BRIEF COMMMUNICATION

Inability to perform 'en bloc' pulmonary vein isolation requiring ablation of the intervenous carina increases recurrence of atrial fibrillation: A meta-analysis

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ABSTRACT

Introduction: Failure to isolate ipsilateral pulmonary veins (PV) 'en bloc' by wide-area circumferential ablation (WACA) may necessitate ablation at the intervenous carina. It is unknown how this scenario impacts rates of atrial fibrillation (AF) recurrence.

Methods: A standard random-effect meta-analysis of randomized or observational studies was performed, where the outcome of first-time AF ablation was reported in patients with 'en bloc' isolation of PVs by WACA as compares with those in whom ablation at the intervenous carina was needed after WACA to achieve complete isolation.

Results: A total of 5 single-centre, observational studies (N=1185) and one, multi-centre randomized trial (N=234) were enrolled. PV isolation could be achieved by WACA 'en bloc' in 902/1419 (63.6%) cases. The rest required additional ablation at one or both of the left and right intervenous carinas to achieve isolation. The follow-up time after ablation ranged from 1 to 2 years in the included trials. The incidence of AF recurrence proved to be significantly lower in patients with successful 'en bloc' isolation compared to those requiring carina ablation(s) to achieve complete bilateral PV isolation (MH-OR 1.89, 95% CI 1.42-2.53, $p<0.01$)

Conclusion: This present meta-analysis demonstrates a lower arrhythmia recurrence rate in patients with bilateral 'en bloc' isolation, as compared to those who needed additional carina ablation for complete PVI. Therefore, it is imperative that every effort be made to isolate ipsilateral PVs 'en bloc' during PVI.

ABBREVIATIONS

AF = atrial fibrillation; CI = confidence intervals; MH-OR = Mantel–Haenszel odds ratios; N = number; PV = pulmonary veins; PVI = pulmonary vein isolation; WACA = wide-area circumferential ablation.

Introduction

Isolation of the pulmonary veins (PVI) for atrial fibrillation (AF) is more effective by wide-area circumferential ablation (WACA) of ipsilateral pulmonary veins (PV) compared to sequential, ostial PVI [1]. When WACA fails to isolate ipsilateral PV pairs 'en bloc', catheter ablation of suspected epicardial connections between the PVs and atrial structures, predominantly at the intervenous carina, is undertaken [2]. However, failure of 'en bloc' PVI with the need for carina ablation may indicate a low quality of WACA, which may adversely increase AF recurrence rates [3]. Therefore, we performed a meta-analysis of studies where the outcome of AF ablation was reported in patients with 'en bloc' isolation of PVs by WACA, versus those in whom additional ablation at the intervenous carina was needed after WACA to achieve complete isolation.

Methods

A systematic search in MEDLINE database was performed up through March 2022 using the following key terms: 'carina ablation' OR 'en bloc isolation' OR 'wide area circumferential ablation' OR 'WACA' AND 'atrial fibrillation' OR 'pulmonary vein isolation'. Randomized or observational studies were eligible for inclusion if: i) they included patients undergoing first-time radiofrequency catheter ablation for paroxysmal/persistent AF; ii) ablation inside WACA was performed only in those in whom PV isolation was not achieved by WACA; iii) reported comparative data on recurrence rate of atrial arrhythmias in patients with/without lesions on the intervenous carina/inside WACA. Studies reporting data on the success rate of 'en bloc' isolation, but not specifying where additional lesions had been placed, were excluded. The detailed search protocol is available in Prospero Database (CRD42021254114). Mantel–Haenszel odds ratios (MH-OR) with 95% confidence intervals (CI) were calculated to pool data into a standard random-effect meta-analysis. Recurrence rate of AF was also analysed in subgroups of patients that needed carina ablation on only one vs. both sides. The I^2 test was used to determine the degree of heterogeneity across the studies. Analyses were performed using Comprehensive Meta Analysis v3.3.070 (Biostat, Inc., USA). Corresponding

authors were contacted for unpublished data and permission in cases of missing relevant data sets.

