Non–vitamin K oral anticoagulants versus warfarin for the treatment of left ventricular thrombus

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ABSTRACT

Introduction: Left ventricular thrombus (LVT) is associated with significant morbidity and mortality. Conventional treatment comprises warfarin-mediated anticoagulation; it is unclear whether non–vitamin K oral anticoagulants (NOACs) exhibit comparable efficacy and safety. Limited data are available for Asian patients. This study compared NOACs with warfarin in terms of clinical efficacy and safety for managing LVT.

Methods: Clinical and echocardiographic records were retrieved for all adult patients with echocardiography-confirmed LVT at a major regional centre in Hong Kong from January 2011 to January 2020. Discontinuation of anticoagulation by 1 year was recorded. Outcomes were compared between patients receiving NOACs and those receiving warfarin. Primary outcomes were cumulative mortality and net adverse clinical events (NACEs). Secondary outcomes were complete LVT resolution and percentage reduction in LVT size at 3 months.

Results: Forty-three patients were included; 28 received warfarin and 15 received NOACs, with follow-up periods (mean ± standard deviation) of 20 ± 12 months and 22 ± 9 months, respectively (P=0.522). Use of NOACs was associated with significantly lower NACE risk (hazard ratio [HR]=0.111, 95% confidence interval [CI]=0.012-0.994; P=0.049) and a tendency towards lower cumulative mortality (HR=0.184, 95% CI=0.032-1.059; P=0.058). There were no significant differences in secondary outcomes. Considering LVT resolution, discontinuation of anticoagulation by 1 year was not significantly associated with different outcomes.

Conclusion: Non–vitamin K oral anticoagulants may be an efficacious and safe alternative to warfarin for LVT management. Future studies should explore the safety and efficacy of anticoagulation discontinuation by 1 year as an overall strategy.

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New knowledge added by this study

- In a Hong Kong cohort, non–vitamin K oral anticoagulant users had fewer net adverse clinical events and tended to exhibit lower mortality, compared with warfarin users.
- Considering left ventricular thrombus (LVT) resolution, discontinuation of anticoagulation by 1 year may be a safe overall strategy.

Implications for clinical practice or policy

- Non–vitamin K oral anticoagulants may be an efficacious and safe alternative to warfarin for LVT management.
- Further studies are needed to explore the safety and efficacy of anticoagulant discontinuation by 1 year as an overall strategy for patients with LVT resolution.

Introduction

Left ventricular thrombus (LVT) primarily occurs in patients who exhibit heart failure with reduced ejection fraction, particularly when these conditions are secondary to dilated cardiomyopathy or myocardial infarction. Recent advances in the treatment of myocardial ischaemia and heart failure have reduced the estimated incidence to 7 cases per 10 000 patients.[1] However, this lower incidence does not reduce the importance of identifying and treating LVT; one study has shown very high risks of major cardiovascular or cerebrovascular events and mortality in patients with LVT.[2]

Although LVT has conventionally been managed with warfarin, multiple guidelines suggest different treatment algorithms based on expert

opinion and small-scale studies, reflecting the lack of evidence that underlies such recommendations.[3,4] This lack of evidence is partly related to the low incidence of LVT, which hinders adequately powered research with high evidence quality. Considering the growing popularity of non–vitamin K oral anticoagulants (NOACs), there has been increasing interest in the use of NOACs as an alternative to warfarin for LVT management.[5] A systematic review in 2020, which involved only relevant case series and case reports, concluded that NOACs constitute a 'reasonable alternative' to warfarin for LVT management.[6] However, another 2020 study of >500 patients showed that NOACs increased the incidence of stroke or systematic embolism compared with warfarin.[7] Nonetheless, only thromboembolic events were compared in that study; safety outcomes, specifically bleeding events, were not investigated. Thus, it remains unclear whether NOACs exhibit efficacy and safety similar to warfarin for LVT management. This retrospective cohort study aimed to evaluate the efficacy and safety of NOACs versus warfarin for the treatment of LVT.

