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CONTEMPORARY REAL LIFE CARDIOVERSION OF ATRIAL FIBRILLATION: RESULTS FROM THE MULTINATIONAL RHYTHM-AF STUDY

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Abstract

Aims

Electrical and pharmacological cardioversion (ECV, PCV) are important treatment options for symptomatic patients with recent onset atrial fibrillation (AF). RHYTHM-AF is an international registry of present-day cardioversion providing information that is not currently available on country differences and acute and long-term arrhythmia outcome of ECV and PCV.

Methods and results

3940 patients were enrolled, of whom 75% underwent CV. All patients were followed for 2 months. There were large variations concerning mode of CV used, ECV being heterogeneous. Choice of PCV drug depended on clinical patient profile. Sinus rhythm was restored in 89.7% of patients by ECV and in 69.1% after PCV. Among patients not undergoing CV during admission, 34% spontaneously converted to sinus rhythm within 24 hours. ECV was most successful in patients pretreated with antiarrhythmic drugs (mostly amiodarone). PCV was enhanced by class Ic antiarrhythmic drugs; conversion rate on amiodarone was similar to that seen with rate control drugs. Female patients and those with paroxysmal and first detected AF as well as those without previous ECV responded well to PCV. The median duration of hospital stay was 16.2 and 24.0 hours for ECV and PCV patients, respectively. There were very few CV-related complications regardless of mode of CV. Chronic maintenance of sinus rhythm was enhanced in patients on chronic antiarrhythmic drugs, beta-blockers or inhibitors of the renin-angiotensin system.

Conclusions

Mode of CV varied significantly, but both PCV and ECV were safe and effective. Class Ic drugs were most effective conversion drugs, but amiodarone is used most frequently despite providing merely rate control rather than foreshortening time to conversion.

Keywords: Atrial fibrillation, Cardioversion, Rhythm control, Stroke

INTRODUCTION

Atrial fibrillation (AF) is common and often accompanied by incapacitating symptoms.(1) The management of newly detected atrial fibrillation (AF) relies on appropriate antithrombotic management, detection and treatment of associated cardiovascular diseases, and symptom alleviation.(2) Since cardiovascular outcomes are similar in AF patients receiving both rate and rhythm control therapy, rate control is often the therapy of choice among physicians.(3, 4) Without adequate symptom relief, restoration of sinus rhythm becomes the eventual target.

Cardioversion (CV) of AF is critical in alleviating symptoms acutely. Both pharmacological (PCV)(5, 6) and electrical cardioversion (ECV)(7) are widely accepted. PCV (including the "pill-in-the-pocket-approach") is frequently performed in patients with recurrent AF, but caution is needed to avoid complications, such as acute heart failure, bradycardia, and ventricular arrhythmias.(5, 8-10) ECV is more effective than PCV, especially in persistent AF, but often requires hospitalization, anesthesiology support and greater recovery time.(11) Both are generally safe and effective in producing sinus rhythm acutely.(9)

Recommendations, treatments, and goals of rhythm control are clearly given in the guidelines;(2) however, contemporary observational data on cardioversion practices are scarce.(9, 12-14) The RHYTHM-AF study described clinical routines and outcomes of CV in patients with AF considered for rhythm control.(15) The present paper describes the main study results, focusing on patient characteristics, treatment patterns, and outcomes related to CV from a prospectively collected international multicenter registry.

METHODS

Design and study population

The design of the study has been reported in detail previously.(15) Briefly, RHYTHM-AF is a prospective international multicenter observational study of 3940 patients with AF for whom CV was considered. The protocol did not recommend or discourage any treatments, procedures, or examinations that were not part of routine care. Informed consent was obtained from all patients and the study was conducted in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies. All data were collected electronically in a central database and follow-up data were collected 60 days after enrollment.

The study was sponsored by Merck & Co., Inc. and its subsidiaries. The Scientific Committee has the authority to make all decisions related to design, conduct, data interpretation and dissemination of study results.

Endpoints

PCV was considered successful if sinus rhythm or atrial rhythm was obtained within 24 hours after its initiation. Time to sinus rhythm was noted separately. ECV was defined as successful if sinus rhythm was obtained and maintained for at least 10 minutes after the last shock. We grouped conversion drugs into Vaughan-Williams (16) Class Ic (flecainide, propafenone), and Class III drugs (almost exclusively amiodarone, and sotalol in only 2 instances). Other drugs used for conversion as reported by physicians included almost exclusively the typical rate control drugs (i.e., digitalis, beta-blockers, and verapamil or diltiazem).

Statistical analysis

Baseline variables were compared by mode of cardioversion, as well as by class of drug used for PCV using χ^2 tests (categorical variables) and Kruskal-Wallis tests (continuous variables). Multivariable logistic regression was performed to detect (a) factors independently associated with success of ECV and PCV, as well as determinants of successful PCV on class Ic and class III antiarrhythmic drugs (AAD); and to detect (b) determinants of maintenance of sinus rhythm at 2 months in all patients discharged in sinus rhythm. Variables were included in the logistic regression for biological relevance and if shown significant ($p<0.1$) in univariate analysis. All statistical analyses were performed with SAS statistical software (SAS Institute, release 9.2, Cary, NC, USA) (17) and statistical significance was assumed for $P<0.05$.

RESULTS

Patient characteristics

Table I shows patient characteristics by mode of treatment. Patients undergoing ECV or no CV at all were more often admitted in cardiology wards; those receiving PCV were mostly treated in the emergency department. Hypertension, coronary artery disease and diabetes were the most prevalent associated comorbidities. Patients undergoing class Ic-PCV had the most favorable clinical profile. Persistent AF was the most frequent type of AF among ECV patients, whereas PCV patients predominantly had either first-detected or paroxysmal AF, nearly all presenting very early after AF onset.

