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Clinical correlates of immediate success and outcome at 1-year follow-up of real-world cardioversion of atrial fibrillation: the Euro Heart Survey

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Aims In atrial fibrillation (AF) cardioversion is the cornerstone of the rhythm management strategy despite the lack of contemporary data on acute and long-term success. We aim to describe present-day cardioversion of AF and identify characteristics associated with immediate and long-term outcome.

Methods and results Based on the 5333 AF patients enrolled in the multi-centre prospective Euro Heart Survey on AF we selected the 1801 patients undergoing cardioversion at enrolment. Sinus rhythm (SR) was restored in 630 of 712 (88%), 458 of 643 (71%), and 333 of 446 (75%) ($P < 0.001$) of the electrical (ECV), intravenous (ivCCV), and oral (oCCV) chemical cardioversions, respectively, at the cost of few (4.2%) major complications. In multivariate analysis, absence of chronic obstructive pulmonary disease (COPD) ($P < 0.001$), presence of paroxysmal AF (PAF) ($P = 0.013$), and use of biphasic waveform ($P = 0.018$) were predictors of successful ECV. For ivCCV PAF ($P < 0.001$), absence of valvular heart disease ($P = 0.004$), and heart failure ($P = 0.009$), the presence of hypertension ($P = 0.018$) and coronary artery disease ($P = 0.007$) were predictive. Success of oCCV was driven by PAF ($P < 0.001$) and a smaller left atrial dimension ($P = 0.001$). At 1-year follow-up 893 of 1271 (70%) patients were in SR. Multivariate analysis revealed PAF ($P < 0.001$), shorter total AF history ($P < 0.001$), continuous use of Class Ic drugs or amiodarone during follow-up ($P < 0.001$), absence of COPD ($P = 0.003$), younger age ($P = 0.004$), and smaller left atrial dimension ($P = 0.005$) as independent predictors of SR at 1-year follow-up.

Conclusions Contemporary cardioversion of AF is routinely successfully and safely performed with a high proportion of patients in SR at 1-year follow-up.

Keywords Atrial fibrillation • Cardioversion • Rhythm control

Introduction

Atrial fibrillation (AF) is responsible for a significant health care burden in the Western world due to its high and growing prevalence,[1,2] incidence,[3,4] chronic nature, and potentially life-threatening complications.[5,6]

In AF management, rate control is not inferior to rhythm control regarding mortality or cardiovascular morbidity.[7–9] Therefore, the rate control is the recommended initial treatment strategy for symptomatic individuals.[10] Nevertheless, many AF patients are symptomatic or experience symptoms in daily practice despite rate control and they therefore receive

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rhythm control.[11] This makes it an important and widely applied strategy.

Since their introduction several decades ago, electrical[12] and chemical cardioversion (CCV)[13] have become important components of the rhythm control strategy for AF management. More recently, catheter ablation of AF has emerged as an attractive approach,[14] possibly becoming a first line rhythm control treatment in subgroups of patients.[15]

However, despite these developments and their common application, contemporary direct and long-term success rates of cardioversion of AF outside a randomized controlled setting are lacking. We therefore aim to provide insight into present-day cardioversion of AF in 'real-life' patients, and identify predictors for both immediate and long-term success.

Methods

The study protocol was submitted to the institutional review board or ethical committee of all participating centres and approved or waived for the requirement of formal approval being an observational survey. The Euro Heart Survey on AF was a registry which only evaluated daily clinical practice, meaning patients were not required to undergo additional tests. As such the regulatory authorities waived the necessity of informed consent.

The design, data collection and validation, main[11] and general follow-up[16] results, and used definitions of the survey have been described previously. Briefly, between September 2003 and July 2004 182 cardiology practices across 35 member countries of the European Society of Cardiology consecutively enrolled 5333 ambulatory and hospitalized AF patients. Patients needed to be >18 years of age and have a qualifying electrocardiogram or Holter recording of AF within the preceding 12 months. Patient characteristics and treatment were collected both at baseline and at clinical follow-up 1 year after the qualifying visit/admission. Absence or presence of AF at follow-up was electrocardiographically confirmed.

For the present analysis we selected only patients undergoing a cardioversion at the time of enrolment. This amounted to 1801 study subjects: 712 AF patients underwent an electrical cardioversion (ECV), 643 patients had an intravenous chemical cardioversion (ivCCV), and in 446 patients an attempt to restore sinus rhythm by oral chemical cardioversion (oCCV) was made.

