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Complications in pulmonary vein isolation in the Netherlands Heart Registration differ with sex and ablation technique

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Aims Pulmonary vein isolation (PVI) has become a cornerstone of the invasive treatment of atrial fibrillation. Severe complications are reported in 1–3% of patients. This study aims to compare complications and follow-up outcome of PVI in patients with atrial fibrillation.

Methods and results The data were extracted from the Netherlands Heart Registration. Procedural and follow-up outcomes in patients treated with conventional radiofrequency (C-RF), multielectrode phased RF (Ph-RF), or cryoballoon (CB) ablation from 2012 to 2017 were compared. Subgroup analysis was performed to identify variables associated with complications and repeat ablations. In total, 13 823 patients (69% male) were included. The reported complication incidence was 3.6%. Patients treated with C-RF developed more cardiac tamponades (C-RF 0.8% vs. Ph-RF 0.3% vs. CB 0.3%, $P \leq 0.001$) and vascular complications (C-RF 1.7% vs. Ph-RF 1.2% vs. CB 1.3%, $P \leq 0.001$). Ph-RF was associated with fewer bleeding complications (C-RF: 1.0% vs. Ph-RF: 0.4% vs. CB: 0.7%, $P = 0.020$). Phrenic nerve palsy mainly occurred in patients treated with CB (C-RF: 0.1% vs. Ph-RF: 0.2% vs. CB: 1.5%, $P \leq 0.001$). In total, 18.4% of patients were referred for repeat ablation within 1 year. Female sex, age, and CHA_2DS_2-VASc were independent risk factors for cardiac tamponade and bleeding complications, with an adjusted OR for female patients of 2.97 (95% CI 1.98–4.45) and 2.02 (95% CI 1.03–4.00) respectively.

Conclusion The reported complication rate during PVI was low. Patients treated with C-RF ablation were more likely to develop cardiac tamponades and vascular complications. Female sex was associated with more cardiac tamponade and bleeding complications.

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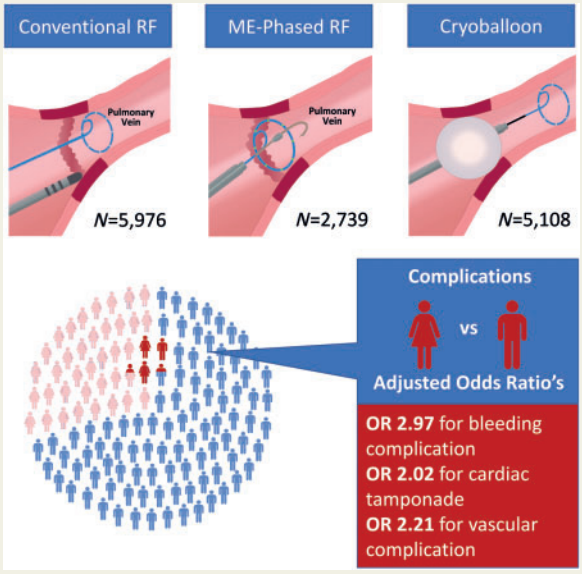
Graphical Abstract



Keywords Atrial fibrillation • Pulmonary vein isolation • Conventional radiofrequency ablation • Multielectrode phased radiofrequency ablation • Cryoballoon

What's new?

- We describe procedural outcomes of three different ablation techniques for pulmonary vein isolation [PVI; conventional radiofrequency (RF), multielectrode phased RF, and cryoballoon ablation] in a large nationwide registry with 13 823 patients.
- The overall reported complication rate during and after PVI was low, irrespective of the ablation technique used. Mortality at 30 days was 0.04%.
- Female sex was associated with an increased risk for developing cardiac tamponade or bleeding complication.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia. The number of patients developing AF is increasing rapidly, with an estimated prevalence of 17.9 million in 2060 within the European Union.[1] Although detection and treatment of AF have improved over the last decades, AF remains associated with an increased risk of mortality and comorbidity.[2] The treatment of AF consists of anticoagulation (in patients at increased stroke risk), and rhythm or rate control. Pulmonary vein (PV) isolation has emerged as an ablation strategy to eliminate triggers of AF, arising from the PVs and maintain sinus rhythm in patients with AF. In comparison with antiarrhythmic drug therapy, PV isolation is more effective at maintaining sinus rhythm, improves quality of life, and has been suggested to reduce mortality in heart failure patients.[3–5] Technologies in AF ablation are continuously emerging, resulting in a higher rate of success (defined as the absence of AF recurrence) and fewer procedural complications.[6] Depending on the type of AF and the rhythm recording used, the 1-year freedom from AF after PV isolation varies between 56% and 81%.[5,7–10] However, in the current literature, severe complications are reported in 1–3% of patients.[7,11] The type of complication and the incidence vary among different ablation modalities and patient characteristics. Female sex, age, and CHA_2DS_2-VASc score have been associated with an increased risk for developing complications.[11]

In the Netherlands, the most commonly used modalities for PV isolation are conventional radiofrequency (C-RF) wide antrum isolation, multielectrode phased radiofrequency ablation (Ph-RF), and cryoballoon (CB). The Netherlands Heart Registration is a nationwide registry in which the procedural and follow-up outcome of all invasive cardiac and cardiothoracic surgical procedures from 22 high-volume heart centres are recorded. The aim of this large-scale registry-based study is to compare procedural complications and follow-up outcome of C-RF, Ph-RF, and CB ablation modalities with a focus on procedural safety.