非維生素K抑制劑類口服抗凝血藥和華法林治療左心室血栓的比較

甘嘉豪、陳士楷、李沛威

引言：左心室血栓的發病率和死亡率十分高，傳統治療方法包括華法林介導的抗凝血藥；目前尚未清楚非維生素K抑制劑類口服抗凝血藥（NOACs）的效用和安全性是否與華法林相若。亞裔患者的數據有限。本研究比較NOACs和華法林在控制左心室血栓方面的臨床效用和安全性。

方法：我們研究於2011年1月至2020年1月期間，在香港一家主要地區醫院透過心臟超聲波檢查發現左心室血栓的所有成年患者的臨床及心臟超聲波記錄，紀錄這些患者停止抗凝血治療1年的情況。我們比較分別服用NOACs及華法林的患者的結果。主要結果是累積死亡率及淨不良臨床事件，次要結果是3個月後左心室血栓完全消退及左心室血栓範圍的減少百分比。

結果：本研究共包括43位患者，當中28位服用華法林，15位服用NOACs，兩者的隨訪時間（平均值 ± 標準差）分別為20 ± 12個月及22 ± 9個月（P=0.522）。使用NOACs與較低淨不良臨床事件風險顯著相關（風險比=0.111，95%置信區間=0.012-0.994；P=0.049），且累積死亡率趨向較低（風險比=0.184，95%置信區間=0.032-1.059；P=0.058）；次要結果方面未發現顯著差異。至於左心室血栓消退，停止抗凝血治療1年與不同結果無顯著相關。

結論：NOACs可能是控制左心室血栓有效安全的華法林替代品。日後研究應探索停止抗凝血治療1年作為整體治療策略的安全性及效用。

Methods

Patient population

This retrospective cohort study included all patients with LVT diagnosed by echocardiography from January 2011 to January 2020 at our institution, a major tertiary university hospital in Hong Kong. Only patients aged ≥18 years were included. Patients were excluded if baseline echocardiography, pharmacotherapy regimen or clinical records were non-retrievable, or if the type of anticoagulation therapy (warfarin or NOACs) was switched within the first 2 years after LVT diagnosis.

At our institution, all patients began anticoagulation therapy upon echocardiography-based diagnosis of LVT. Patients either received warfarin with titration and maintenance of a therapeutic international normalised ratio of 2-3, or they received NOAC therapy. Because there are no specific treatment recommendations in current guidelines, anticoagulant selection was performed at the treating physicians' discretion, generally considering patient-specific factors such as renal function, presence of other indications, and drug compliance. Follow-up echocardiography was performed 3 months after diagnosis of LVT, and further follow-up echocardiography was performed as clinically indicated. Anticoagulation was only discontinued if LVT had been resolved; this step required a shared, informed decision between the patient and the physician. Anticoagulation discontinuation was not considered for patients with persistent LVT.

Outcomes and measurements

All patients were followed up for ≤3 years. Echocardiographic images of all included patients at baseline and the 3-month follow-up were reviewed. The left ventricular ejection fraction, baseline size of LVT, and any resolution of LVT by the 3-month follow-up or the size of residual LVT at the 3-month follow-up were recorded. Clinical records of all patients were reviewed using the Clinical Management System of the Hong Kong Hospital Authority; important pre-morbid conditions, types of anticoagulants used, and pre-specified clinical outcomes were recorded. Any discontinuation of anticoagulation by 1 year was recorded.

The primary outcomes were cumulative mortality and net adverse clinical events (NACEs), defined as any of the following: ischaemic stroke, intracranial haemorrhage, systemic thromboembolism other than cerebral embolism, fatal bleeding (Bleeding Academic Research Consortium class 5[8]), and major non-fatal bleeding (Bleeding Academic Research Consortium class 3[8]). Secondary outcomes were complete resolution of LVT and percentage reduction of LVT size at the 3-month follow-up. Outcomes were also compared between patients who had discontinued anticoagulation by 1 year and those who continued anticoagulation for >1 year.