Definitions

Success of chemical cardioversion was defined as restoration of sinus rhythm within 24 h after the onset of pharmacological treatment. Successful ECV was defined as achieving and maintaining sinus rhythm for at least 10 min after shock. Failed ECV was classified either as (a) no sinus rhythm obtained, (b) immediate recurrence of AF (IRAF) defined as a recurrence within 2 min after the last shock, or (c) an acute AF recurrence, defined as a recurrence later than 2 min but within 10 min after the last shock. Pharmacological agents used to restore sinus rhythm were grouped according to the Vaughan-Williams classification[17] and appropriateness of use was checked.[10] From a clinical perspective, all used chemical cardioversion drugs without cardioversion properties—digitalis, magnesium, Class II (beta-blockers, not including sotalol), and Class IV (diltiazem, verapamil) agents were defined as non-antiarrhythmic drugs. This allowed evaluation of differences in short- and long-term success between an approach using true antiarrhythmic drugs compared to use of non-antiarrhythmic drugs. Furthermore, beside the standard clinical classification of AF type, the present AF episode was termed 'breakthrough' when antiarrhythmic drugs were in use during the onset of this episode. Rhythm control during follow-up was defined as the use of a Vaughan-Williams Class I or III antiarrhythmic drug or an attempt at cardioversion at any time during the follow-up period. Major complications following cardioversion consisted of the previously defined major adverse events[16] as well as sick sinus syndrome, asystole, syncope, torsade des pointes, ventricular tachycardia, or ventricular fibrillation occurring within 14 days after enrolment, leading to hospitalization following the outpatient consultation or prolonged hospital admission. The above-mentioned events occurring beyond 14 days were considered to be follow-up events.

Statistical analysis

SPSS statistical software version 17.0 (SPSS Inc., Chicago, IL) was used to perform data analysis. Continuous variables are reported as mean (standard deviation) or median (25–75th percentiles) and categorical variables as number of observed patients (percentage). When comparing categorical variables between groups, Fisher's exact test was used. Student's *t*-test and analysis of variance (ANOVA) were used for comparison of normally distributed continuous variables between, respectively, two and three groups. When the continuous variable did not follow a normal distribution the Mann–Whitney or Kruskal–Wallis test was used when comparing between two and three groups, respectively.

Identifying predictors of success of cardioversion and long-term maintenance of sinus rhythm was done by incorporating all biologically plausible variables with a significant univariate relationship (P value <0.10) after non-parametric testing for correlation, into a logistic regression model with stepwise reduction of the model. For these analyses, paroxysmal AF was compared with persistent/permanent AF. All variables in the final model with a P value <0.05 were considered significant independent predictors and were tested for interactions. In order to maximize patients included in the multivariate analysis, we used the average values of total AF history and the duration of the current AF episode within the respective cardioversion groups and the average values of the echocardiographic measures from the entire cohort (5333 patients) to replace missing values.

Results

Between September 2003 and July 2004 a total of 1801 patients underwent a cardioversion at the time of enrolment into the survey. In all, 1271 of 1801 (71%) of these had a known rhythm status at follow-up. The last follow-up took place on 18 December 2005. Overall, the majority of patients were male (59%) and had a mean age of 64.1 (SD, 12.6) years. Patients were mainly enrolled from the cardiology ward (70%), outpatient clinic (19%), or emergency department (6%). *Table 1* depicts patient baseline characteristics according to cardioversion strategy and *Table 2* procedural characteristics. In general, patients of the oral chemical cardioversion strategy more often suffered from cardiovascular disease and patients undergoing ECV had a longer current AF episode.

Patients lost to follow-up had similar rates of successful cardioversion and differed in that they were more often female (46 vs. 39%, $P = 0.009$) and diabetic (20 vs. 16%, $P = 0.02$), had a shorter AF history (median [interquartile range] 0.09 [0.0–1.2] vs. 0.28 [0.01–0.28] years, $P = 0.002$) and less often suffered from a prior stroke or transient ischaemic attack (6 vs. 10%, $P = 0.02$) and hypertension (60 vs. 65%, $P = 0.04$).

Table 1 Patient baseline characteristics[a]