Methods

The aim of this study is to describe procedural complication incidence and to compare complications and follow-up outcome of PV isolation in patients with AF who were treated with one of the following ablation

modalities: conventional RF (multiple vendors), multielectrode phased RF (PVAC, Medtronic, Minneapolis, MN, USA) or cryoballoon (Medtronic, Minneapolis, MN, USA). All patients received ablation therapy from January 2012 to December 2017. Data were extracted from the value-based healthcare (VBHC) programme, which is part of the Netherlands Heart Registration (NHR). In this programme, which focusses on measuring and improving outcomes that matter most to patients, 22 Dutch cardiac centres submit baseline characteristics procedural, and outcome data on complex cardiac procedures. Fourteen out of 16 Dutch ablation centres participated in presenting the outcomes of AF ablation.

Patients who, apart from the index PV isolation which led to inclusion in the registry, received a previous left atrium (LA) ablation in a non-participating centre or before the start of the registry were also included in this study. The NHR database is stored on a local driver at the Amsterdam University Medical Centres, Amsterdam, The Netherlands. The local ethics committee from Catharina Hospital, Eindhoven, The Netherlands issued a waiver for informed consent for the current analysis of the anonymized data.

NHR VBHC programme

Participating hospitals delivered a predefined dataset to the NHR VBHC programme. The following variables were collected for AF patients. (i) Patient demographics included: age, sex, height, weight, type of AF (paroxysmal ≤ 7 days, persistent > 7 days–1 year and longstanding persistent > 1 year),[4] CHA_2DS_2-VASc score (one point for, congestive heart failure, hypertension, age ≥75 (2), diabetes, stroke (2), vascular disease, age 65–74 and sex), previous LA ablation, LA volume index (mL/m^2), left ventricle ejection fraction, and pre-operative mitral valve regurgitation. (ii) Procedural outcome variables included: ablation volume [cut-off values were selected based on tertiles of PV isolations/year and categorized as; low 34–108 PV isolations/year ($k = 5$), medium 144–183 PV isolations/year ($k = 5$), or high 207–381 PV isolations/year ($k = 6$)], ablation method (C-RF, Ph-RF, CB, other) cardiac tamponade within 30 days (for which intervention was required), thromboembolic complication within 72 h, bleeding complication during the hospital stay, vascular complication within 30 days, and persistent phrenic nerve palsy (PNP) (lasting ≥ 24 h). Thromboembolic event included ischaemic stroke, peripheral embolism, and pulmonary embolism. Bleeding was considered a complication if it was Bleeding Academic Research Consortium (BARC) criteria Type 2 or higher. This included, any actionable sign of haemorrhage (Type 2), overt bleeding plus haemoglobin drop of 1.86–3.10 mmol/L or any transfusion with overt bleeding (Type 3a), overt bleeding with haemoglobin drop of > 3.10 mmol/L, bleeding requiring surgical intervention, or intravenous vasoactive agents (Type 3b), intra-cranial or -ocular bleeding (Type 3c), and fatal bleeding (Type 5). The Type 3b complication cardiac tamponade was collected separately since this is an important complication during PV isolation.[12] Minor and major vascular complication criteria from the Valve Academic Research Consortium 2 (VARC-2) were used for the diagnosis of vascular complication.[13] The variables vascular complication and PNP were added as outcome variables from 2016 onwards. (iii) Follow-up outcome variables included: repeat LA ablation within 1 year, and live status was confirmed with the municipal death registration (Basisregistratie Personen) to determine 30-day mortality. Repeat LA ablation within 1-year included all patients who were reassigned for LA ablation after 10–14 months. Both, surgical and transvenous approach were considered as repeat LA ablation. To obtain reliable data, the NHR has an advanced, certified data-quality control system in place, and an audit by the NHR on AF outcomes was completed in 2018. Furthermore, additional analysis on deviating outcomes and outliers (defined as two times the standard deviation of the cohort mean) was performed and compared to previous years. The ablation strategy used was at the discretion of, and selected by the participating centre, based on operator preference and patient characteristics. All centres used a locally approved ablation protocol.

The complication incidence of PV isolation was compared between patients treated with C-RF, Ph-RF, and CB ablation. A subgroup analysis for complications and repeat LA ablation was performed with the characteristics sex, age, height, weight, body mass index (BMI), CHA_2DS_2 VASc, type AF, previous LA ablation, AF ablation volume, and ablation method.

Statistical analysis

Normally distributed continuous variables are presented as mean and a standard deviation, non-normally distributed as median and interquartile range, and categorical variables as number and percentages. Parametric one-way ANOVA or a non-parametric Kruskal–Wallis test, in case of non-normality, is used for statistical analysis of continuous variables between the ablation modalities. A χ^2 test was used to compare frequencies between groups. Univariable logistic regression analysis is performed with the occurrence of procedural complications and repeat LA ablation as dependent variables and ablation modality and the baseline characteristics as independent variables. For each variable, odds ratios (ORs) with corresponding 95% confidence intervals (CIs) and *P*-values are reported. Variables with a *P*-value < 0.1 are included in a multivariable logistic regression analysis. If the *P*-values for BMI and height or weight are < 0.1, multivariable analysis is presented with BMI. For the variables age, BMI, height, and weight used in the logistic regression, we used increments of 10 years, 5 points, 10 cm, and 10 kg, respectively.

