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Prevention of long-lasting atrial fibrillation through antitachycardia pacing in DDDR pacemakers

Short title: Antitachycardia pacing in DDDR pacemakers

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Abstract

Objective. The MINERVA trial showed that in pacemaker patients with atrial fibrillation (AF) history, DDDRP pacing combining 3 algorithms - 1) atrial antitachycardia pacing with Reactive ATP enabled, 2) atrial preventive pacing and 3) managed ventricular pacing (MVP) - may effectively delay progression to persistent/permanent AF compared with standard DDDR pacing.

We performed a comparative non-randomized evaluation to evaluate if Reactive ATP can be the main driver of persistent/permanent AF reduction independently on preventive pacing.

Methods. Thirty-one centers included consecutive dual-chamber pacemaker patients with AF history. Reactive ATP was programmed in all patients while preventive atrial pacing was not enabled. These patients were compared with the 3 groups of MINERVA randomized trial (Control DDDR, MVP and DDDRP). The main endpoint was incidence of AF longer than 7 consecutive days.

Results. A total of 146 patients (73 years old, 54% male) were included and followed for a median observation period of 31 months. The 2-year incidence of AF>7 days was 12% in the Reactive ATP group, very similar to that found in the DDDRP arm of the MINERVA trial (13.8%, p=0.732) and

significantly lower than AF incidence found in the MINERVA Control DDDR arm (25.8%, p=0.012) and in the MINERVA MVP arm (25.9%, p=0.025).

Conclusions. In a real-world population of dual-chamber pacemaker patients with AF history, use of Reactive ATP is associated with low incidence of persistent AF, highlighting that the positive results of the MINERVA trial were related to the effectiveness of Reactive ATP rather than to preventive pacing.

Key-words: antitachycardia pacing, atrial fibrillation, atrioventricular block, bradyarrhythmias, permanent atrial fibrillation, sinus node disease.

Introduction

Atrial fibrillation (AF) is the most prevalent heart rhythm disorder in clinical practice and is associated with poor quality of life and increased risks of heart failure, dementia, stroke, and death. [1-3] Moreover, the management of AF causes important healthcare system utilization. [4] AF is irregular, typically originates from the pulmonary veins, and as such, is generally considered to be not susceptible to pace-termination. However, the MINERVA trial found that AF may show a dynamic process with frequent occurrence of slower organized rhythms such as atrial flutter or atrial tachycardia, which can often be terminated by atrial antitachycardia pacing (ATP). [5-6] In particular, the Reactive ATP algorithm has been designed to monitor atrial arrhythmias rate and rhythm and to deliver Ramp or Burst pacing stimuli to attempt termination when an atrial tachyarrhythmia becomes slower or more regular. [6] The main publication of MINERVA trial showed that in pacemaker patients with clinical history of AF the combination of ATP, preventive atrial pacing algorithms and minimal ventricular pacing (MVP) was associated with lower progression to persistent and permanent AF compared with standard DDDR pacing mode and to MVP mode. [5] A secondary analysis of the MINERVA trial suggested that Reactive ATP algorithm was the main driver of the reduction in permanent or persistent AF. [6]

The clinical question that originates from the MINERVA trial is what can be the respective role of Reactive ATP vs preventive algorithms in reducing progression to persistent and permanent AF.

We therefore designed the Minerva Adoption research project to evaluate the impact of Reactive ATP, used without preventive pacing, in a series of patients implanted with a dual-chamber pacemaker.

Methods

Project design

In the framework of MINERVA trial research (ClinicalTrials.gov Identifier: NCT00262119), we performed a comparative analysis between patients enrolled in the MINERVA trial and consecutive real-world patients implanted with a dual-chamber pacemaker equipped with Reactive ATP algorithm. These Reactive ATP patients were prospectively followed by 31 Italian and Japanese Cardiology hospitals in the framework of the ClinicalService project, a medical care project targeted to quality improvement in the use of Medtronic cardiac electronic implantable devices (CIED) in clinical practice (ClinicalTrials.gov Identifier: NCT01007474). The Reactive ATP patients were included in the project from January 2014 to May 2019.

The design and results of MINERVA trial were previously published. [5-6] Both for MINERVA trial and for ClinicalService project, data collection, reporting and analysis were approved by the relevant Institutional Review Boards and conform to the ethical guidelines of the 1975 Declaration of Helsinki. Each patient signed an informed consent for participation.

Patient and Public Involvement

This research was done without patient involvement. Patients were not invited to comment on the study design and were not consulted to develop patient relevant outcomes or interpret the results. Patients were not invited to contribute to the writing or editing of this document for readability or accuracy.

Sample size

The MINERVA trial randomized 1166 patients; the methods for simple size calculation have been previously reported. [5]. The sample size for the Reactive ATP group has been defined to achieve a similar estimation than the MINERVA trial group.