At enrollment, one-third of patients had a breakthrough arrhythmia, i.e. they were using prophylactic class Ic (8%) or class III AADs (23%). Among those who did not undergo CV, reasons for avoiding the intervention were spontaneous sinus rhythm, planned CV after discharge, spontaneous echo-contrast or left atrial thrombus on transesophageal

echocardiography (TEE), or uncertain duration of current AF episode duration (Figure 1). Palpitations were reported by 72% of PCV patients and only by 40% of ECV patients; in contrast shortness of breath was more frequent in ECV patients (44% vs. 29%). Standard echocardiography was performed most frequently in patients not receiving CV (61%) and least frequently in class Ic drug PCV patients (29%). Pre-procedural TEE was done mostly in patients undergoing ECV.

Cardioversion characteristics and outcomes

Overall, CV was performed a median of 4.0 (IQR 1.4-25.5) hours after admission, i.e. after 6 (2.4-40) hours for ECV and 1.7 (0.6-8.7) hours for PCV. Among patients undergoing class Ic PCV and class III PCV, treatment was administered at 1.1 (IQR 0.34-2.3) and 1.5 (IQR 0.37-25) hours, respectively. Use of antithrombotic treatment is summarized in Figure 2.

Overall, CV was successful in 82.6% of the patients. ECV (89.7%) was more successful than PCV (69.1%). Class Ic and class III PCV (amiodarone) was successful in 77% and 68% of cases, whereas 57% of patients treated by non-antiarrhythmic drugs converted to sinus rhythm. Intravenous and oral PCV were successful in 72% and 63% of patients, respectively.

The increase in the use of class III drugs after cardioversion was significant, mainly due to change in amiodarone prescriptions. Far fewer patients were managed long term with class Ic drugs. The rise in class III and Ic drug prescription after conversion was especially apparent in patients undergoing class III (amiodarone) and class Ic drug conversion, respectively (Figure 3).

The median duration of hospital stay was 16.2 (IQR 5.2-69) and 24.0 hours (IQR 7.6-87.3) for ECV and PCV patients, respectively. It was longer in patients undergoing Class III PCV (57.5 hours [range: 15.3-162.3]) compared to Class Ic PCV (8.4 hours [range: 4.4-

22.6]). The duration of hospitalization was longer in patients with unsuccessful compared to successful CV: 22.8 vs. 15.8 for ECV and 34.5 vs. 20.0 hours for PCV, respectively.

There were few complications experienced during the first 5 days after admission, regardless of CV strata (Table II). Two months after admission, 64.3% of patients were in sinus rhythm. Factors independently associated with successful ECV or PCV and maintenance of sinus rhythm at 2 months follow-up, after multivariate adjustment, are presented in Table III.

DISCUSSION

RHYTHM-AF provides new comprehensive data on clinical cardioversion of AF. Herein we show that CV modality applied depends on type and duration of AF, cardioversion history, and patient symptoms. Class Ic drugs are most effective but their use is relatively limited to healthier patients. Of note, amiodarone does not perform better for PCV than the typical rate control drugs in accelerating conversion, but is used most frequently, especially in patients in whom class Ic drugs are contraindicated. We observed PCV to shorten time to conversion and if successful, also reduce time spent in the hospital after cardioversion. Early cardiovascular complications related to CV appear infrequent.

Amiodarone pretreatment and the presence of an anesthesiologist were associated with successful ECV. Pretreatment with amiodarone, but also with flecainide, ibutilide, propafenone, or sotalol may enhance success of ECV. (2, 18) In Rhythm-AF, amiodarone was used most frequently, likely due to the fact that pretreatment with other agents maybe unsafe, while rational application of amiodarone always includes pretreatment for its remarkable pharmacokinetics. The presence of an anesthesiologist during ECV also appeared to enhance cardioversion. This may relate to deeper sedation with less adrenergic activation upon

awakening, use of less arrhythmogenic sedation, or to increased focus of the healthcare provider on the cardioversion itself with more aggressive application of repeated shocks as needed. In light of these observations, institutions with below average ECV cardioversion rates may consider revising local procedure, type of sedation, engaging anesthesiologist assistance, or amiodarone pretreatment.(2,11)

PCV shortens time to conversion (Figure 4), thereby effectively limiting symptoms and reducing time spent in the hospital. Especially class Ic drugs accelerated conversion to sinus rhythm and were also associated with a significantly higher conversion rate within 24 hours compared to amiodarone and the rate control drugs. Conversion to sinus rhythm was independently associated with gender, type of AF, and history of ECV. It is uncertain why women responded better to PCV, although pharmacokinetic differences may have played a role as dose adjustments are rarely performed in clinical practice. It is well known that paroxysmal AF patients respond much better to PCV than persistent AF; the same may hold for first-detected AF, which may include a significant number of self-terminating AF. Prior ECV appeared to be associated with a reduced conversion rate of PCV. Apparently, a previous ECV may indicate more resistant AF precluding successful conversion when PCV is chosen.

Drug choice for PCV depended on patient characteristics, with amiodarone mainly used in patients with higher disease burden. Indeed, a relatively high prevalence of CHA_2DS_2-VASc score >1 among amiodarone PCVs was observed, compared to all other PCVs. Specifically the prevalence of heart failure, coronary artery disease and valvular heart disease was relatively high in amiodarone PCVs. A similar disease burden was seen among no CV patients, a potential reason for deferring CV.

In patients with structural heart disease, amiodarone is one of the recommended conversion drugs (2); however, when absent, class Ic drugs are preferred since cardioversion with amiodarone occurs many hours later than with flecainide or propafenone (19) (Figure 4). Despite recommendations, amiodarone and even typical rate control drugs were used in many patients, which may have led to avoidable CV failure, the need for back-up ECVs, and prolonged hospitalisation. Of note, amiodarone performed similarly to rate control drugs, rendering its application for shortening conversion time futile. On the other hand, amiodarone provides acute rate control which is crucial in the wait-and-see approach to CV.