Statistical package for the social science (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

In total, 13 823 consecutive patients (C-RF $n = 5976$, Ph-RF $n = 2739$, and CB $n = 5108$) were included, of whom, 15% ($n = 2056$) had an LA ablation prior to the ablation in the registry. Ablation modality of the prior LA ablation was not documented in the database. Baseline demographics per ablation modality are listed in *Table 1*. Sixty-nine percent ($n = 9532$) of the patients were male, and mean age was 60.0 ± 9.9 years, mean CHA_2DS_2-VASc 1.5 ± 1.3, and BMI was 27.3 ± 4.1 kg/m^2. Paroxysmal, persistent, and longstanding persistent AF was present in 73.8%, 23.7%, and 2.5%, respectively of patients. Of the patients with paroxysmal AF 38%, 21.7%, and 40.3% underwent C-RF, Ph-RF, or CB, respectively. In persistent AF, 54.6% were treated with C-RF, 15.3% Ph-RF, and 30.1% CB ablation. Patients with longstanding persistent AF were most frequent treated with C-RF ablation (65.1%) compared to Ph-RF (11.8%) and CB (23.1%) ablation. Of the 2056 patients who had received an LA ablation before the ablation in this registry, 1782 (86.7%) were treated with C-RF in comparison with 59 patients (2.9%) with Ph-RF and 215 patients (10.4%) with CB ablation.

Procedural outcomes

Pulmonary vein isolation with all three strategies combined was associated with an overall complication rate of 3.6% within 30 days. Data for cardiac tamponade, for which intervention was required were reported in 13 706 (99.2%) patients and observed in 69 (0.5%) patients. Cardiac tamponade was more commonly seen in patients treated with C-RF (C-RF: 0.8% vs. Ph-RF: 0.3% vs. CB: 0.3% $P \leq 0.001$). Thromboembolic events were registered in 13 636 (98.7%)

Table 1 Baseline characteristics

	Conventional RF ($n = 5976$)	Phased RF ($n = 2739$)	Cryoballoon ($n = 5108$)	*P*-value
Male	4216 (70.5)	1886 (68.9)	3430 (67.1)	0.001
Age	60.5 ± 9.9	60.5 ± 10	60.4 ± 9.9	0.713
Body mass index (kg/m^2)	$n = 5851$	$n = 2676$	$n = 4995$	<0.001
	27.4 ± 4.2	26.9 ± 3.8	27.3 ± 4.3	
CHA_2DS_2-VASc	$n = 5759$	$n = 2690$	$n = 5083$	0.155
	1.5 ± 1.3	1.5 ± 1.3	1.5 ± 1.3	
LAVI (mL/m^2)	$n = 2654$	$n = 1224$	$n = 2492$	<0.001
	36.5 ± 12.4	34.1 ± 9.9	34.3 ± 10.7	
LV ejection fraction (%)	$n = 4562$	$n = 2205$	$n = 4537$	<0.001
	52.8 ± 6.4	53.8 ± 5.2	54.3 ± 5.5	
Mitral valve regurgitation	$n = 5013$	$n = 2465$	$n = 4484$	<0.001
None/mild	4628 (92.3)	2285 (92.7)	4260 (95)	
Moderate	377 (7.5)	179 (7.3)	216 (4.8)	
Severe	8 (0.2)	1 (0.0)	8 (0.2)	
Type atrial fibrillation	$n = 5806$	$n = 2725$	$n = 5085$	<0.001
Paroxysmal	3821 (65.8)	2192 (80.4)	4043 (79.3)	
Persistent	1759 (30.3)	492 (18.1)	971 (19.1)	
Longstanding persistent	226 (3.9)	41 (1.5)	80 (1.6)	
Previous LA ablation	$n = 5968$	$n = 2739$	$n = 5102$	<0.001
	1782 (29.9)	59 (2.2)	215 (4.2)	

CHA_2DS_2-VASc, congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, age, sex; LAVI, left atrium volume index; LV, left ventricle; LA, left atrium, RF, radiofrequency.

Table 2 Complications

	Conventional RF	Phased RF	Cryoballoon	*P*-value
Bleeding complication	$n = 5942$	$n = 2739$	$n = 5106$	0.020
	58 (1.0)	12 (0.4)	35 (0.7)	
Cardiac tamponade	$n = 5954$	$n = 2731$	$n = 5021$	<0.001
	47 (0.8)	7 (0.3)	15 (0.3)	
Thromboembolic event	$n = 5893$	$n = 2654$	$n = 5089$	0.32
	16 (0.3)	11 (0.4)	22 (0.4)	
Phrenic nerve palsy	$n = 2235$	$n = 590$	$n = 2597$	<0.001
	2 (0.1)	1 (0.2)	38 (1.5)	
Vascular complication	$n = 2208$	$n = 585$	$n = 2515$	<0.001
	37 (1.7)	7 (1.2)	33 (1.3)	
30-day mortality	$n = 4534$	$n = 972$	$n = 4970$	0.81
	2 (<0.1)	0	2 (<0.1)	
Repeat LA ablation	$n = 3024$	$n = 1582$	$n = 3002$	<0.001
	738 (19.6)	544 (25.6)	430 (12.5)	
Repeat LA ablation (without patients with previous LA ablation)	$n = 1959$	$n = 1539$	$n = 2856$	<0.001
	554 (22.0)	532 (25.7)	407 (12.5)	

Comparison between three different modalities, conventional RF, phased RF, and cryoballoon. Bleeding complication during the hospital stay defined as Bleeding Academic Research Consortium criteria type 2 or higher, vascular complication within 30 days defined as minor or major complications according to the Valve Academic Research Consortium 2, cardiac tamponade within 30 days (for which intervention was required), thromboembolic event within 72 h (including ischaemic stroke, peripheral embolism, and pulmonary embolism), phrenic nerve palsy >24 h.
LA, left atrium; RF, radiofrequency.

patients and occurred in 0.4% ($n = 49$) of the patients, with no statistically significant difference among ablation modalities (C-RF: 0.3% vs. Ph-RF: 0.4% vs. CB: 0.4% $P = 0.32$). Data for bleeding complication were reported in 13 787 (99.7%) patients. In total, 105 (0.7%) patients had a bleeding complication during hospital stay. The lowest incidence was observed in patients treated with Ph-RF (C-RF: 1.0%