Patients Matching

With the aim of comparing Reactive ATP patients with MINERVA trial patients, while controlling for possible imbalances between the two groups, we performed individual patients matching using baseline data. In particular to get matched pairs of Reactive ATP patients with the 3 MINERVA arms patients a one-to-three (1:3) propensity score matching was performed. Patients were matched for age, sex,

antiarrhythmic drugs, pacemaker implant indication (i.e. atrioventricular block (AVB) or sinus node disease (SND)), and other variables that are known risk factors for AF development.

Objectives and endpoints

The main objective of the analysis was to compare the 2-year incidence of AF longer than 7 consecutive days between the propensity score matched Reactive ATP population and MINERVA trial patients. Additionally, the 2-years incidence of AF longer than 1 day and the main predictors for reduction in progression to AF longer than 7 days were also evaluated.

The same objective was also evaluated in the non-propensity score matched cohorts.

Information about AF occurrence and episodes duration was derived from device diagnostics; in this perspective AF longer that 7 days was considered as an objective burden of clinical relevance, avoiding the variability in defining persistent or permanent AF when data are derived from observational research.

Follow up and data collection

While the MINERVA population was managed according to the study protocol, the clinical follow-ups for the Reactive ATP group occurred according to each center practice. Clinical data were collected during follow up visits, while device data were collected through the CareLink® Network.

Device programming

Reactive ATP programming in the MINERVA population and in the Reactive ATP group were equal. Differently from the MINERVA DDDRP+MVP arm, in the Reactive ATP population the atrial preventive pacing algorithms were not enabled and the device pacing mode, DDDR or MVP, was chosen according to physician discretion.

Statistical methods

Variables on a continuous scale have been described as mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate. Variables on a categorical scale were presented as counts and percentages. Summary statistics were reported with maximum 2 decimals.

Comparisons between the two groups have been performed using Wilcoxon's Test for continuous variables, while comparisons of categorical variables have been performed by means of the Chi-square test or Fisher exact test for extreme proportions, as appropriate. Statistical tests were based on a two-sided significance level of 0.05.

The analyses of time-to-the-first event have been described by means of Kaplan-Meier curves and compared among the groups by means of the log-rank test.

To find predictors of 7-day AF, Cox regressions have been performed for both univariable and multivariable analyses, and the proportional hazard hypothesis has been tested. Unless otherwise stated, parameters which resulted statistically significant in univariable analysis (p-value <0.10) have been analyzed in multivariable analysis with the appropriate selection. For the stepwise selection, entry criteria = 0.30 and stay criteria = 0.05 have been used.

An alpha-level of 0.05 was considered for each test. All statistical analyses were performed using SAS 9.4 version software (SAS Institute Inc., Cary, NC, USA).

Results

The propensity score matched cohorts were composed by 146 Reactive ATP patients and 438 MINERVA trial patients, specifically 156 patients programmed in DDDR mode (Control DDDR arm), 132 patients programmed in MVP mode (MVP arm) and 150 patients programmed with MVP plus Reactive ATP and preventive algorithms (DDDRP+MVP arm).

The baseline characteristics of the MINERVA trial population and the Reactive ATP patients are reported in Table 1. In particular patients with III-degree AV block had actually paroxysmal block, as persistent III-degree AV block was a study exclusion criterium in the MINERVA trial. All the patients involved in the analysis had history of AF.

Table 1 – Baseline characteristics by treatment after 3:1 match on propensity score