	ECV ($n = 712$)	ivCCV ($n = 643$)	oCCV ($n = 446$)	*P* value[b]	*P* value[c]	*P* value[d]
Demographics						
Age, mean (SD), years	64.5 (12.0)	64.5 (13.2)	63.0 (12.6)	0.96	0.055	0.035
Women	249/712 (35)	286/643 (45)	211/446 (47)	<0.001	0.39	<0.001
Body mass index, mean (SD)	28.0 (7.0) ($n = 673$)	28.0 (7.1) ($n = 609$)	27.3 (14.3) ($n = 437$)	0.37	0.11	0.13
Type of AF	($n = 697$)	($n = 637$)	($n = 443$)			
First detected AF	130 (19)	240 (38)	123 (28)	<0.001	0.001	<0.001
Paroxysmal AF	156 (22)	271 (45)	204 (46)	<0.001	0.26	<0.001
Persistent AF	411 (59)	126 (20)	116 (26)	<0.001	0.014	<0.001
Breakthrough episode	282/683 (42)	156/608 (26)	133/427 (31)	<0.001	0.057	0.001
Total AF history, median (IQR), days[e]	331 (59–1568) ($n = 381$)	4 (0–257) ($n = 438$)	87 (1–1499) ($n = 296$)	<0.001	<0.001	<0.001
Duration present episode, median (IQR), days[e]	30 (3–90) ($n = 378$)	0.5 (0.2–2) ($n = 508$)	2 (0.4–14) ($n = 320$)	<0.001	<0.001	<0.001
Admission duration, median (IQR), days[e]	1 (0–5) ($n = 704$)	2 (0–6) ($n = 632$)	4 (1–9) ($n = 442$)	<0.001	<0.001	<0.001
Previous CCV	169/710 (24)	290/643 (45)	296/446 (66)	<0.001	<0.001	<0.001
Previous ECV	313/711 (44)	70/641 (11)	18/445 (18)	<0.001	0.001	<0.001
$CHADS_2$ score	($n = 700$)	($n = 634$)	($n = 443$)			
0–1	434 (62)	374 (59)	257 (58)	0.26	0.75	0.19
2	161 (23)	151 (24)	100 (23)	0.75	0.66	0.89
>2	105 (15)	109 (17)	86 (19)	0.30	0.38	0.061
AF symptoms[f]	526/711 (74)	595/643 (93)	408 (92)	<0.001	0.57	<0.001
Patient history						
Hypertension	432/711 (61)	422/643 (66)	295/446 (66)	0.071	0.90	0.070
Coronary artery disease	167/708 (24)	235/639 (37)	154/440 (35)	<0.001	0.56	<0.001
Diabetes mellitus	106/711 (15)	127/641 (20)	71/446 (16)	0.017	0.11	0.68
Valvular heart disease	178/710 (25)	134/631 (21)	95/444 (21)	0.11	1.0	0.16
Cerebrovascular accident/TIA	51/707 (7)	43/638 (7)	65/445 (15)	0.75	<0.001	<0.001
Heart failure	188/708 (27)	169/640 (26)	122/444 (28)	1.00	0.73	0.73
COPD	74/711 (10)	89/641 (14)	88/440 (20)	0.054	0.009	<0.001
Pacemaker	42/712 (6)	12/640 (2)	6/445 (1)	<0.001	0.63	<0.001
Major bleeding	10/709 (1)	6/641 (1)	12/444 (3)	0.46	0.030	0.13
LVEF, mean (SD)	51.1 (14.7) ($n = 457$)	51.6 (14.7) ($n = 447$)	48.7 (14.6) ($n = 354$)	0.62	0.006	0.023
LA dimension, mean (SD), mm	46.5 (8.0) ($n = 555$)	43.5 (7.2) ($n = 496$)	42.3 (7.2) ($n = 378$)	<0.001	0.015	<0.001
Medication in use						
Vitamin K antagonist	569/693 (82)	143/579 (25)	167/419 (40)	<0.001	<0.001	<0.001
Aspirin	11/694 (21)	245/583 (47)	166/422 (32)	<0.001	0.40	<0.001
Antiarrhythmic drug	327/694 (47)	192/583 (33)	177/422 (42)	<0.001	0.004	0.094
Amiodarone	209 (30)	107 (18)	103 (24)	<0.001	0.023	0.039
Sotalol	58 (8)	34 (6)	32 (8)	0.083	0.30	0.73
Flecainide	22 (3)	8 (1)	7 (2)	0.041	0.79	0.17
Propafenone	41 (6)	38 (7)	31 (7)	0.73	0.62	0.38
Disopyramide	3 (0.4)	2 (0.3)	3 (0.7)	1.0	0.66	0.69
Quinidine	0 (0)	4 (1)	8 (2)	0.043	0.14	<0.001
Rate control drug[g]	266/694 (38)	185/583 (32)	144/422 (34)	0.016	0.45	0.16
ARB or ACE inhibitor	415/693 (60)	324/583 (56)	251/422 (60)	0.13	0.22	0.90
Statin[h]	170/694 (25)	148/583 (25)	80/422 (19)	0.75	0.018	0.032

Abbreviations: ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; ECV, electrical cardioversion; LA, left atrial; LVEF, left ventricular ejection fraction; IQR, interquartile range; CCV, pharmacological cardioversion; TIA, transient ischaemic attack. The $CHADS_2$ score is a measure of the risk of stroke in patients with AF, with scores ranging from 0 to 6 and higher scores indicating a greater risk. Congestive heart failure, hypertension, an age of 75 years or older, and diabetes are each assigned one point, and previous stroke or transient ischaemic attack is assigned two points; the score is calculated by summing all the points for a given patient.

[a]Data are presented as No. (%) unless otherwise specified. Fisher exact test for comparison of categorical outcomes. Unless otherwise specified Students's *t*-test and ANOVA one-way variance analysis for continuous outcomes, respectively, between two and three groups.

[b]*P* value between ECV and ivCCV.

[c]*P* value between ivCCV and oCCV.

[d]*P* value between ECV and oCCV.