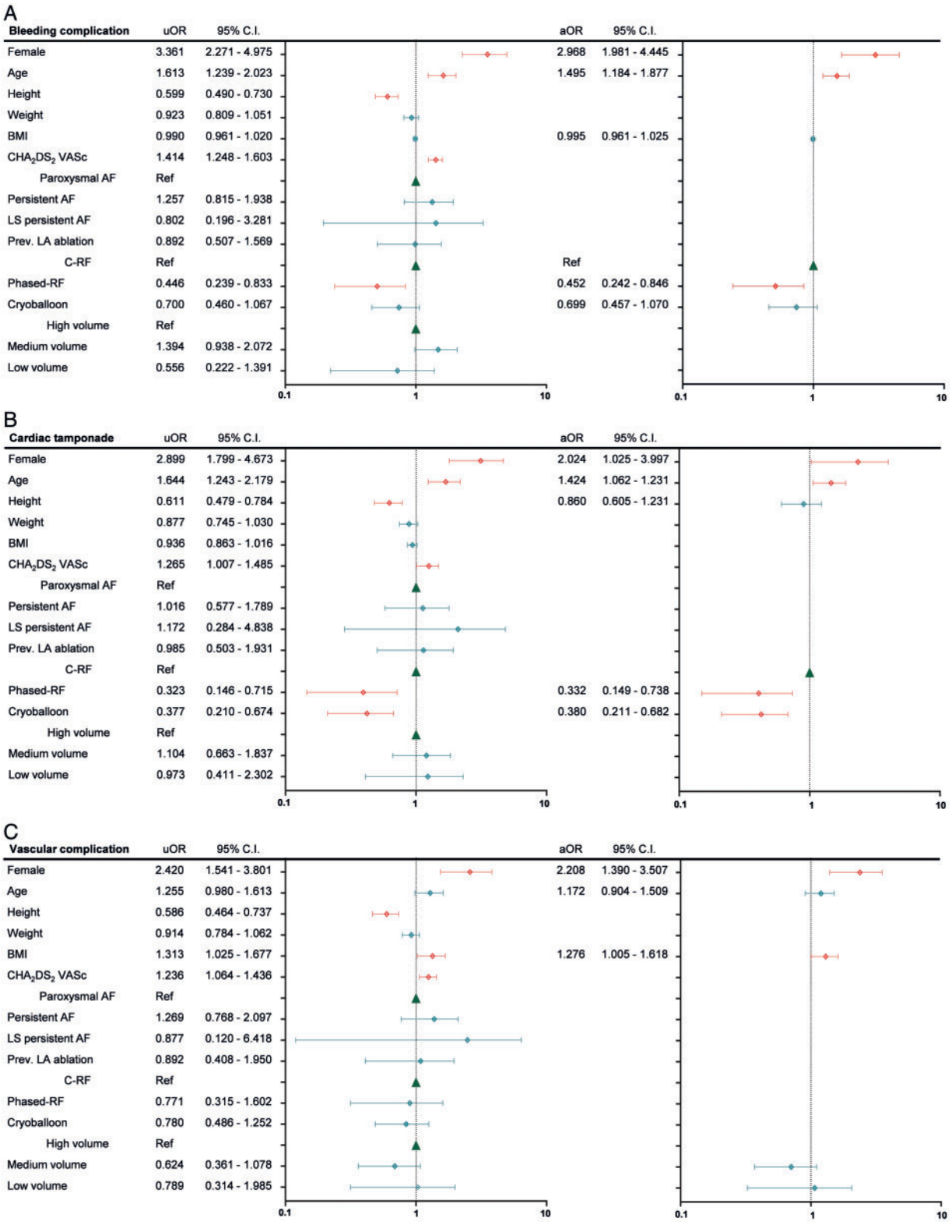


Figure 1 A-E Logistic regression analysis for complications. uORs with corresponding 95% CI are presented in the left table and forest plot. Statistically significant variables are presented in red. Multivariable analyses were performed with variables with a *P*-value < 0.10. aORs with the corresponding 95% CI are presented in the right table and forest plot. Age is presented with an increment of 10 years, height with 10 cm, weight with 10 kg, and BMI with 5 points. AF, LS, CHA_2DS_2-VASc, LA, and RF. Ablation volume categorized as low- 34–108, medium- 144–183, or high-volume 207–381 PV isolations included in the registry per year. AF, atrial fibrillation; aORs, adjusted odds ratios; BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, age, sex; CI, confidence interval; LA, left atrium; LS, longstanding; RF, radiofrequency; uORs, unadjusted odds ratios.