Oral propafenone appeared less effective in producing sinus rhythm than flecainide, perhaps due to the relatively low dose of oral propafenone used. Whereas flecainide was applied as recommended, (2,5) propafenone was underdosed (median dose 300 mg). It is uncertain (but not very likely for short timelines) whether propafenone underdosing related to recent clinical experience indicating that especially home cardioversion with 600 mg propafenone can produce significant adverse events despite a previous uneventful in-hospital drug trial. (10)

Before enrollment, two thirds of patients had one or more previous AF episodes, of whom only one third had a breakthrough arrhythmia, i.e. a new AF episode while using an antiarrhythmic drug, consistent with previous research. (9) This suggests that most patients do not use an antiarrhythmic to prevent new attacks between episodes, presumably because of a low attack rate, experiencing the first ever cardioversion (two-thirds of included patients), or because of the risks of chronic antiarrhythmic drug prophylaxis. Finally patient's preference may have played a role in not starting antiarrhythmic drug prophylaxis after previous attack(s) before study entry. Although breakthrough AF may be considered more severe to treat, add-on class Ic drug treatment was similarly effective compared to class Ic conversion in drug-free patients. Patients on chronic drug treatment with breakthrough AF frequently add on

flecainide or propafenone at home, although, pill-in-the-pocket propafenone has been reported to be associated with adverse events. (10) Nevertheless, many patients with breakthrough AF fare well with such a strategy, thus avoiding hospitalizations.

Patients using AAD both at admission and discharge maintained sinus rhythm in the short term (2 months) significantly better than those who were put on these agents only at discharge or who were kept off AAD. In line with recent studies, (20,21) the registry supports the notion that pretreatment and continued antiarrhythmic drug prophylaxis is more effective than other antiarrhythmic drug strategies or no prophylaxis. Additionally, we observed that beta-blockers and inhibitors of the renin-angiotensin system reduced short term recurrences. Several previous studies have shown that in the presence of amiodarone, angiotensin receptor blockers (ARB) and ACE-inhibitors (ACE-i) help to prevent recurrences after cardioversion both in paroxysmal as well as persistent AF. (2) In the present study, the effect of ACE-i/ARB was independent of continued antiarrhythmic drug use. This may relate to the relatively short term follow-up of 2 months during which mainly subacute recurrences (whose mechanism may differ from that of recurrences occurring later on during follow-up) happen. (11) Aldosterone antagonists have also been reported to reduce recurrences of AF after ECV, (22) but this effect could not be studied since few used these agents in this study. First detected AF was observed to be associated with a worse short term arrhythmia prognosis than persistent AF, for which we do not have an explanation (Table III). Likewise, it is uncertain why stable angina pectoris or absence of AF symptoms would be associated with better rhythm outcome at 2 months.

This study had several strengths, including its large size, the short period of overall study time enhancing robustness of the data, the standardized collection of data, and the broad scope of patients. It was not without limitations, including lack of full control on representativeness of sites and on consecutiveness of patients as well as a relatively short

follow-up period. Nevertheless, it offers insight into the importance of considering patient's preferences concerning mode of CV.

Conclusions

In current practice, pharmacological and electrical cardioversion are safe and effective. Electrical cardioversion seems well developed, but improvement may be obtained through pharmacological pretreatment. The class Ic drugs are most effective as acute conversion drugs. Amiodarone enhances electrical cardioversion and maintenance of sinus rhythm, but as a conversion drug it is not more effective than the typical rate control drugs. Arrhythmia outcome after cardioversion is a strong driver for admission duration and hence improvement of cardioversion by new drugs and combination of drugs and electrical cardioversion may reduce costs incurred by cardioversion. Finally, accounting for patients' preferences for one or the other type of cardioversion may enhance the medical service to patients with atrial fibrillation.

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FIGURE LEGENDS

Figure 1: Modes of cardioversion and procedural characteristics

CV: cardioversion; PCV: pharmacological cardioversion; ECV: electrical cardioversion; TEE: transesophageal echocardiography; AAD: antiarrhythmic drug; IV: intravenous; PM: pacemaker;

Figure 2: Use of anti-thrombotic drugs at enrollment

Percentages add up to > 100% because some patients used combinations of antithrombotic drugs. APD: antiplatelet drug; ATT: antithrombotic treatment; ECV: electrical cardioversion; PCV: pharmacological cardioversion; VKA: vitamin K agonist

Figure 3: Change of antiarrhythmic treatment after inclusion: comparison of the distribution of antiarrhythmic drugs used at admission and discharge in all patients as well as per type of cardioversion

Figure 4: Time to conversion on intravenous and oral AAD by type of drug

Table I a. Baseline characteristics by mode of cardioversion

	TOTAL (n=3940)	All CV (n=2972)	ECV (n=1946)	PCV (n=1026)	No CV (n=968)	P-value (ALL CV / no CV)	P-value (ECV / no CV)	P-value (PCV / no CV)	P-value ECV / PCV
DEMOGRAPHICS									
Number of patients (%)	3940	2972 (75)	1946 (49)	1026 (26)	968 (25)				
Age (years)	66±12	66±12.2	67±11	66±14.2	67±12	0.24	0.17	0.59	0.58
Female sex, n (%)	1479 (37.6)	1108 (37,3)	633 (32.5)	475 (46.3)	371 (38.4)	0.53	<0.01	<0.001	<0.0001
BMI (kg/m2)	28.4±61	28.3±5.5	28.6±5.8	27.8±4.9	28.7±7.7	0.57	0.08	0.13	<0.001
Heart Rate (beats per minute)	106±31	105±31	95±27	126±28	108±31	<0.05	<0.0001	<0.0001	<0.0001
SITE OF ADMISSION									
Emergency department	33.0%	34.6%	15.9%	70.1%	28.1%	<0.001	<0.0001	<0.0001	<0.0001
Cardiology ward	46.1%	45.0%	59.2%	17.9%	49.6%	<0.05	<0.0001	<0.0001	<0.0001
Intensive care unit	5.1%	4.8%	4.3%	5.9%	5.7%	0.29	0.09	0.81	<0.05
Other	15.8%	15.5%	20.6%	6.0%	16.5%	0.47	<0.01	<0.0001	<0.0001
COMORBIDITY									
Hypertension, n (%)	62.4%	62.2%	62.5%	61.7%	62.8%	0.74	0.87	0.61	0.67
Systolic blood pressure (mmHg)	131.6±20.3	131.7±20.4	131.1±19.0	132.9±22.7	131.5±19.8	0.72	0.85	0.24	0.11