Statistical analysis

Unless otherwise specified, all continuous variables are expressed as mean ± standard deviation. Premorbid conditions and clinical outcomes in the two anticoagulation therapy groups were compared using Fisher's exact test (for dichotomous variables) or Mann-Whitney *U* test (for continuous variables); the Mann-Whitney *U* test was chosen over parametric tests because the sample sizes were unlikely to support an assumption of data normality. Kaplan-Meier survival curves were used to visualise survival status and freedom from NACEs throughout the study period; Cox regression was used to compare mortality and NACE use between the two groups. Cases with missing values were excluded from analysis of the respective variables; no imputation was performed. All P values were two-sided, and P<0.05 was considered statistically significant. All statistical analyses were performed using SPSS software (Windows version 25.0; IBM Corp, Armonk [NY], United States).

TABLE 1. Baseline characteristics of included patients*

	Warfarin cohort (n=28)	NOAC cohort (n=15)	P value
Male sex	24 (85.7%)	13 (86.7%)	1.000
Age, y	61 ± 16	61 ± 12	0.828
LVEDD, mm	59 ± 5	58 ± 4	0.858
LVEF, %	32 ± 15	28 ± 13	0.436
LVEF at 3-month follow-up, %	36 ± 12	38 ± 12	0.848
LVT size, mm	18.6 ± 7.7	17.5 ± 7.3	0.788
Ischaemic dilated cardiomyopathy	17 (60.7%)	12 (80.0%)	0.308
Smoking	12 (42.9%)	8 (53.3%)	0.540
Diabetes mellitus	4 (14.3%)	10 (66.7%)	0.001
Hyperlipidaemia	16 (57.1%)	11 (73.3%)	0.342
Hypertension	13 (46.4%)	9 (60.0%)	0.526
Stroke	4 (14.3%)	3 (20.0%)	0.680
Peripheral arterial disease	4 (14.3%)	0	0.280
Atrial fibrillation or flutter	1 (3.6%)	4 (26.7%)	0.043
Serum creatinine, μmol/L	95 ± 23	104 ± 15	0.372
Aspirin use	18 (64.3%)	8 (53.3%)	0.528

Abbreviations: LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVT = left ventricular thrombus; NOAC = non–vitamin K oral anticoagulant

* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified

TABLE 2. Comparison of outcomes between warfarin and non–vitamin K oral anticoagulant cohorts*

	Warfarin cohort (n=28)	NOAC cohort (n=15)	P value
Follow-up period, mo	20 ± 12	22 ± 9	0.522
Net adverse clinical events	13 (46.4%)	1 (6.7%)	0.049†
Ischaemic stroke	5 (17.9%)	0	
Intracranial haemorrhage	2 (7.1%)	1 (6.7%)	
Systemic thromboembolism	1 (3.6%)	0	
Fatal bleeding (BARC class 5)	4 (14.3%)	1 (6.7%)	
Major non-fatal bleeding (BARC class 3)	4 (14.3%)	0	
Cumulative mortality	12 (42.9%)	2 (13.3%)	0.058†
Resolution of LVT at 3-month follow-up	20 (71.4%)	13 (86.7%)	0.451
Reduction in LVT size at 3-month follow-up, %	88.1 ± 24.2	93.0 ± 18.8	0.390

Abbreviations: BARC = Bleeding Academic Research Consortium; LVT = left ventricular thrombus; NOAC = non–vitamin K oral anticoagulant

* Data are shown as No. (%) or mean ± standard deviation, unless otherwise specified

† Determined by Cox regression after adjustment for diabetes mellitus and atrial fibrillation/flutter

Results

In total, 43 patients (37 men) with LVT were included in this study: 28 received warfarin and 15 received NOACs. No patients were excluded for switching anticoagulant therapy during the first 2 years after LVT diagnosis. Of the patients treated with NOACs, 10 received apixaban, four received dabigatran, and one received rivaroxaban. Their baseline characteristics are summarised in Table 1; the two cohorts were generally comparable, except the NOAC cohort included more patients with diabetes mellitus (P=0.001) and atrial fibrillation or flutter (P=0.043). Eleven patients in the warfarin cohort and three patients in the NOAC cohort had non-ischaemic cardiomyopathy (P=0.308), including one patient with non-compaction cardiomyopathy and another patient (lost to follow-up after 6 months) with myocarditis. Both of these patients were in the warfarin cohort.