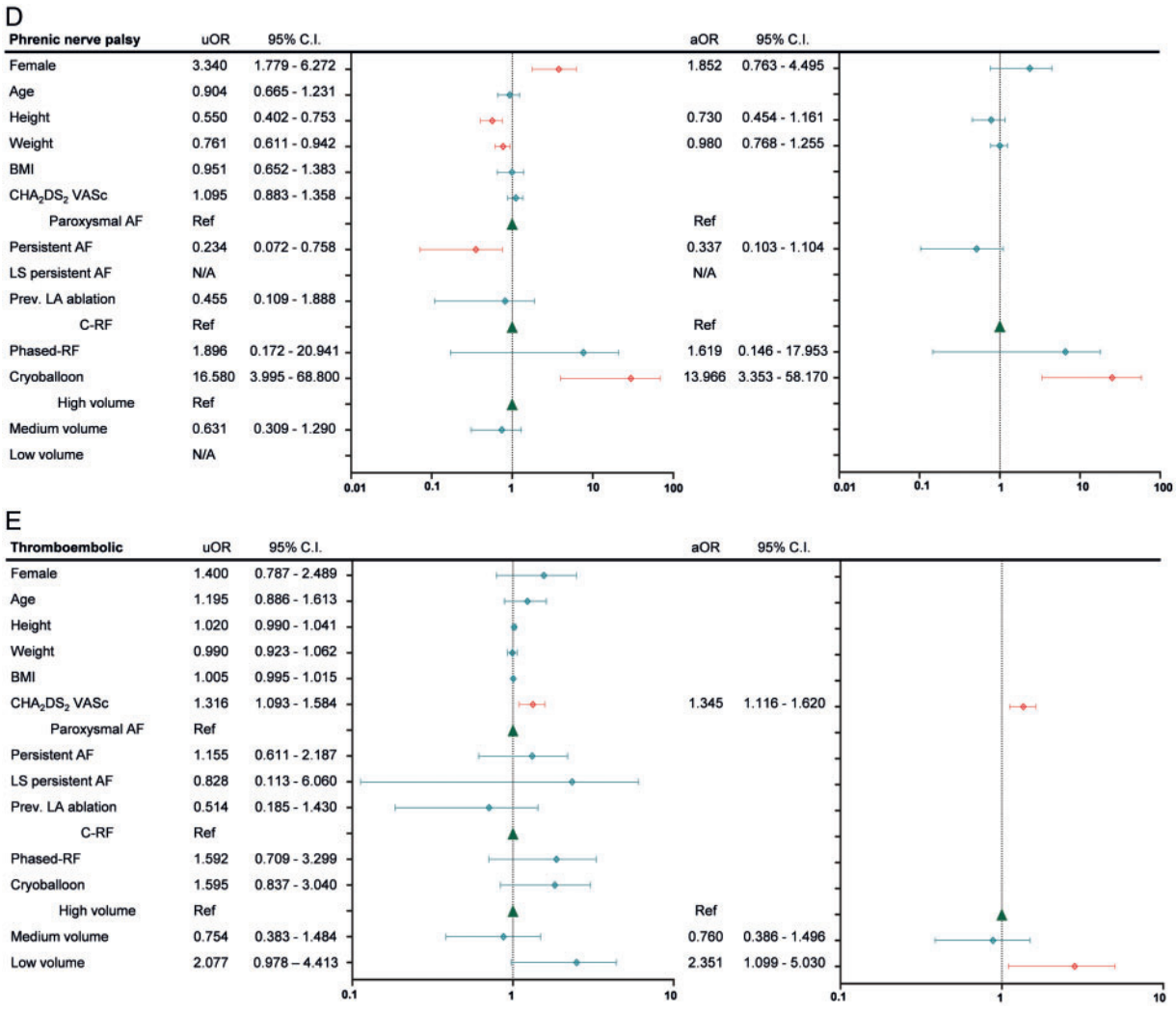


Figure 1 (Continued)

vs. Ph-RF: 0.4% vs. CB: 0.7% $P = 0.020$). Phrenic nerve palsy (≥24 h) data were reported in 5422 (39.2%) patients, and PNP almost exclusively occurred when treated with CB ablation (C-RF: 0.1% vs. Ph-RF: 0.2% vs. CB: 1.5% $P \leq 0.001$). Vascular complication data were reported in 6314 (45.7%) patients. Compared to Ph-RF and CB ablation, we observed more vascular complications in patients undergoing C-RF ablation (C-RF 1.7% vs. Ph-RF 1.2% vs. CB 1.3% $P \leq 0.001$). Mortality data were available in 11 710 (84.7%) patients. Some of the contributing centres had a backlog in querying mortality status in the municipal death. We excluded four ablation centres because of a large number of missing values (range 12.5–92.8%). No mortalities were reported in these centres. Completeness of the remaining centres was 99.7%. In the remaining centres, 4/10 700 (0.04%) patients died within 30 days after the ablation procedure. We observed a higher mortality rate in high-volume centres compared to low- or medium-volume centres (low $n = 1$, medium $n = 0$, high $n = 3$, $P \leq 0.001$). There was no data available on the cause of death. Documented complications are listed in *Table 2*.

Repeat left atrium ablation within 1 year

Overall, 18.4% of patients were referred for a repeat LA ablation within one year after the index LA procedure. More patients were referred for repeat LA ablation after initially being treated with C-RF ablation (19.6%) or Ph-RF ablation (25.6%) than with CB ablation (12.5%, $P \leq 0.001$). This included also patients in whom the LA ablation was the second repeat LA ablation. Comparable outcomes were observed in patients who did not have a previous LA ablation, and for whom the redo ablation was the first repeat LA ablation (C-RF 22.0% vs. Ph-RF 25.7% vs. CB 12.5%, $P \leq 0.001$).

Factors associated with procedural complications and repeat ablation

Subgroup analysis was performed for complications. *Figure 1* displays the unadjusted ORs and adjusted ORs for each complication including a corresponding forest plot.