Diastolic pressure (mmHg)	80.0±13.3	80.2±13.7	80.2±12.9	80.1±15.0	79.5±12.0	0.07	<0.05	0.33	0.55
Coronary artery disease, n (%)	893 (22.7)	663 (22.3)	457 (23.5)	206 (20.1)	230 (23.8)	0.35	0.87	<0.05	<0.05
Valvular heart disease, n (%)	539 (13.7)	395 (13.3)	285 (14.6)	110 (10.7)	144 (14.9)	0.21	0.87	<0.01	<0.01
Diabetes mellitus, n (%)	679 (17.3)	485 (16.3)	323 (16.6)	162 (15.8)	194 (20.3)	<0.01	<0.05	<0.01	0.57
HF NYHA I-II	11.3%	11.3%	13.1%	8.1%	11.1%	0.81	0.12	<0.05	<0.0001
HF NYHA III-IV	3.7%	3.5%	4.0%	2.4%	4.4%	0.16	0.58	<0.05	<0.05
Chronic obstructive pulmonary disease	7.8%	7.7%	5.8%	11.2%	8.2%	0.62	<0.05	<0.05	<0.0001
Thromboembolism, n (%)	239 (6.1)	180 (6.1)	126 (6.5)	54 (5.3)	59 (6.1)	0.97	0.69	0.42	0.19
History of Stroke	2.9%	2.8%	3.0%	2.5%	3.1%	0.67	0.90	0.41	0.41
History of TIA	2.5%	2.5%	2.6%	2.4%	2.3%	0.74	0.65	0.97	0.67
Peripheral vascular disease	6.3%	6.2%	5.6%	7.1%	6.7%	0.56	0.27	0.70	0.11
Hemorrhagic complication, n (%)	47 (1.2)	32 (1.1)	20 (1.1)	12 (1.2)	15 (1.6)	0.24	0.23	0.45	0.76
Hyperthyroidism	4.3%	4.6%	5.3%	3.3%	3.2%	0.07	<0.05	0.92	<0.05
CHA2DS2-VASc >1	69.7%	69.1%	69.3%	68.0%	71.4%	0.20	0.38	0.11	0.35
AF CHARACTERISTICS									
1st detected AF	32.1%	31.3%	23.1%	46.8%	34.6%	0.05	<0.0001	<0.0001	<0.0001
Paroxysmal AF	29.4%	28.8%	21.7%	42.4%	31.2%	0.16	<0.0001	<0.0001	<0.0001
Persistent AF	31.2%	33.0%	45.5%	9.2%	25.5%	<0.0001	<0.0001	<0.0001	<0.0001

Total AF history (years)	4.5±5.5	4.6±5.5	4.4±5.5	5.0±5.5	4.5±5.2	0.61	0.98	0.15	0.06
Current episode <48h, n (%)	1575 (50.7)	1235 (50.6)	419 (27.0)	816 (91.6)	340 (51.4)	0.69	<0.0001	<0.0001	<0.0001
Previous Cardioversion	33.2%	35.1%	38.6%	28.5%	27.4%	<0.0001	<0.0001	0.59	<0.0001
Previous ECV	45.2%	47.3%	55.8%	22.4%	37.9%	<0.001	<0.0001	<0.0001	<0.0001
Previous PCV	28.5%	28.5%	15.7%	64.3%	28.7%	0.94	<0.0001	<0.0001	<0.0001
Currently symptomatic, n (%)	3338 (85.0)	2526 (85.0)	1574 (80.9)	952 (92.8)	812 (84.8)	0.91	<0.01	<0.0001	<0.0001
ECHOCARDIOGRAPHY (n=2024)									
TTE / TEE performed	51.6 / 24.1%	48.6 / 23.9%	51.5 / 33.6%	43.1 / 5.6%	60.7 / 24.7%	<0.0001 / 0.62	<0.0001	<0.0001	<0.0001
Left atrial diameter (mm)	44.2±7.4	44.5±7.5	45.6±7.1	42.0±7.7	43.6±7.2	<0.05	<0.0001	<0.01	<0.0001
Left atrial diameter > 40mm	55%	55%	60%	43.4%	55.3%	0.82	0.09	<0.001	<0.0001
LVEF <40%	19.7%	20.5%	22.7%	15.5%	18%	0.21	<0.05	0.30	<0.01
MEDICATION AT INCLUSION (n=3926)									
Vitamin K antagonist, n (%)	2206 (56.1)	1744 (58.7)	1514 (77.8)	230 (22.4)	462 (48.3)	<0.0001	<0.0001	<0.0001	<0.0001
Heparin, n (%)	340 (8.6)	221 (7.4)	144 (7.4)	77 (7.5)	118 (12.2)	0.0001	<0.0001	<0.001	0.92
No antithrombotic treatment, n (%)	796 (20.3)	583 (19.6)	1541 (7.9)	429 (41.8)	213 (22.3)	0.07	<0.0001	<0.0001	<0.0001
ACE-inhibitor / ARB, n (%)	2171 (55.1)	1641 (55.2)	1157 (59.5)	484 (47.2)	530 (54.8)	0.80	<0.05	<0.001	<0.0001
Beta-blocker, n (%)	1648 (42)	1247 (42.0)	1008 (51.9)	239 (23.3)	401 (42.0)	1.00	<0.0001	<0.0001	<0.0001