[e]Mann–Whitney and Kruskal–Wallis one-way variance analysis for continuous outcomes, respectively, between two and three groups.

[f]The following were considered AF symptoms: palpitations, shortness of breath, fatigue, dizziness, syncope, and chest pain.

[g]Combined or single use of a beta-blocker (no sotalol), digitalis, diltiazem, or verpamil.

[h]Statin are defined here as 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors.

Table 2 (Peri)procedural characteristics[a]

CCV			ECV	
Drug	**Intravenous (*n* = 643)**	**Oral (*n* = 446)**	**(*n* = 712)**	
VW Class III	426 (66)	156 (35)	Anaesthesiologist present	474/711 (67)
VW Class Ic	143 (22)	134 (30)	Pre-ECV pacemaker check	94/161 (61)
Other AAD	22 (3)	43 (10)	Serum potassium check	634/706 (89)
Amiodarone	402 (63)	136 (31)	Number of shocks	(*n* = 687)
Dose, mg	(*n* = 401)	(*n* = 135)	Median	1
Median	900	1000	IQR	1–2
IQR	450–1200	400–2000	Energy first shock, J	(*n* = 688)
Sotalol	3 (1)	20 (5)	Median	200
Dose, mg	(*n* = 3)	(*n* = 19)	IQR	100–200
Median	40	160	Energy final shock, J	(*n* = 621)
IQR	40-	80–240	Median	200
Ibutilide	21 (3)	Not applicable	IQR	125–300
Dose, mg	(*n* = 11)	Not applicable	External cardioversion	698/709 (98)
Median	1	Not applicable	Biphasic waveform	424/686 (60)
IQR	1–2		Handheld paddles	527/693 (74)
Propafenone, mg	86 (13)	113 (25)	Antero-lateral paddle position	493/682 (69)
Dose	(*n* = 83)	(*n* = 113)	Post-ECV pacemaker check	90/161 (56)
Median	140	600	Failure to achieve sinus rhythm	54/82 (66)
IQR	140–225	450–600	IRAF	8/82 (10)
Flecainide, mg	57 (9)	21 (5)	Acute recurrence	20/82 (24)
Dose	(*n* = 54)	(*n* = 21)		
Median	150	200		
IQR	137.5–150	200–300		
Non-AAD	52 (8)	113 (25)		
Digitalis	28/52 (54)	22/113 (20)		
Beta-blocker[b]	10/52 (19)	51/113 (45)		
Verapamil	8/52 (15)	21/113 (19)		
Diltiazem	3/52 (6)	17/113 (15)		
Magnesium	3/52 (6)	Not applicable		
	CCV		ECV	
Management following failed cardioversion				
AF accepted	51/290 (18)		40/77 (52)	
CCV	81/290 (28)		6/77 (8)	
ECV	146/290 (50)		22/77 (29)	
Other procedure to treat AF	12/290 (4)		9/77 (12)	
Major complications				
Non-sudden cardiac death	1 (0.1)		2 (0.3)	
Sick sinus syndrome	5 (0.5)		5 (0.7)	
Ventricular tachycardia	2 (0.2)		6 (0.8)	
Torsades de pointes	3 (0.3)		1 (0.1)	
Ventricular fibrillation	0		3 (0.4)	
Asystole	7 (0.7)		2 (0.3)	
Cardiac syncope	8 (0.8)		1 (0.1)	
Pulmonary embolism	1 (0.1)		0	
Myocardial infarction[c]	4 (0.4)		0	
Transient ischaemic attack	13 (1.3)		2 (0.3)	
Non-haemorrhagic stroke	1 (0.1)		2 (0.3)	
Heart failure[d]	9 (1.0)		7 (1.1)	

Continued

Table 2 *Continued*

	CCV		ECV
Drug	**Intravenous ($n = 643$)**	**Oral ($n = 446$)**	**($n = 712$)**
Major bleeding	10 (1.0)		9 (1.3)

Abbreviations: AF, atrial fibrillation; AAD, antiarrhythmic drug; ECV, electrical cardioversion; IRAF, immediate recurrence of atrial fibrillation; IQR, interquartile range; CCV, chemical cardioversion; VW, Vaughan-Williams.
[a]Data are presented as No. (%) of events within the cardioversion group unless otherwise specified.
[b]Not including sotalol.
[c]The $n = 58$ patients presenting with acute myocardial infarction on admission were excluded from this specific analysis.
[d]The $n = 271$ patients presenting with heart failure on admission were excluded from this specific analysis.

Success of cardioversion

In 630 (88%) of the ECV patients the procedure was successful. Procedural success was similar when using handheld paddles 469 of 527 (89%) compared to adhesive pads 143 of 166 (86%) ($P = 0.33$) and in an antero-posterior compared to an antero-lateral paddle position, respectively, 158 of 176 (90%) vs. 431 of 493 (87%), $P = 0.29$. Biphasic waveform was more successful than monophasic waveform, respectively, 387 of 424 (91%) vs. 218 of 260 (84%), $P = 0.003$.