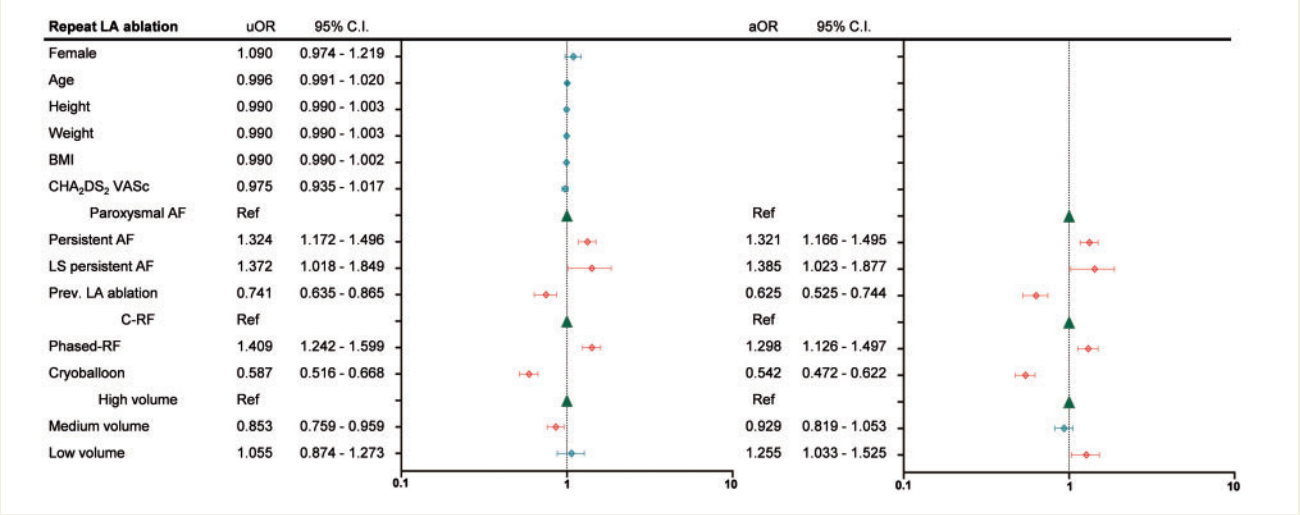


Figure 2 Logistic regression analysis for repeat LA ablation within 1 year. uORs with corresponding 95% CI are presented in the left table and forest plot. Statistically significant variables are presented in red. Multivariable analyses were performed with variables with a *P*-value < 0.10. aORs with the corresponding 95% CI are presented in the right table and forest plot. Age is presented with an increment of 10 years, height with 10 cm, weight with 10 kg, and BMI with 5 points. Of note, as mentioned in the discussion, the results may be influenced by patient selection. AF, LS, CHA_2DS_2-VASc, LA, and RF. Ablation volume categorized as low 34–108, medium 144–183, or high volume 207–381 PV isolations included in the registry per year. AF, atrial fibrillation; aORs, adjusted odds ratios; BMI, body mass index; CHA_2DS_2-VASc, congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, age, sex; CI, confidence interval; LA, left atrium; LS, longstanding; RF, radiofrequency; uORs, unadjusted odds ratios.

Increased risk of bleeding complications (*Figure 1A*) was observed in female patients, older patients, and patients with a higher CHA_2DS_2-VASc score (OR = 3.36, 95% CI 2.27–4.98, OR = 1.61, 95% CI 1.24–2.02, and OR = 1.41, 95% CI 1.25–1.60, respectively), where shorter patients and patients treated with Ph-RF had a lower risk for developing a bleeding complication (OR = 0.60, 95% CI 0.49–0.73 and OR = 0.45, 95% CI 0.24–0.83, respectively). After adjustment for the variables with a *P*-value <0.1, the OR remained significant for female sex (OR = 2.97, 95% CI 1.98–4.45), age (OR = 1.50, 95% CI 1.18–1.88) and Ph-RF (OR = 0.45, 95% CI 0.24–0.85). Of note, CHA_2DS_2-VASc was not included in the multivariable analysis.

The risk to develop a cardiac tamponade (*Figure 1B*) was higher in female patients (OR = 2.90, 95% CI 1.80–4.67), older patients (OR = 1.64, 95% CI 1.24–2.18), and in patients with a higher CHA_2DS_2-VASc (OR = 1.27, 95% CI 1.01–1.49). Lower risk was observed in patients with a shorter height (OR = 0.61, 95% CI 0.48–0.78) and in patients treated with Ph-RF (OR = 0.32, 95% CI 0.15–0.72) or CB (OR = 0.38, 95% CI 0.21–0.67). After adjustment, the OR remained significant for female sex (OR = 2.02, 95% CI 1.03–4.00), age (OR = 1.42, 95% CI 1.06–1.23), Ph-RF (OR = 0.33, 95% CI 0.15–0.74), and CB (OR = 0.38, 95% CI 0.21–0.68).

Variables associated with vascular complication (*Figure 1C*) were female sex (OR = 2.42, 95% CI 1.54–3.80), CHA_2DS_2-VASc (OR = 1.24, 95% CI 1.06–1.44), BMI (OR = 1.31, 95% CI 1.03–1.68), and height (OR = 0.59, 95% CI 0.46–0.74). Medium-volume centre was included in the multivariable analysis because of a *P*-value <0.10. Sex and BMI remained significant after adjustment with ORs of 2.21 (95% CI 1.39–3.51) and 1.28 (95% CI 1.05–1.62), respectively. Notably, after correction for height and age, female sex was no longer a significant risk factor for vascular complications (OR = 1.32, 95% CI 0.70–2.50).

An increased risk for PNP (*Figure 1D*) was observed in patients treated with CB (OR = 16.58, 95% CI 4.00–68.80) and in female patients (OR = 3.34, 95% CI 1.88–6.27). Patients with a shorter height, patients with a lower bodyweight and patients with persistent AF had a lower risk to develop PNP with corresponding ORs of 0.55 (95% CI 0.40–0.75), 0.76 (95% CI 0.61–0.94), and 0.23 (95% CI 0.07–0.76), respectively. Except for patients treated with CB, none of these variables remained significant after adjustment.

For thromboembolic events (*Figure 1E*), we included CHA_2DS_2-VASc score and AF ablation volume in a multivariable analysis. After adjustment, both CHA_2DS_2-VASc score and low ablation volume were associated with thromboembolic events (OR = 1.35, 95% CI 1.12–1.62 and OR = 2.34, 95% CI 1.10–5.03, respectively).