Three patients (all in the warfarin group) were lost to follow-up: one after 6 months (as noted above), one after 22 months, and one after 26 months. One of these patients had discontinued anticoagulation therapy by 1 year. The warfarin and NOAC cohorts were followed up for mean intervals of 20 ± 12 months (median, 20; interquartile range, 7-33) and 22 ± 9 months (median, 19; interquartile range, 15-31), respectively (P=0.522). All patients were examined by follow-up echocardiography at 3 months after initiation of anticoagulation therapy, except one patient in the warfarin cohort who died 1 month after diagnosis of LVT. In total, 14 deaths were observed in the NOAC (n=2; 13.3%) and warfarin (n=12; 42.9%) cohorts during the study period. Causes of death in the NOAC cohort were cardiovascular (sudden death; n=2); in the warfarin cohort, the causes of death were cardiovascular (n=8), intracerebral haemorrhage (n=3), gastrointestinal haemorrhage (n=1), and malignancy (n=2). Of the 34 patients who completed 1 year of follow-up, nine had discontinued anticoagulation therapy.

All primary and secondary outcomes are summarised in Table 2. We observed a significantly

lower risk of NACEs in the NOAC cohort (n=1 [6.7%] in the NOAC cohort vs n=13 [46.4%] in the warfarin cohort; hazard ratio [HR]=0.124, 95% confidence interval [CI]=0.016-0.952; P=0.045), which remained statistically significant after adjustment for the clinical statuses of diabetes mellitus and atrial fibrillation or flutter (HR=0.111, 95% CI=0.012-0.994; P=0.049) [Fig 1]. There was a tendency towards lower mortality in the NOAC cohort (n=2 [13.3%] in the NOAC cohort vs n=12 [42.9%] in the warfarin cohort; HR=0.285, 95% CI=0.064-1.275; P=0.101 [before adjustment of clinical statuses]), which remained similar after adjustment for the clinical statuses of diabetes mellitus and atrial fibrillation or flutter (HR=0.184, 95% CI=0.032-1.059; P=0.058) [Fig 2]. Numerically lower rates of ischaemic stroke (n=0 [0%] in the NOAC cohort vs n=5 [17.9%] in the warfarin cohort), major non-fatal bleeding (n=0 [0%] in the NOAC cohort vs n=4 [14.3%] in the warfarin cohort), and fatal bleeding (n=1 [6.7%] in the NOAC cohort vs n=4 [14.3%] in the warfarin cohort) were observed among patients receiving NOACs.

Concerning secondary outcomes, there were no significant differences between the two cohorts in LVT resolution (P=0.451) or percentage reduction in LVT size (P=0.390) at the 3-month follow-up.

The outcomes of patients whose had or had not discontinued anticoagulation therapy by 1 year are summarised in Table 3. There were no significant differences between the two cohorts.

Discussion

In this retrospective cohort study, we explored the use of NOACs as an alternative to warfarin for LVT management in a Hong Kong hospital. Although the sample size was limited, we found that NOAC use was associated with significantly fewer NACEs, with a tendency towards differences in cumulative survival. Additionally, anticoagulation discontinuation by 1-year post-diagnosis was not associated with significantly different clinical outcomes.

Our results confirm and extend previous findings concerning similar rates of LVT regression between NOAC and warfarin therapies; moreover, it has been reported that NOAC use is at least non-inferior to warfarin in terms of cumulative survival.[2] Importantly, we demonstrated significantly lower rates of NACEs in NOAC users, a key finding that was likely driven by tendencies towards reductions in ischaemic stroke and major non-fatal bleeding. The numerically lower rate of major non-fatal bleeding in NOAC users was consistent with previous findings of lower bleeding risk among patients receiving NOACs compared with patients receiving warfarin.[9-11] This reduction in bleeding risk is more prominent among Asian individuals than among non-Asian individuals.[12] Therefore, it is possible that clinical practice recommendations for Asian individuals should be different from that for non-Asian individuals.