Restoration of sinus rhythm within 24 h after administration of the chemical cardioversion drug was accomplished in 458 of 643 (71%) of the ivCCV patients vs. 333 of 446 (75%) of the oCCV, $P = 0.21$. No antiarrhythmic drug-specific differences in success rate were observed. Pharmacological cardioversion using non-antiarrhythmic drugs was successful in 98 of 113 (87%) oCCVs compared to 30 of 52 (58%) ivCCVs, $P < 0.001$.

Success of cardioversion was equal in the breakthrough compared to the antiarrhythmic drug-free patients for ECVs, ivCCVs, and oCCVs: 253 of 282 (90%) vs. 377 of 430 (88%) $P = 0.47$, 106 of 156 (68%) vs. 352 of 487 (72%) $P = 0.31$, and 99 of 133 (74%) vs. 234 of 313 (75%) $P = 1.0$, respectively.

In all strategies, patients with a current AF episode of unknown duration or $\geq$48 h were less likely to convert compared to patients with a current episode of $<$48 h: 537 of 616 (87%) vs. 93 of 96 (97%), $P = 0.003$; 118 of 217 (54%) vs. 340 of 426 (80%), $P < 0.001$; and 181 of 272 (67%) vs. 152 of 174 (87%), $P < 0.001$ for ECVs, ivCCVs, and oCCVs, respectively.

In all, 41of 630 (7%) ECVs, 15 of 458 (3%) ivCCVs, and 17 of 333 (5%) oCCVs that were successful were associated with a relapse to AF or atrial flutter prior to discharge. Taking this into account, the 'net success rate' for ECV, ivCCV, and oCCV was 81, 67, and 70%, respectively.

Table 3 shows the univariately associated and independent determinants of successful cardioversion. After multivariate analysis absence of chronic obstructive pulmonary disease (COPD) ($P < 0.001$), paroxysmal AF ($P = 0.01$), and the use of a biphasic waveform device ($P = 0.02$) remained associated with success of ECV. For ivCCVs significant factors were paroxysmal AF ($P < 0.001$), absence of valvular heart disease ($P = 0.004$), absence of heart failure ($P = 0.009$), and the presence of hypertension ($P = 0.02$) and coronary artery disease ($P = 0.007$). Sinus rhythm in oCCVs was driven by paroxysmal AF ($P < 0.001$) and a smaller left atrial dimension ($P = 0.001$).

Complications

Except for four patients who died following a non-sudden cardiovascular cause, all were discharged alive. Overall, 76 of 1801 (4.2%) of the patients undergoing cardioversion suffered a major complication with a similar event rate in breakthrough compared to antiarrhythmic drug-free patients, respectively, 29 of 571 (5.1%) vs. 47 of 1230 (3.8%), $P = 0.26$. A complete overview of all major complications is displayed in *Table 2*. Patients with a current AF episode of $<$48 h had a equal number of major complications compared to those with an episode of unknown duration or $\geq$48 h, 24 of 657 (3.7%) vs. 52 of 1086 (4.8%) $P = 0.28$, respectively.

Appropriate procedural anticoagulation and antiarrhythmic drug use

Figure 1 provides details on the antithrombotic treatment. Anticoagulant use at the time of cardioversion because of an AF episode of unknown duration or $\geq$48 h was 90, 42, and 52% in ECVs, ivCCVs, and oCCVs, respectively. Discharge anticoagulation use increased to 93% for ECV and 61% for both ivCCV and oCCV patients.

In total, 399 of 712 (56%) ECV and 684 of 1089 (63%) CCV patients either had coronary artery disease, heart failure, or echo- or electrocardiographic evidence of left ventricular hypertrophy, i.e. a contra-indication to the use of Class Ic drugs or sotalol. However, despite the presence of such a contra-indication these drugs were used prior to admission in 48 of 399 (12.0%) ECV and 81 of 684 (11.8%) CCV patients. Furthermore, in 126 of 1089 (11.6%) of the CCV patients with a contra-indication a Class Ic drug was used to attempt cardioversion and in 73 of 1089 (6.7%) CCV patients digitalis or sotalol were used. This brings the total number of CCVs using a non-recommended antiarrhythmic drug to 199 of 1089 (18.2%). Pharmacological cardioversions using non-recommended antiarrhythmic drugs had success and complications rates similar to the other CCVs, 138 of 199 (69%) vs. 653 of 890 (73%), $P = 0.25$ and 9 of 199 (4.5%) vs. 67 of 1602 (4.2%), $P = 0.84$, respectively.