Digoxin or digitoxin	9.0%	8.9%	12.0%	3.0%	9.2%	0.77	<0.05	<0.0001	<0.0001
Verapamil or diltiazem	3.3%	3.3%	3.8%	2.2%	3.4%	0.83	0.59	0.11	<0.05
Flecainide or propafenone	8.0%	8.1%	6.6%	10.8%	8.0%	0.90	0.19	<0.05	<0.0001
Sotalol	3.6%	3.8%	4.3%	2.8%	2.9%	0.22	0.08	0.89	<0.05
Amiodarone	16.8%	16.9%	22.5%	6.2%	16.6%	0.86	<0.001	<0.0001	<0.0001
Dronedarone	2.7%	2.7%	3.8%	0.8	2.5%	0.72	0.08	<0.01	<0.0001

Table I b. Baseline characteristics by class of cardioversion drug

	PCV Class Ic (n=306)	**PCV Class III[*)] (n=489)**	**PCV Other drugs[#)] (n=231)**	**P-value (Ic / III)**	**P-value (Ic / other)**	**P-value (III / other)**
DEMOGRAPHICS						
Number of patients (%)	306 (8)	489 (12)	231 (6)			
Age (years)	61±14	70±13	65±15	<0.0001	<0.01	<0.001
Female sex, n (%)	130 (42.5)	241 (49.3)	104 (45.0)	0.06	0.56	0.29
BMI (kg/m2)	27.4±4.7	28.2±5.0	27.8±5.1	<0.05	0.27	0.46
Heart Rate (beats per minute)	125±26	125±28	130±27	0.80	<0.05	0.06
SITE OF ADMISSION						

Emergency department	81.4%	61.3%	73.6%	<0.0001	<0.05	<0.01
Cardiology ward	14.7%	19.6%	18.6%	0.08	0.23	0.75
Intensive care unit	0.7%	11.7%	0.9%	<0.0001	0.78	<0.0001
Other	3.3%	7.4%	6.9%	<0.05	0.05	0.83
COMORBIDITY						
Hypertension, n (%)	50.0%	69.9%	59.7%	<0.0001	<0.05	<0.01
Systolic blood pressure (mmHg)	134.3±21.3	131.9±23.0	133.1±23.6	0.19	0.43	0.71
Diastolic pressure (mmHg)	82.0±14.0	78.3±15.4	81.5±15.0	<0.01	0.66	<0.05
Coronary artery disease, n (%)	27 (8.8)	137 (28.0)	42 (18.2)	<0.0001	<0.01	<0.01
Valvular heart disease, n (%)	12 (3.9)	70 (14.3)	28 (12.1)	<0.0001	<0.001	0.42
Diabetes mellitus, n (%)	34 (11.1)	90 (18.4)	38 (16.5)	<0.01	0.07	0.52
HF NYHA I-II	4.6%	9.2%	10.4%	<0.05	<0.01	0.61
HF NYHA III-IV	0.3%	4.3%	1.3%	<0.001	0.19	<0.05
Chronic obstructive pulmonary disease	8.2%	12.9%	11.7%	<0.05	0.17	0.65
Thromboembolism, n (%)	7 (2.3)	28 (5.7)	19 (8.2)	<0.05	<0.01	0.21
History of Stroke	1.3%	2.9%	3.1%	0.15	0.16	0.90
History of TIA	1.0%	2.3%	4.4%	0.19	<0.05	0.12
Peripheral vascular disease	4.3%	9.4%	6.2%	<0.01	0.33	0.15
Hemorrhagic complication, n	4 (1.3)	6 (1.2)	2 (0.9)	0.92	0.63	0.66

(%)						
Hyperthyroidism	2.7%	3.5%	3.7%	0.56	0.54	0.90
CHA2DS2-VASc >1	50.7%	79.3%	56.4%	<0.0001	<0.001	<0.0001
AF CHARACTERISTICS						
1st detected AF	35.9%	53.6%	46.8%	<0.0001	<0.05	0.09
Paroxysmal AF	54.6%	34.4%	43.3%	<0.0001	<0.01	<0.05
Persistent AF	8.8%	9.4%	9.1%	0.78	0.91	0.89
Total AF history (years)	5.8±5.7	4.3±5.4	4.6±5.1	<0.01	0.05	0.32
Current episode <48h, n (%)	280 (94.9)	348 (89.7)	188 (90.4)	<0.05	<0.05	0.79
Previous Cardioversion	38.2%	23.1%	26.8%	<0.0001	<0.01	0.28
Previous ECV	23.9%	22.0%	20.2%	0.69	0.51	0.74
Previous PCV	68.5%	59.2%	66.2%	0.10	0.73	0.30
Currently symptomatic, n (%)	299 (97.7)	437 (89.4)	216 (93.5)	<0.0001	<0.05	0.07
ECHOCARDIOGRAPHY (n=2024)						
TTE / TEE performed	28.8/ 3.3%	56.2/ 6.3%	34.2/ 6.9%	<0.0001 / 0.06	0.18 / 0.05	<0.0001 / 0.77
Left atrial diameter (mm)	40.8±7.0	42.2±7.2	42.5±9.9	0.09	0.33	0.63
Left atrial diameter > 40mm	37%	46%	41%	0.14	0.63	0.39
LVEF <40%	1.1%	19%	19.7%	<0.0001	<0.0001	0.88
MEDICATION AT INCLUSION						

(n=3926)						
Vitamin K antagonist, n (%)	64 (20.9)	114 (23.3)	52 (22.5)	0.43	0.66	0.81
Heparin , n (%)	11 (3.5)	49 (10.0)	18 (7.8)	<0.001	0.05	0.25
No antithrombotic treatment, n (%)	148 (48.4)	180 (36.8)	101 (43.7)	<0.01	0.29	0.08
ACE-inhibitor / ARB, n (%)	114 (37.3)	265 (54.2)	105 (45.5)	<0.0001	0.06	<0.05
Beta-blocker, n (%)	79 (25.8)	117 (23.9)	43 (18.6)	0.55	<0.05	0.11
Digoxin or digitoxin	1.0%	4.3%	3.0%	<0.01	0.08	0.41
Verapamil or diltiazem	2.0%	2.2%	2.6%	0.78	0.62	0.77
Flecainide or propafenone	21.2%	4.9%	9.5%	<0.0001	<0.001	<0.05
Sotalol	5.2%	1.4%	2.6%	<0.01	0.13	0.27
Amiodarone	2.3%	9.4%	4.8%	<0.0001	0.11	<0.05
Dronedarone	1.0%	0.6%	0.9%	0.56	0.89	0.70