	MINERVA N=438 (75%)	Reactive ATP N=146 (25%)	p-value
Age, mean ± SD	73 ± 9	73 ± 9	0.881
Gender (Male), % (n/Pts)	50.2% (220/438)	54.3% (76/140)	0.403
NYHA Class III or IV, % (n/Pts)	5.9% (22/372)	7.1% (6/84)	0.672
Ischemic Cardiomyopathy, % (n/Pts)	19.9% (87/438)	14.6% (21/144)	0.157
QRS, mean ± SD	94 ± 24	101 ± 31	0.187
MI, % (n/Pts)	8.9% (39/438)	6.8% (10/146)	0.438
CABG, % (n/Pts)	5.5% (24/437)	7.2% (8/111)	0.491
LBBB, % (n/Pts)	5.5% (24/438)	4.8% (7/146)	0.749
Diabetes, % (n/Pts)	17.1% (73/427)	19.1% (26/136)	0.590
Hypertension, % (n/Pts)	70.5% (299/424)	66.7% (96/144)	0.385
History of Stroke/TIA, % (n/Pts)	9.7% (42/435)	10.4% (12/115)	0.803
CHADS2 ≥ 2, % (n/Pts)	53.1% (212/399)	54.1% (72/133)	0.841
First degree AV block, % (n/Pts)	16.0% (70/438)	19.3% (28/145)	0.353
Second degree AV block, % (n/Pts)	4.8% (21/438)	4.8% (7/146)	1.000
Third degree AV block, % (n/Pts)	6.2% (27/438)	4.8% (7/146)	0.540
RBBB, % (n/Pts)	5.9% (26/438)	8.9% (13/146)	0.213
Left Hemiblock, % (n/Pts)	4.8% (21/438)	5.5% (8/145)	0.729
History of Syncope, % (n/Pts)	28.1% (119/423)	26.8% (30/112)	0.777
Valvular Surgery, % (n/Pts)	4.8% (21/438)	8.2% (12/146)	0.121
COPD, % (n/Pts)	6.6% (28/423)	8.5% (11/129)	0.459
SND, % (n/Pts)	85.2% (373/438)	84.8% (123/145)	0.922
LVEF, mean ± SD	57 ± 10	59 ± 9	0.089
LVEDD, mean ± SD	51 ± 10	53 ± 19	0.810
Class IC antiarrhythmic drugs, % (n/Pts)	6.8% (30/438)	6.8% (10/146)	1.000
Class II antiarrhythmic drugs, % (n/Pts)	40.9% (179/438)	37.7% (55/146)	0.495
Class III antiarrhythmic drugs, % (n/Pts)	18.9% (83/438)	19.2% (28/146)	0.951
Diuretic, % (n/Pts)	24.9% (109/438)	26.7% (39/146)	0.660
Anti-platelet, % (n/Pts)	37.4% (164/438)	30.3% (44/145)	0.122
OAC, % (n/Pts)	49.5% (217/438)	49.3% (72/146)	0.962
Digitalis, % (n/Pts)	2.7% (12/438)	3.4% (5/146)	0.670

NYHA=New York Heart Association; MI=myocardial infarction; CABG=coronary artery bypass graft; LBBB=left bundle branch block; RBBB=right bundle branch block; COPD=chronic obstructive pulmonary disease; SND=sinus node disease, LVEF=left ventricular ejection fraction; LVEDD=left ventricular end-diastolic diameter; OAC=oral anticoagulant therapy.

As shown in Figure 1, the 2-year incidence of AF >7 days in the real-world Reactive ATP group was very similar to that found in the MINERVA DDDRP+MVP arm: 12% (95%CI=7.1%-19.7%) vs. 13.8% (95%CI=8.9%-21.0%; p=0.732) respectively. Moreover, the incidence of AF found among the Reactive ATP population was significantly lower than the incidence measured in the MINERVA Control DDDR arm and the MINERVA MVP arm, corresponding to 25.8% (95%CI=19.4%-33.8%; p=0.012) and 25.9% (95%CI=18.7%-35.4%; p=0.025), respectively.

Similar comparisons were found for the 2-year incidence of AF >1 day, (Figure 2). The actuarial incidences of different burden of AF according to the two analysed groups are reported in Table 2.

Table 2 – Actuarial incidence of AF

Months	Control DDDR Incidence of event, % (95% CI)	MVP Incidence of event, % (95% CI)	DDDRP + MVP Incidence of event, % (95% CI)	Reactive ATP Incidence of event, % (95% CI)
1 day AF				
0	0.0% (0.0% - 0.0%)	0.0% (0.0% - 0.0%)	0.0% (0.0% - 0.0%)	0.0% (0.0% - 0.0%)
6	29.7% (23.1% - 37.7%)	23.1% (16.7% - 31.6%)	12.4% (8.0% - 18.9%)	16.6% (11.1% -24.3%)
12	38.3% (31.0% - 46.6%)	31.3% (23.8% - 40.4%)	20.5% (14.7% - 28.2%)	20.2% (14.1% - 28.5%)
18	42.6% (35.1% - 51.1%)	33.1% (25.5% - 42.4%)	23.6% (17.4% - 31.6%)	21.4% (15.0% - 29.9%)
24	44.3% (36.6% - 52.8%)	36.6% (28.5% - 46.2%)	28.0% (21.1% - 36.4%)	22.9% (16.1% - 31.9%)°
7 days AF				
0	0.0% (0.0% - 0.0%)	0.0% (0.0% - 0.0%)	0.0% (0.0% - 0.0%)	0.0% (0.0% - 0.0%)
6	16.1% (11.1% - 23.1%)	13.0% (8.2% - 20.4%)	4.9% (2.3% - 9.9%)	8.6% (4.8% - 15.0%)
12	20.4% (14.8% - 27.9%)	18.4% (12.5% - 26.7%)	7.9% (4.5% - 13.9%)	10.4% (6.1% - 17.3%)
18	24.2% (18.0% - 32.0%)	21.3% (14.9% - 29.9%)	9.5% (5.6% - 15.8%)	10.4% (6.1% - 17.3%)
24	25.8% (19.4% - 33.8%)	25.9% (18.7% - 35.4%)	13.8% (8.9% - 21.0%)	12.0% (7.1% - 19.7%)*