Outcome and rhythm status at 1-year follow-up

During the median follow-up period of 374 (range, 363–410) days a total of 28 of 1271 (2%) patients died. No statistically

Table 3 Determinants of sinus rhythm

	Univariate, *P* value	Multivariate, *P* value	Odds ratio (95% CI)
Following ECV (672/712)[a]			
COPD	<0.001	<0.001	0.23 (0.13–0.41)
Paroxysmal AF	0.014	0.014	2.04 (1.15–3.61)
Biphasic waveform	0.003	0.020	1.79 (1.10–2.91)
Total AF history, per year	0.039	0.078	0.96 (0.92–1.01)
Current duration of AF episode, per month	0.001	0.62	1.01 (0.99–1.03)
Following ivCCV (620/643)[a]			
Paroxysmal AF	<0.001	<0.001	3.01 (2.00–4.51)
Valvular heart disease	0.002	0.004	0.52 (0.34–0.81)
Coronary artery disease	0.029	0.007	1.76 (1.16–2.67)
Heart failure	0.001	0.009	0.56 (0.37–0.87)
Hypertension	0.002	0.018	1.60 (1.09–2.37)
Left atrial dimension, per millimetre	0.002	0.13	0.98 (0.95–1.01)
Current duration AF episode, per month	<0.001	0.26	0.96 (0.89–1.03)
Total AF history, per year	0.002	0.73	1.01 (0.94–1.09)
Following oCCV (402/446)[a]			
Paroxysmal AF	<0.001	<0.001	5.11 (3.07–8.49)
Left atrial dimension, per millimetre	<0.001	0.001	0.94 (0.90–0.97)
Amiodarone as CCV drug	0.009	0.069	0.61 (0.36–1.04)
Thyroid disease	0.021	0.073	0.50 (0.23–1.07)
Renal failure	0.061	0.25	0.51 (0.17–1.59)
Current duration of AF episode, per month	<0.001	0.25	0.97 (0.93–1.02)
Valvular heart disease	0.024	0.27	0.71 (0.38–1.31)
Left ventricular ejection fraction, per per cent	0.028	0.50	1.01 (0.99–1.03)
Amiodarone at baseline	0.038	0.76	1.13 (0.55–2.53)
Total AF history, per year	<0.001	0.84	0.99 (0.92–1.07)
Age, per year	0.071	0.84	1.00 (0.98–1.02)
At 1-year follow-up (1210/1271)[a]			
Age, per year	<0.001	0.004	0.98 (0.97–0.99)
Paroxysmal AF	<0.001	<0.001	6.32 (4.71–8.48)
Total AF history, per year	<0.001	<0.001	0.92 (0.89–0.97)
Left atrial dimension, per millimetre	<0.001	0.005	0.92 (0.95–0.99)
Continuous use of AAD[b] during follow-up	<0.001	<0.001	2.11 (1.56–2.86)
Heart failure	<0.001	0.090	0.76 (0.55–1.04)
COPD	<0.001	0.003	0.54 (0.36–0.81)
Left ventricular ejection fraction, per per cent	0.047	0.61	1.00 (0.99–1.01)
Diabetes mellitus	0.091	0.83	0.96 (0.66–1.40)
Valvular heart disease	0.068	0.99	1.00 (0.71–1.41)
Renal failure	0.002	0.32	0.71 (0.37–1.38)

Abbreviations: AAD, antiarrhythmic drugs; AF, atrial fibrillation; CI, confidence interval; ECV, electrical cardioversion; CCV, pharmacological cardioversion.
[a]Number of patients in multivariate analysis.
[b]Vaughan-Williams Class Ic drug or amiodarone.

significant difference in follow-up duration or death was observed between cardioversion strategies, $P = 0.1$ and $P = 1.0$, respectively. However, non-recommended antiarrhythmic drugs use at discharge was associated with more cardiovascular deaths compared to appropriate use, respectively, 5 of 133(3.8%) vs. 6 of 619 (1.0%), $P = 0.03$. Major cardiac or cerebrovascular events occurred in 5.7, 9.4, and 13.6% of the ECV, ivCCV, and oCCV patients, respectively (for all comparisons $P < 0.001$, except when comparing ivCCV and oCCV, $P = 0.01$). For the ECV, ivCCV, and oCCV patients the events consisted of an acute coronary syndrome in 2.4, 6.3, and 8.1% ($P = 0.001$) of patients, respectively; thromboembolism in, respectively, 1.7, 2.7, and 4.2% ($P = 0.08$) and major bleeding in, respectively, 1.8, 0.7, and 1.6% ($P = 0.33$).

At follow-up, 157 of 529 (30%) ECV, 115 of 409 (28%) ivCCV, and 106 of 295 (36%) oCCV patients had AF symptoms.