Figure 2 presents the outcomes of the subgroup analysis for repeat LA ablation. Of note, the outcomes retrieved from this analysis may depend on patients' characteristics, differences in strategy regarding repeat LA ablation between centres, operator, and patients' preferences. Since the patients in this study are not randomized, selection bias should be taken in to account. Patients with a previous LA ablation and patients treated with CB had a lower risk of being reassigned for repeat LA ablation within 1 year (adjusted ORs 0.63, 95% CI 0.53–0.74 and 0.54, 95% CI 0.47–0.62, respectively). In addition, patients treated in a low-volume centre, patients treated with Ph-RF, and patients with persistent- or longstanding persistent AF were associated with more repeat LA ablation. Adjusted ORs 1.23 (95% CI 1.03–1.53), 1.30 (95% CI 1.13–1.50), 1.32 (95% CI 1.17–1.50), and 1.39 (95% CI 1.02–1.88), respectively.

Discussion

We describe a large nationwide contemporary PV isolation registry with three different ablation modalities, focusing on procedural safety. Women and patients with a higher CHA_2DS_2-VASc had an increased risk to develop cardiac tamponade or bleeding complications. Patients treated with C-RF developed more cardiac tamponades and vascular complications. The lowest bleeding complications incidence was observed in patients treated with Ph-RF; and PNP almost exclusively occurred in patients treated with CB. Furthermore, the proportion of patients with paroxysmal AF was higher in patients treated with either Ph-RF or CB than in patients treated with C-RF.

Complication rates following pulmonary vein isolation in the recent literature

Although the procedural complication rate for PV isolation is low, it is not negligible and should be considered before ablation. The various ablation techniques are associated with different types of complications. The reported incidence of cardiac tamponade ranges between 0.3% and 1.7%.[7,9,11,14] Studies comparing Ph-RF or CB with C-RF did not report a statistically significant difference between the modalities, although, they observed a trend towards less cardiac tamponades when patients were treated with one of these single-shot devices.[9,11] Bollmann *et al.*[15] observed less cardiac tamponades when patients were treated with CB in comparison with C-RF. In our study population, there were significantly more cardiac tamponades when patients were treated with C-RF in comparison with either Ph-RF or CB. However, overall, the incidence of cardiac tamponade was low, with the highest incidence of 0.8% in the C-RF group. This number, however, may be an underestimation as only cardiac tamponades for which intervention was required were registered in the NHR registry. For C-RF ablation, a double transseptal puncture is commonly used to access the LA, in contrast with single-shot devices, where only one transseptal puncture is needed to perform PV isolation. Furthermore, ablation catheters used for C-RF have a small catheter tip diameter (7–8 Fr). Focal atrial wall force is much higher with this small catheter tip, which may add to the risk of perforation and tamponade. Contact-force technology has been introduced recently, and is now often used in AF ablation, and has been demonstrated to enhance long-term outcomes.[16] Although we would expect that real-time contact-force feedback results in a reduced risk of myocardial perforation, it is in fact associated with more cardiac tamponades (1.07% vs. 0.44%, $P = 0.009$).[17] We cannot conclude that the finding of more tamponades in C-RF relates to technology or the number of transseptal punctures. It may indeed relate to the patients' characteristics (more persistent or longstanding persistent AF, more extensive ablation therapy) or the power setting, and it cannot be excluded that more inexperienced operators in training used C-RF. However, these data are not available within NHR.

Phrenic nerve palsy remains a CB-specific complication, and it mainly occurs during ablation of the right PVs where the distance between the PVs and the phrenic nerve is smallest. Diaphragm paresis may cause shortness of breath and exercise intolerance. Continuous phrenic nerve monitoring is therefore recommended during ablation. Most of the PNP recover within 1 year. However, PNP can be disabling until recovery.[7]

In line with other studies, we observed thromboembolic events in 0.3% of the patients, no difference was found between the groups.[7,11,14,18] The NHR does not provide data on the type of anticoagulation management around the PV isolation, although, it would be interesting whether anticoagulation type and periprocedural management will influence these outcomes.

Low-volume centre was associated with more thromboembolic events. These results should be interpreted with caution as the event rate within the thromboembolic events is very low ($n = 49$). A small change in the occurrence of thromboembolic events may affect the outcomes. The same applies for mortality; we observed a higher mortality in high-volume centres; however, only four patients died within 30 days.

Patient population

In this Dutch registry, the majority of the patients were male (69%) and had a history of paroxysmal AF (74%). The mean BMI in our population was 27.3 ± 4.1 kg/m^2, compared to data from the USA that report paroxysmal AF in 63% of the patients, and a median BMI of 31 kg/m^2 (interquartile range 27–35).[19] In accordance with our findings, Mortsell *et al.*[14] showed that fewer patients with paroxysmal AF were treated with C-RF ablation in comparison with CB ablation. Also, they observed that more extensive LA ablation strategies were used in patients treated with C-RF. We presume that the group of patients treated with C-RF could potentially be more complex even when they presumably have the same type of clinical AF, as for example, persistent AF encompasses any duration of AF ranging between 8 and 365 days. Our data do not provide information on additional ablation lines. It is an ongoing discussion if additional ablation therapy is needed during the first AF ablation. In this study, we report that 30.1% of the patients with persistent AF were treated with CB. These findings are in line with combined study of ESC-EHRA AF ablation long-term and Swedish catheter ablation registry who report that 24.6% of the patients treated with CB had a history of persistent AF.[14] Also, in our study, we observed that 15.3% of the patients with persistent AF were treated with Ph-RF. It is very uncommon to perform additional ablation with these techniques. We thus observed that a large number of patients with persistent AF solely received PV isolation during the first AF ablation procedure. Also, we observed, in contrast with the German ablation registry,[20] that 10.5% of patients with a previous LA ablation were treated with CB. Of note, patients with a previous LA ablation were only included in this study if they received the LA ablation before the start of the registry or in a non-participating ablation centre. Patients who received repeat LA ablation may have been treated with CB for repeat ablation because of the clinical suspicion for PV reconnection. Although in the NHR active follow-up of patients is mandatory, different follow-up methods were used, which precludes calculation of the AF recurrence rate. To overcome this issue, we used repeat LA ablation within 1 year as an outcome variable. Indeed, this variable does not reflect the actual recurrence rate, and the patients' symptoms, the preference of different operators with respect to early re-intervention as well as the ablation settings will affect the repeat ablation rate within 1 year. This variable does, however, provide information about the course after the ablation. Within 1 year of the index ablation, >18% of the patients