Results

From 142 studies, 5 single-centre, observational studies (total patients=1185) [2-6] and one international, multi-centre randomized trial (total patients=234) [7] were enrolled (Figure 1). PV isolation could be achieved by WACA 'en bloc' in 902/1419 (63.6%) cases and the rest required additional ablation at one or both of the left and right intervenous carinas. The follow-up time after ablation ranged from 1 to 2 years in the included trials. The incidence of AF recurrence was significantly lower in patients with successful 'en bloc' isolation as compared to those requiring additional carina ablation(s) to achieve complete bilateral PV isolation (MH-OR 1.89, 95% CI 1.42-2.53, $p<0.01$) (Figure 2A). A low degree of heterogeneity among studies was determined ($I^2=11\%$, $p=0.35$), confirming the results of the meta-analysis. Three studies also provided subgroup data for one-sided vs. two-sided carina ablation [3,4,6]. A gradual increase in estimated recurrence rate was observed when unilateral vs. bilateral carina ablation was required (16% for 'en bloc' PVI, 20% for one-sided carina ablation, 46% for two-sided carina ablation)(Figure 2B).

Discussion

This present meta-analysis of 5 observational and 1 randomized trial comprising 1419 patients undergoing first-time ablation for AF demonstrates lower arrhythmia recurrence rate in patients with bilateral 'en bloc' isolation as compared to those who required additional carina ablation for completion of PVI. There appears to be a dose-response relationship between the inability to perform 'en bloc' PVI on one vs. both sides and recurrence rates of AF. Of note, the present work is subject to all potential limitations of this type of analysis, particularly the relevant heterogeneity between ablation protocols used in the included studies should be mentioned (i.e. testing entrance and/or exit block, use of adenosine, different catheter or energy regimens, etc.).

The association between the failure to isolate the PVs without carinal ablation and recurrence of AF is not necessarily causal and differences in anatomical considerations between patients may play a significant role. Nevertheless, several findings suggest a lower quality of WACA may be associated with the need for carina ablation. Myocardial fibers from the upper and lower PVs intersect along the intervenous carina [8]. This unique arrangement may explain the frequent occurrence of carinal breakthrough after incomplete WACA, because preferential conduction by fibers spared by ablation along the WACA line can converge on the carina. Carinal breakthrough after WACA has been correlated with lower indices of lesion quality in the WACA line [3]. Hence, inadequate WACA may be considered as a reason behind higher recurrence in cases needing carina ablation.

Previous studies have shown the important role of the intervenous carina in persistent PV conduction after WACA [9]. This has led some authors to suggest routine carinal ablation to improve PV isolation rates [9]. Of note, the above cited paper by Udyavar et al. could not be included in the current meta-analysis, since the absolute numbers of patients with and without recurrence were not reported and could not be accessed. The strategy of routine carinal ablation was, however, discredited by a later randomized trial - that was included in this meta-analysis - which showed no effect on the outcome of PVI [7]. It also showed in a subgroup of patients, that the inability to perform 'en bloc' isolation by WACA, necessitating ablation at the carina, is detrimental. We corroborated this finding in this meta-analysis including all eligible studies and several hundreds of outcome events.

Conclusion

In patients undergoing first-time AF ablation, this meta-analysis of 5 observational and 1 randomized trials demonstrated lower arrhythmia recurrence rates with bilateral 'en bloc' isolation as compared to those who required additional carina ablation for completion of PVI. Therefore, 'en bloc' isolation of ipsilateral PVs is essential in AF ablation, and should be reliably achieved before considering less commonly targeted areas.

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FIGURE 1 PRISMA flow-chart of study selection