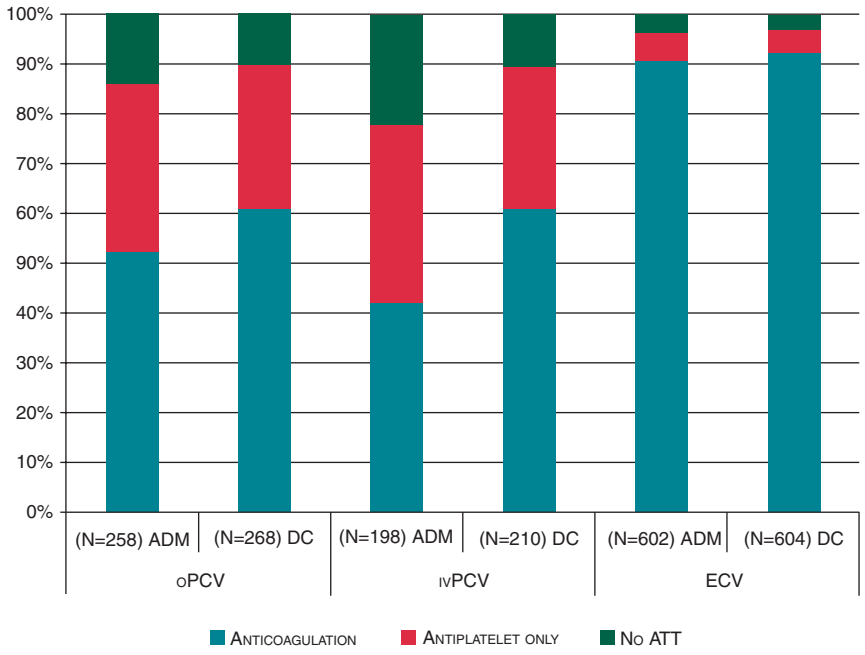

Figure 1 Antithrombotic regimen by cardioversion strategy in patients with AF of unknown duration or ≥48 h. ADM, admission; AF, atrial fibrillation; ATT, antithrombotic treatment; DC, discharge; ECV, electrical cardioversion; oCCV, oral pharmacological cardioversion; ivCCV, intravenous pharmacological cardioversion.

Predictors of sinus rhythm at follow-up

In total, 893 of 1271 (70%) of the patients were in sinus rhythm at follow-up consisting of 331 (61%) ECV and 562 (77%) CCV patients, $P < 0.001$, without a difference between patients in the ivCCV and oCCV groups, respectively, 330 (79%) vs. 232 (75%), $P = 0.29$. Overall, a rhythm control strategy during follow-up was applied in 804 of 1052 (63%) of the patients of which 600 of 804 (47%) used an antiarrhythmic drug at some point in time during follow-up. The rhythm control strategy had a tendency to increase maintenance of sinus rhythm when compared with no rhythm control: 572 of 804 (71%) vs. 165 of 248 (67%), $P = 0.18$. Patients discharged with non-recommended antiarrhythmic drugs had a similar rate of sinus rhythm at follow-up compared to those receiving recommended antiarrhythmic drugs, respectively, 102 of 144 (71%) vs. 429 of 612 (70%), $P = 0.92$.

Univariate and independent predictors of sinus rhythm at follow-up after multivariate logistic analysis are shown in *Table 3*. Logistic regression revealed paroxysmal AF ($P < 0.001$), shorter total AF history ($P < 0.001$), continuous use of Class Ic or amiodarone during follow-up ($P < 0.001$), absence of COPD ($P = 0.003$), younger age ($P = 0.004$), and smaller left atrial dimension ($P = 0.005$) as independent predictors of sinus rhythm at follow-up.

Discussion

The multicentre, prospective Euro Heart Survey on AF demonstrated that contemporary cardioversion of AF in real-life patients was widely applied in both symptomatic and asymptomatic individuals, had a high success rate and achieved maintenance of sinus rhythm at 1-year follow-up in a moderate proportion, at the cost of few major complications, for all strategies.

Electrical cardioversion

The high success of ECV is within the range reported previously,[18–21] taking into account differences in patient characteristics,[22] duration of AF and technical aspects. Although the study was not designed to address optimum technical aspects of ECV a biphasic was clearly better than a monophasic waveform.[23] The benefit of an antero-posterior position[24] was likely cancelled out by predominant use of self-adhesive pads in this position[25] (data not shown). After multivariate analysis, biphasic waveform remained an independent predictor of success together with paroxysmal AF and COPD. The importance of trans thoracic resistance—largely driven by chest size—in success of cardioversion[26] together with the pathophysiological changes, the observed influence of COPD is biologically plausible. Finally, the strong association between paroxysmal AF and successful ECV is not surprising since, by definition, this arrhythmia tends to convert spontaneously.

Pharmacological cardioversion

For both oral and intravenous administration, the observed success rates of chemical cardioversion with amiodarone and Class Ic drugs are in line with the reports of randomized clinical trials,[27–33] keeping in mind that our study could not identify differences in the time to conversion.

Interestingly, oCCV was frequently attempted and underlying heart disease appeared to have a less dramatic negative effect on success than expected in patients with the 'pill-in-the-pocket'[33]

(or here, the perhaps more appropriate[34] 'pill-in-the-hospital') approach.