*) Class III drugs included amiodarone, in all but 7 cases of other class III drugs. #) Other Abbreviations: ACE-I: angiotensin-converting-enzyme inhibitor, ARB: Angiotensin II receptor blockers, AF: atrial fibrillation, TTE: transthoracic echocardiogram, TEE: transesophageal echocardiogram

Table II. Distribution of complications over time after ECV, PCV or no CV

Complications	ECV n=1946	PCV n=1026	no CV n=968	Total n=3940
Death				
≤ 5 days	1 (0.05%)	1 (0.10%)	1 (0.10%)	3 (0.08%)
> 5 days ≤ 70 days	6 (0.31%)	7 (0.68%)	9 (0.93%)	22 (0.56%)
> 70 days	_	1 (0.10%)	2 (0.21%)	3 (0.08%)
Thromboembolic Event				
≤ 5 days	_	_	_	_
> 5 days ≤ 70 days	5 (0.26%)	4 (0.39%)	2 (0.21%)	11 (0.28%)
> 70 days	4 (0.21%)	_	_	4 (0.10%)
Heart Failure				
≤ 5 days	1 (0.05%)	1 (0.10%)	_	2 (0.05%)
> 5 days ≤ 70 days	8 (0.41%)	4 (0.39%)	4 (0.41%)	16 (0.41%)
> 70 days	1 (0.05%)	_	_	1 (0.03%)
Major Bleeding				
≤ 5 days	_	_	_	_
> 5 days ≤ 70 days	_	2 (0.19%)	3 (0.31%)	5 (0.13%)
> 70 days	1 (0.05%)	_	_	1 (0.03%)
Bradycardia / Hypotension				
≤ 5 days	_	_	_	_
> 5 days ≤ 70 days	9 (0.46%)	4 (0.39%)	5 (0.52%)	18 (0.46%)
> 70 days	3 (0.15%)	1 (0.10%)	_	4 (0.10%)

Table III. Factors independently associated with obtaining and maintaining sinus rhythm

	OR	95% CI	P
ECV[a] (n=1861)			
VKA before admission	0.558	0.367-0.849	0.006
Amiodarone before admission (pretreatment)	1.557	1.04-2.33	0.03
Anesthesiologist present at CV	1.634	1.188-2.248	0.003
PCV[b] (n=880)			
Female gender	1.439	1.055-1.961	0.0215
AF type (Persistent AF as reference):			
1st Detected AF	2.668	1.491-4.773	0.0009
Paroxysmal AF	2.216	1.269-3.870	0.0052
Previous ECV	0.531	0.319-0.883	0.0147
Heart Failure (No heart failure as reference):			
NYHA I-II	0.583	0.342-0.993	0.0469
NYHA III-IV	0.400	0.144-1.111	0.0787
Valvular heart disease	0.581	0.364-0.926	0.0224
CLASS Ic PCV[c](n=272)			
Female gender	2.263	1.072-4.779	0.0323
AF type (Persistent AF as reference):			
1st Detected AF	3.328	1.117-9.914	0.0309
Paroxysmal AF	2.993	1.095-8.181	0.0326
Previous ECV	0.346	0.141-0.848	0.0203
Chronic renal failure	0.080	0.015-0.425	0.0030
CLASS III PCV[d] (n=437)			
AF type (persistent AF as reference):			
1st detected AF	2.198	1.065-4.538	0.0332
Paroxysmal AF	1.925	0.920-4.028	0.0823
Previous ECV	0.241	0.108-0.539	0.0005

COPD	0.522	0.287-0.949	0.0330
AT 2 MONTHS FOLLOW-UP[e] (n=2709)			
Height	1.013	1.003-1.024	0.0130
Stable angina pectoris	1.438	1.029 – 2.008	0.0333
No AF symptoms	1.388	1.062 – 1.813	0.0164
AF type (persistent AF as reference)			
1st detected	0.772	0.612–0.974	0.0291
Paroxysmal	0.877	0.706-1.090	0.2370
BB at admission	1.323	1.045-1.675	0.0200
AAD Use (no AAD as reference)			
Continuous treatment (admission + discharge)	1.571	1.251-1.972	0.0001
Initiating treatment (discharge only)	1.240	0.995-1.547	0.0557
BB at discharge	1.398	1.107 – 1.765	0.0049
ACE-i/ARB at discharge	1.469	1.235 – 1.747	<0.0001

To maximize patients included in the multivariable analysis, for those who had missing durations of current AF episode, median values of all paroxysmal and persistent AF patients with known duration of current AF episode were used. Patients with unknown AF type were reclassified into paroxysmal AF if they were selected for PCV whereas all other patients with unknown type of AF were considered to have persistent AF. AAD: anti-arrhythmic drugs, ACE-i: ACE (angiotensin-converting-enzyme) inhibitors, ARB: angiotensin receptor blocker, VV_blood pressure, COPD: chronic obstructive pulmonary disease, ECV: electrical cardioversion, NYHA class: New York Heart Association functional classification PCV: pharmacological cardioversion, VKA: vitamin K antagonists