A recent study by Abdelnabi et al[13] demonstrated significantly more effective resolution of LVT with rivaroxaban. We did not observe such

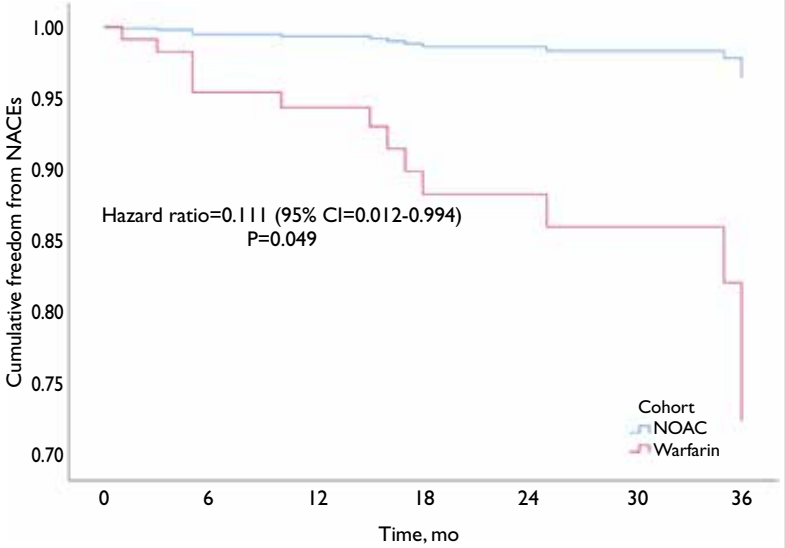

FIG 1. Kaplan-Meier curve of cumulative freedom from net adverse clinical events (NACEs) during the study period. The hazard ratio was calculated by Cox regression with adjustment for clinical statuses of diabetes mellitus and atrial fibrillation or flutter

Abbreviations: 95% CI = 95% confidence interval; NOAC = non–vitamin K oral anticoagulant

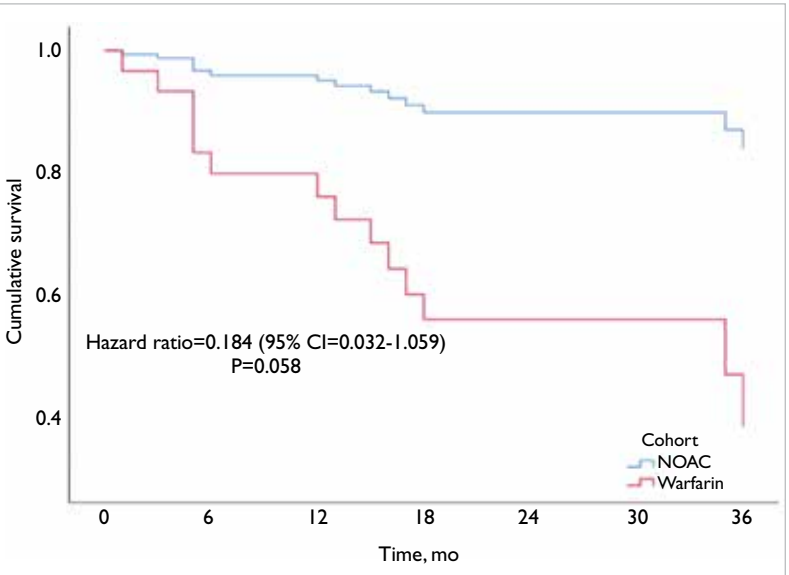

FIG 2. Kaplan-Meier curve of cumulative survival during the study period. The hazard ratio was calculated by Cox regression with adjustment for clinical statuses of diabetes mellitus and atrial fibrillation or flutter

Abbreviations: 95% CI = 95% confidence interval; NOAC = non–vitamin K oral anticoagulant

TABLE 3. Comparison of outcomes between patients with or without anticoagulation discontinuation at 1 year*

	Not discontinued (n=25)	Discontinued (n=9)	P value
NOAC use	15 (60.0%)	6 (66.7%)	1.000
Net adverse clinical events	6 (24.0%)	3 (33.3%)	0.275†
Ischaemic stroke	2 (8.0%)	2 (22.2%)	
Systemic thromboembolism	0	0	
Intracranial haemorrhage	2 (8.0%)	0	
Fatal bleeding (BARC class 5)	2 (8.0%)	0	
Major non-fatal bleeding (BARC class 3)	2 (8.0%)	1 (11.1%)	
Cumulative mortality	6 (24.0%)	2 (22.2%)	0.602†