Remarkable is the number and success of CCV using non-antiarrhythmic drugs, likely reflecting the known occurrence of spontaneous conversion of recent onset AF. However, even more concerning is the observation that a considerable number of patients received contra-indicated antiarrhythmic therapy prior to admission, at discharge and even as cardioversion drug.[10,35]

Data on predictors of pharmacological cardioversion are scarce and conflicting. However, shorter duration of AF and smaller left atrial dimension are probably most consistently identified as predictors of successful CCV.[29,36–42] Multivariate analysis revealed paroxysmal AF to be the strongest independent predictor of success in CCV, followed by shorter AF duration and smaller left atrial size in oCCVs. Strikingly, we observed both hypertension and coronary artery disease to be positively associated with ivCCV success as opposed to heart failure and valvular heart disease. Possibly, the former two conditions are markers of a more early disease state and prompt presentation.

Complications

Although cardioversion is potentially life threatening, no patients died from sudden cardiac or thrombo-embolic causes. Despite the antithrombotic under-treatment the thrombo-embolic rate observed in this study is in line with the study by Gallagher *et al.*[43] However, considering the time-dependent occurrence of thrombo-embolic complications post-cardioversion, the true rate may have been underestimated.[44] Based on a similar rate of major complications, cardioversion of recent onset compared to more persistent AF does not appear to be safer.

Long-term outcome

Although substantial, the number of deaths and major cardiac or cerebrovascular events during follow-up were not surprising. The difference in events between ECV and CCV patients was largely driven by an increased number of acute coronary syndromes in the CCV group. However, inadequate anticoagulation and use of contra-indicated antiarrhythmic drugs were strikingly high. It is unclear to what extend this contributed to the long-term outcome and (peri)procedural complications. Altogether, these observations re-emphasize the importance of comprehensive treatment of AF patients rather than simply treating the electrocardiogram.

In all three groups, sinus rhythm at follow-up was promising at least, but perhaps most striking in the ECV group in light of previous studies.[19,45–47] Beside rhythm control during follow-up and improved treatment of underlying heart disease, patient selection might be part of the explanation. The observed independent predictors of sinus rhythm at 1-year follow-up confirm what is known.[19,46]

As this is a subgroup analysis of the Euro Heart Survey on AF, consecutive inclusion of cardioversions cannot be guaranteed and careful data interpretation is warranted. Important to note, however, is that all reported peri-procedural details were pre-specified in the case record form and prospectively collected. Although missing rhythm status on follow-up excluded 32% of the cardioversions performed at baseline from the current analyses, significant differences from most of the presented data are unlikely considering that patient characteristics of those lost to follow-up were quite similar to those who were successfully followed. Inherent to the used definition of success, spontaneous conversion needs to be taken into consideration especially in recent onset and paroxysmal AF patients.[30] Finally, as we used a single ECG at the follow-up visit to check for AF we underestimate the number of patients who still suffer from (paroxysmal) AF at 1-year follow-up.

Clinical implications

Potential clinical implications include emphasis on avoidance of non-guideline recommended drugs for chemical cardioversion and long-term rhythm control and on the importance of appropriate peri-procedural anticoagulation. Also, an initial (i.e. in the first 24 h following the onset of AF) pursuit of adequate rate control before attempting cardioversion might prove to be (cost-effectively) worthwhile. Finally, a biphasic waveform is always preferred, but especially in COPD patients.

Overall, our data provide a comprehensive, up-to-date overview of cardioversion of real-life AF patients, confirming its extensive successful implementation at the cost of few major complications.

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Conflict of interest

R.P. reported receiving research grants from Bayer Health Care; consulting fees from Boehringer-Ingelheim, Bayer Health Care, Roche Diagnostics, and Sanofi-Aventis; and lecture fees from Boehringer-Ingelheim. J.-Y.L.H. reported receiving research grants from Sanofi Aventis; consulting fees from Sanofi Aventis and Medapharma; and board membership fees from Sanofi Aventis and Medapharma. A.J.C. reported receiving consulting fees from Sanofi Aventis, Menarini, Richmond Pharmacology, Medtronic, Boston Scientific; expert testimony from Johnson and Johnson; research grants from Bayer Health Care, Boehringer Ingelheim, Sanofi Aventis, Servier and Daiichi-Sankyo; lecture fees from Menarini, Sanofi Aventis and Boehringer Ingelheim; fees for development of educational presentations from Merck; and royalties from Elsevier and Oxford University Press. H.J.G.M.C. reported receiving consulting fees from Boehringer Ingelheim, Sanofi-Aventis, and AstraZeneca; grant support from St Jude Medical, Boston Scientific, Boehringer Ingelheim, Sanofi-Aventis, Medapharma, and Merck; and honoraria from Medtronic, Sanofi-Aventis, Medapharma, Merck, Boehringer Ingelheim, and Biosense Webster. No other potential conflict of interest relevant to this article was reported.

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