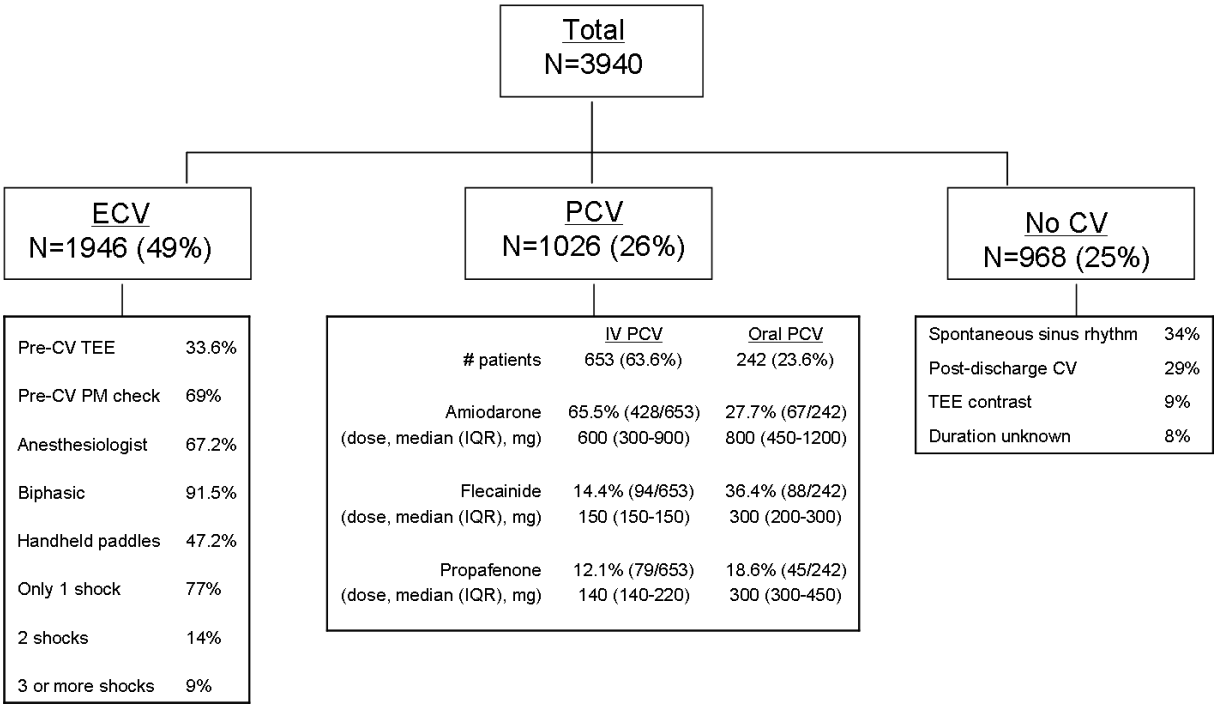
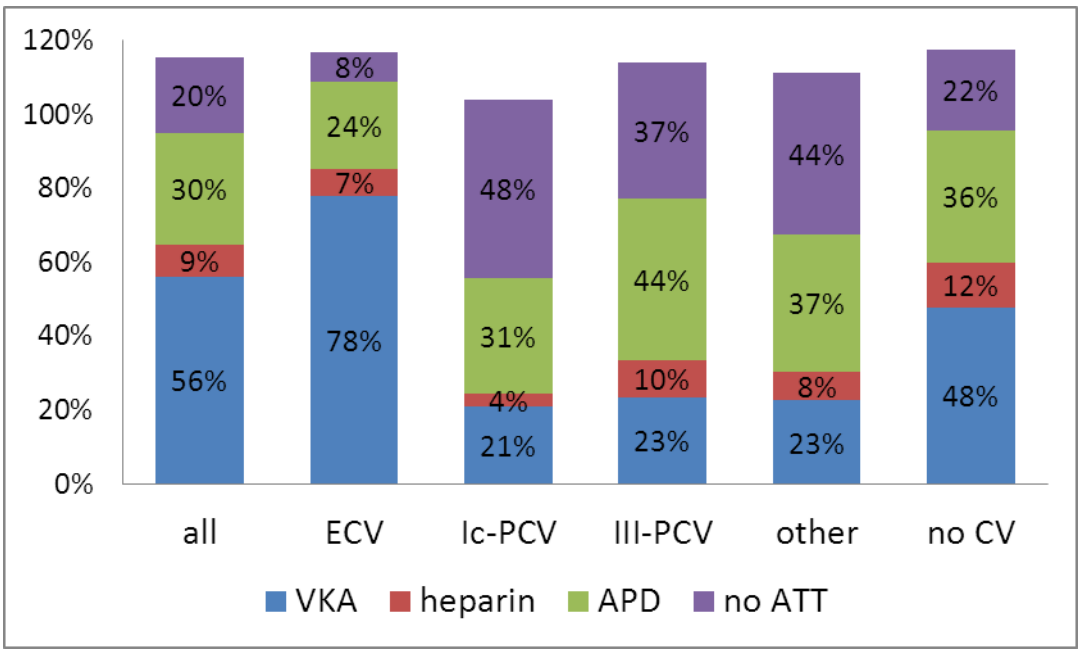


Figure 1. Modes of Cardioversion and Procedural Characteristics

CV: cardioversion; PCV: pharmacological cardioversion; ECV: electrical cardioversion; TEE: transesophageal echocardiography; AAD: antiarrhythmic drug; IV: intravenous; PM: pacemaker;

Figure 2. Use of antithrombotic drugs at enrollment



Percentages add up to > 100% because some patients used combinations of antithrombotic drugs. APD: antiplatelet drug; ATT: antithrombotic treatment; ECV: electrical cardioversion; PCV: pharmacological cardioversion; VKA: vitamin K agonist

Figure 3. Change in antiarrhythmic treatment after inclusion: Distribution of antiarrhythmic drugs used at admission and discharge by type of cardioversion

