (CHA_2DS_2-VASc score ≥ 2, for aged ≥65, hypertension), while in the present study, both high and low thromboembolic risk patients were included. We found that in patients with CHA_2DS_2-VASc score < 2 (male)/<3 (female), the risk of thromboembolism was low (<1% per patient-year) regardless of AHRE presence.

In this study, the presence of other thromboembolic risk factors seemed more important, and considering that TE incidence was 1.38% per patient-year for patients with CHA_2DS_2-VASc score ≥ 2 (male)/≥3 (female) without AHRE, this may be already exceed the threshold for anticoagulation initiation in patients with AF (i.e. 0.9% per patient-year of thromboembolic risk for non-vitamin K antagonist anticoagulants) [21].

4.1. Strength and limitations

In this study, we demonstrated that the comorbidity burden (i.e., higher CHA_2DS_2-VASc score), plays an important role in increasing TE risk. Patients without AHRE had high annual stroke risk if associated with high CHA_2DS_2-VASc scores, appealing for more attention on this group of patients for stroke prevention. The relatively small low number of TEs may limit us from drawing a firm relationship between AHRE and the risk of TE. Also, we were unable to analyze the role of AHRE burden on thromboembolic risk, which might give more details regarding this topic, especially for the combined role of AHRE burden and the CHA_2DS_2-VASC score. In this study, we used 5 min as a cut off time duration for AHRE, which may have minor impact when comparing our results with those from previous studies. There were 8 patients who experienced AHRE prior to TE events, but we are unable to show if there was AHRE in one month before their events.

5. Conclusion

Thromboembolic risk in patients with CIED is mainly driven by cardiovascular risk factors, as reflected by the CHA_2DS_2-VASc score, rather than AHRE per se. Decision-making on stroke prevention needs to focus on other stroke risk factors, and not merely on the presence or absence of AHRE in CIED patients.

Acknowledgements

Y.G.L. and G.Y.H.L. are guarantors of the manuscript. Y.G.L., K.M., D.P., O.S., F.S. and G.Y.H.L. contributed to the original idea, data collection, and data analyses. Y.G.L., K.M., D.P. and G.Y.H.L contributed to the manuscript drafting and revisions.

Source of funding

This work was supported by China Scholarship Council (201708110232).

Conflicts of interest

None directly related to this paper. GYHL: Consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon and Daiichi-Sankyo. Speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are directly received personally.

Other authors: None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.04.055.

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