were reassigned for repeat LA ablation. Interestingly, CB was associated with fewer repeat LA ablations within 1 year in patients with paroxysmal and persistent AF. It remains speculative what determines this outcome difference. Patient selection can be an important factor for these outcomes since randomized controlled trials did not observe any differences in efficacy when comparing the modalities.[5,7,9] Aside from patient characteristics, in comparison with C-RF, CB ablation has been associated with less reconnected PV during repeat ablation.[21] We cannot exclude that additional left atrial ablation lines were made in patients treated with C-RF, which could be prone for recurrence of AF or other atrial arrhythmias.[8]

Women developing AF are older, have more comorbidity, are more symptomatic and have lower quality of life scores.[22,23] Despite this, female patients tend to receive rhythm control and AF ablation therapy less frequently.[22] In recent AF ablation studies, only 28–39% of patients were female.[7,11,14] Furthermore, it has been previously reported that women develop more procedural complications including cardiac tamponade, vascular, and bleeding complications.[24] Women also had 38% more AF recurrences and 48% higher AF readmission rate.[24,25] The higher predominance of atrial fibrosis and atrial septal aneurysms may contribute to this increased complication risk and higher AF recurrence rate.[26,27]

Registries

Large datasets used in registries and other databases enable high-precision research and the detection of small effect sizes using a large number of patients. However, the clinical significance of some of those findings should always be considered with care. For example, in our study, BMI was statistically highly significant at only 0.5 kg/m^2 difference when comparing the ablation modalities. One could question whether such changes (consistent with a weight change of <2 kg) have are clinical significant. The intrinsic quality of the dataset relies on well-defined variables, but data can be biased because of the different interpretation of the variables. Besides, in general, registries tend to have a larger number of missing values compared to randomized studies, which may result in selection bias.[28] Although registries are not randomized, they do provide important information about routine clinical care. Decisions were made by the clinician based on patient characteristics and preferences, and it should be noted that, although this may influence the outcomes, these data do reflect daily practice in the Netherlands.

Study strength

In this study, we used data extracted from a nationwide database. AF ablation outcomes from 14 out of 16 ablation centres in the Netherlands are reported. To our knowledge, this is the largest study to date that compares procedural outcomes related to sex and ablation modalities C-RF, Ph-RF, and CB. We were able to identify risk factors for complications with a low event rate, because of the large sample size.

Study limitations

There are some limitations in this study. First, the complications described are the reported complications. Due to the nature of this study (registry), there are missing values and the data could be prone to underreporting. We assume that the potential underreporting constituted a systematic error and was similar for each group. To obtain reliable data, the NHR has a certified data-quality control system in place and performed an audit on the AF data to check for underreporting, in which there no evidence for underreporting was found. In addition, some patient characteristics of interest were not collected or incomplete in the database and we were therefore unable to adjust outcomes for comparison of the ablation techniques for these variables. Secondly, this study consists of a healthy study population and generalizability of our findings may be limited in a population with more comorbidity. However, the study does reflect the population who receive PV isolation in the Netherlands. Third, ablation technique was chosen by the operator. Reasons to select ablation technique were not recorded in the database, but selection of patients for certain techniques could have introduced a bias. This is evident for patients with previous LA ablation, where 22.9% of the patients treated with C-RF had a previous LA ablation, in comparison with 2.2% and 4.2% for patients treated with Ph-RF or CB, respectively ($P \leq 0.001$). Fourth, there is no data available on whether patients received more extensive ablation therapy besides PV isolation. Fifth, we used to repeat LA ablation as a follow-up outcome measurement. As mentioned before, this does not reflect the actual recurrence rate in this population and it may be influenced by operator, referring physician, and patients' preferences.

Conclusion

Pulmonary vein isolation was associated with a low-reported complication rate. Cardiac tamponade more often occurred in patients treated with C-RF. Patients developed less bleeding complications when treated with Ph-RF. CB was associated with fewer repeat LA ablations within 1 year. Most patients with paroxysmal AF were treated with Ph-RF or CB. Female sex and CHA_2DS_2-VASc were independent risk factors for developing cardiac tamponade and bleeding.

Supplementary material

Supplementary material is available at *Europace* online.

Conflict of interest: Y.B. is proctor for Boston Scientific, Abbott, and Medtronic. All companies are producers of atrial fibrillation ablation tools. The author received research grants from Medtronic and AtriCure. J.G.L. reports grants from Biotronik, personal fees and other from Medtronic, outside the submitted work. J.R.d.G. reports grants from Atricure, Abbott, Boston Scientific, and Medtronic; personal fees from Atricure, Bayer, Daiichi Sankyo, Servier, Johnson & Johnson, Novartis, and Medtronic, outside the submitted work.

Data availability

The data underlying this article were provided by the Netherlands Heart Registration by permission of the participating hospitals. Data will be shared on request to the corresponding author with permission of the Netherlands Heart Registration.

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