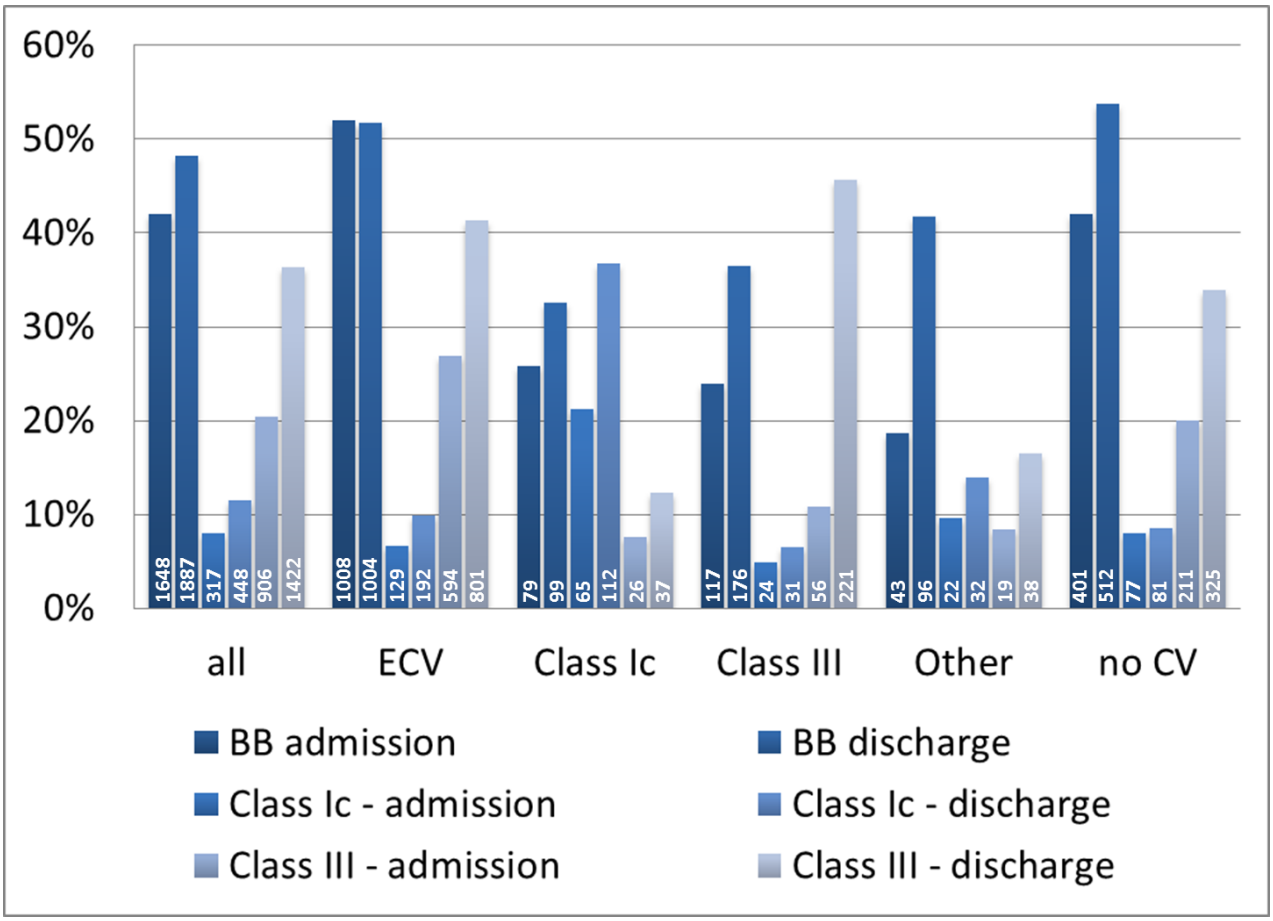
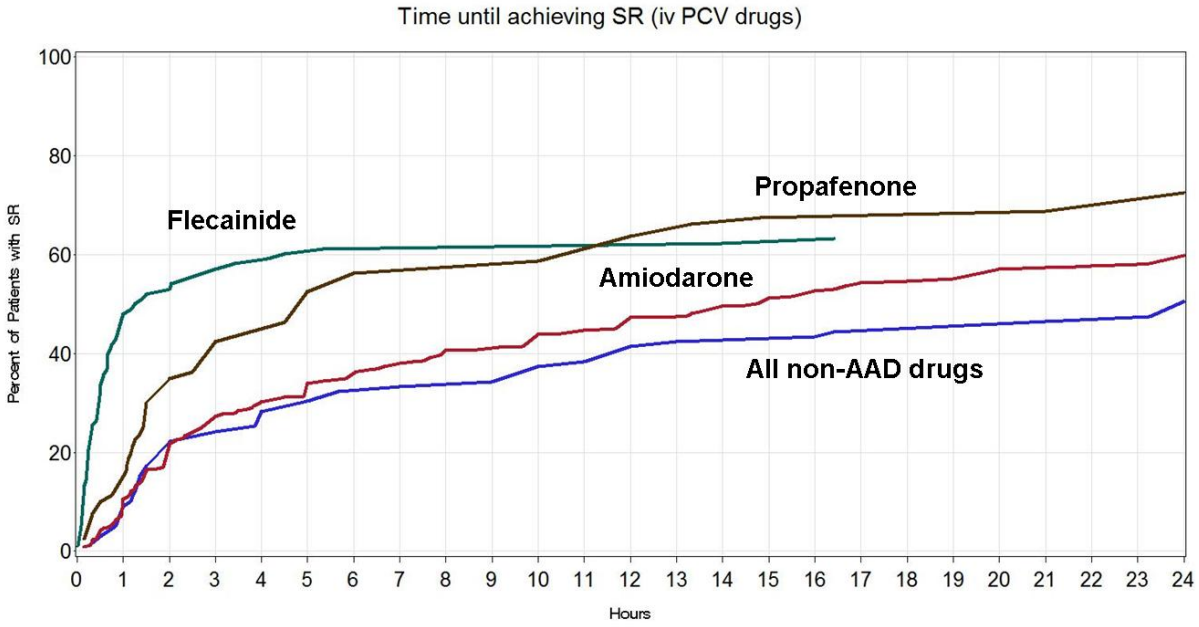


Figure 4. Time to conversion on intravenous (panel A) and oral (panel B) antiarrhythmic drugs

A.



B.