Abbreviations: BARC = Bleeding Academic Research Consortium; NOAC = non–vitamin K oral anticoagulant

* Data are shown as No. (%), unless otherwise specified

† Determined by Cox regression after adjustment for diabetes mellitus and atrial fibrillation/flutter

a difference, consistent with recent findings by Iqbal et al.[14] These discrepancies may be related to differences in imaging intervals: we repeated echocardiography at 3 months and Iqbal et al[14] repeated imaging at a mean interval of 233 days, whereas Abdelnabi et al[13] repeated imaging at 1 month. Importantly, Abdelnabi et al[13] observed converging rates of thrombus resolution by 3 and 6 months after initiation of anticoagulation, when they performed additional imaging. It is thus possible that frequent imaging intervals (more frequent than that recommended by societal guidelines[3,4]) are required to demonstrate differences in the rate of thrombus resolution. Although the clinical benefits of NOACs in our cohort were mainly driven by a reduction in bleeding events, more rapid thrombus resolution may be relevant in other populations. Further investigation in this area may be warranted.

Another recent study by Robinson et al[7] revealed significantly higher rates of systemic thromboembolism among patients receiving NOACs, compared with those receiving warfarin. In the present study, systemic embolism was rare, and there were no pronounced numerical differences in the rates of systemic embolism between cohorts. Although this finding may be partly related to our small sample size, ethnic differences in thromboembolic tendencies could also play important roles. It has been observed that Asian individuals are generally less susceptible to thromboembolism than Caucasian and Hispanic individuals,[15] consistent with the rarity of systemic thromboembolism in our cohort. These findings may imply that any increase in systemic thromboembolism associated with NOAC use, as detected by Robinson et al,[7] is less relevant for Asian patients. Considering this lack of relevance and the reduction in NACEs observed in the present study, NOAC use may be preferrable to warfarin in Asian patients. Further studies with larger cohorts should be conducted to confirm these findings.

Additionally, we observed that considering the resolution of LVT, anticoagulation discontinuation by 1 year probably did not lead to significantly different rates of adverse outcomes, despite the numerically higher rate of cerebrovascular accidents. Although Lattuca et al[2] showed that anticoagulation for ≥3 months reduced the incidence of major adverse cardiovascular events, it has been unclear whether anticoagulation can be discontinued after resolution of LVT. Our results, derived from a small cohort, warrant further investigation in larger cohorts.

Limitations

There were several limitations in this study. First, the sample size was limited, primarily due to the rarity of LVT—although the study was conducted in a large tertiary hospital, only 43 patients could be included over a 9-year period. Second, various NOACs were used. Nonetheless, subgroup analysis was precluded by the small sample size; the present study design remains valid as a general comparison of vitamin K versus non–vitamin K anticoagulants, especially because all included NOACs are commonly prescribed. Third, more patients in the NOAC cohort had diabetes mellitus and atrial fibrillation or flutter. Despite these co-morbidities, we found that NOACs remained statistically superior to warfarin for NACEs; we also found a tendency for better cumulative mortality among patients receiving NOACs after adjustment for these two co-morbidities. Thus, our results remain valid in terms of demonstrating the probable superiority of NOACs over warfarin for LVT management in Asian patients.

Conclusion

The use of NOACs to treat patients with LVT was associated with significantly fewer NACEs, with a tendency towards lower cumulative mortality. Additionally, anticoagulation discontinuation by 1 year might be safe for patients with LVT resolution. Overall, NOACs may be superior to warfarin for LVT management. Further studies are required to confirm our findings and determine the optimal duration of anticoagulation therapy for LVT management.

Author contributions

Concept or design: KKH Kam, JSK Chan.
Acquisition of data: KKH Kam.
Analysis or interpretation of data: JSK Chan.
Drafting of the manuscript: JSK Chan.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

KKH Kam and JSK Chan have disclosed no conflicts of interest. APW Lee received grants, consulting fees/honoraria, and research support from Boehringer Ingelheim, Bayer, and Pfizer.

Declaration

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Ethics approval

This research was approved by The Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee (Ref No.: 2020.425). The need for individual patient consent was waived by the Committee due to the retrospective nature of the study.

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