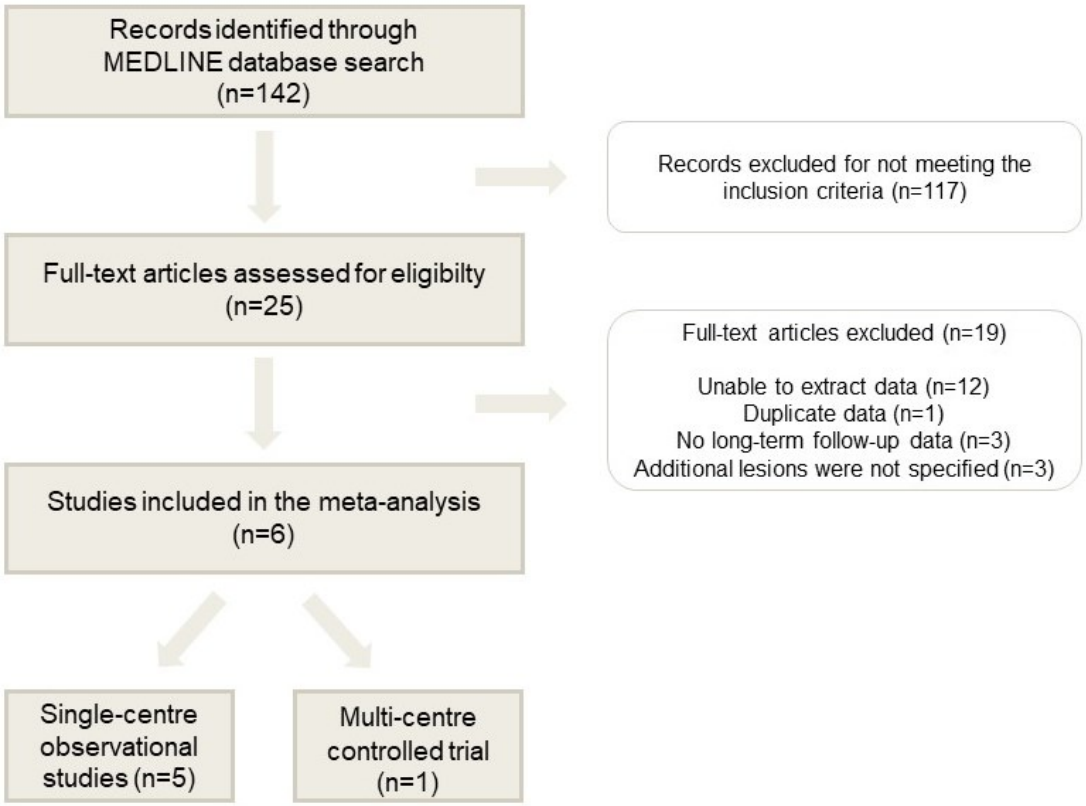
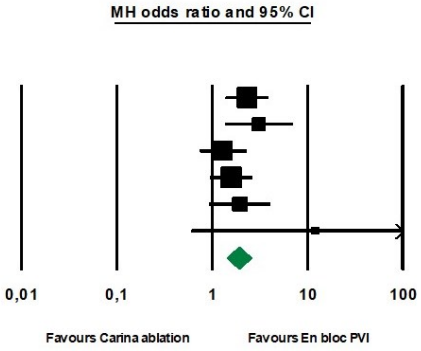


FIGURE 2

PANEL A Forest plot of studies comparing the effect 'en bloc' PVI vs. PVI requiring additional carina lesions on one or both sides.

Study name	Recurrance / Total		Statistics for each study			
	Carina ablation	En block PVI	MH odds ratio	Lower limit	Upper limit	p-Value
Takigawa et al. 2014 (PMID 24366102)	75 / 220	24 / 132	2,33	1,38	3,93	0,00
McLellan et al. 2015 (PMID 25920401)	22 / 51	13 / 66	3,09	1,36	7,03	0,01
Mulder et al. 2020 (PMID 32406138)	39 / 105	34 / 109	1,30	0,74	2,30	0,36
Barrio-Lopez et al. 2020 (PMID 31940223)	31 / 70	143 / 427	1,58	0,95	2,64	0,08
Jankelson et al. 2022 (PMID 34911157)	14 / 53	25 / 161	1,95	0,93	4,11	0,08
Pap et al. 2022 (J AFIB&EP)	8 / 18	0 / 7	12,14	0,60	244,42	0,10
			1,89	1,42	2,53	0,00



PANEL B Subgroup analysis of studies which provided comparative data of patients with 'en bloc' PVI vs. one-sided vs. bilateral carina ablation (event rate=rate of AF recurrence)

Study name	Statistics for each study				
	Total	Event rate	Lower limit	Upper limit	p-Value
Takigawa 2014 (En bloc)	24 / 132	0,18	0,12	0,26	0,00
Jankelson 2022 (En bloc)	25 / 161	0,16	0,11	0,22	0,00
Pap 2022 (En bloc)	0 / 7	0,06	0,00	0,54	0,06
		0,16	0,08	0,28	0,00
Takigawa 2014 (One-sided carina abl.)	49 / 150	0,33	0,26	0,41	0,00
Jankelson 2022 (One-sided carina abl.)	3 / 44	0,07	0,02	0,19	0,00
Pap 2022 (One-sided carina abl.)	1 / 8	0,13	0,02	0,54	0,07
		0,20	0,10	0,36	0,00
Takigawa 2014 (Bilateral carina abl.)	26 / 70	0,37	0,27	0,49	0,03
Jankelson 2022 (Bilateral carina abl.)	4 / 9	0,44	0,18	0,75	0,74
Pap 2022 (Bilateral carina abl.)	7 / 10	0,70	0,38	0,90	0,22
		0,46	0,28	0,66	0,73
		0,25	0,11	0,47	0,03