° $p<0.001$ vs. Minerva Control DDDR, $p=0.045$ vs. Minerva MVP

* $p=0.012$ vs. Minerva Control DDDR, $p=0.025$ vs. Minerva MV

Factors associated with occurrence of AF > 7 days

In the univariate analysis Reactive ATP enabled, MVP enabled and history of syncope were found associated with reduced occurrence of AF > 7 days, while previous CABG, I-degree AV block, II-degree AV block, valvular surgery and LVEF <50% were found associated with increased occurrence of AF > 7 days, (Table 3). Notably, AF reduction resulted not correlated with geographical origin: HR 1.66, 95% CI, p=0.270.

Table 3 – Factors associated with occurrence of AF>7 days (univariate analysis).

Variable	HR (95% CI)	p-value
Age (yrs)	1.00 (0.98 - 1.02)	0.987
Gender (Male)	0.96 (0.65 - 1.43)	0.848
Origin (European)	1.66 (0.67 - 4.08)	0.270
Reactive ATP	0.48 (0.31 - 0.73)	**0.001**
MVP	0.66 (0.44 - 0.99)	**0.047**
History of HF	0.72 (0.33 - 1.55)	0.396
NYHA Class III or IV	1.27 (0.55 - 2.92)	0.574
Ischemic Cardiomyopathy	1.48 (0.93 - 2.35)	0.095
QRS > 120	1.39 (0.68 - 2.81)	0.364
MI	1.36 (0.71 - 2.62)	0.353
CABG	2.64 (1.37 - 5.08)	**0.004**
LBBB	1.37 (0.64 - 2.96)	0.418
Diabetes	0.83 (0.48 - 1.43)	0.499
Hypertension	1.42 (0.88 - 2.27)	0.147
History of Stroke/TIA	0.71 (0.33 - 1.54)	0.389
CHADS2 ≥ 2	1.12 (0.74 - 1.71)	0.593
First degree AV block	1.68 (1.05 - 2.68)	**0.030**
Second degree AV block	2.18 (1.10 - 4.32)	**0.026**
Third degree AV block	0.85 (0.34 - 2.09)	0.720
RBBB	0.58 (0.21 - 1.58)	0.287
Left Hemiblock	0.56 (0.18 - 1.77)	0.324
History of Syncope	0.53 (0.31 - 0.91)	**0.022**
Valvular Disease	1.03 (0.32 - 3.27)	0.959
Valvular Surgery	2.63 (1.40 - 4.93)	**0.003**
COPD	0.96 (0.42 - 2.20)	0.927
SND	0.73 (0.45 - 1.20)	0.212

LVEF < 50 %	2.22 (1.19 - 4.15)	**0.013**
LVEDD > 50 mm	1.63 (0.85 - 3.13)	0.140

ATP=antitachycardia therapy pacing; MVP=managed ventricular pacing; NYHA=New York Heart Association; MI=myocardial infarction; CABG=coronary artery bypass graft; LBBB=left bundle branch block; TIA=transient ischemic attack; RBBB=right bundle branch block; COPD=chronic obstructive pulmonary disease; SND=sinus node disease, LVEF=left ventricular ejection fraction; LVEDD=left ventricular end-diastolic diameter.

In the multivariate model, Reactive ATP enabled, II-degree AV block, history of syncope and valvular surgery were found as independently associated with the risk of AF > 7 days (Table 4). Particularly, enabled Reactive ATP was associated with a risk reduction of 55% (HR 0.45, 95% CI, p=0.001).

Table 4 – Factors associated with occurrence of AF > 7 days – (multivariate analysis).

Variable	**HR (95% CI)**	**p-value**
Reactive ATP	0.45 (0.28 - 0.72)	**0.001**
Second degree AV block	2.22 (1.10 - 4.49)	**0.026**
History of Syncope	0.53 (0.31 - 0.91)	**0.022**
Valvular Surgery	2.21 (1.06 - 4.64)	**0.035**

Non-matched populations

The comparison between the 342 non-matched Reactive ATP patients and the MINERVA trial patients is reported in the Supplementary materials (Table S1, Figure S1).

Discussion

Main results

Our multicenter multinational research shows that: 1) Reactive ATP is associated with low incidence of persistent AF in real-world settings, confirming the findings of the MINERVA trial [5-6]. Results may suggest that the clinical benefit associated with Reactive ATP, previously tested in sinus node disease patients [6], may be extended also to patients with complete AV block.

Reactive ATP in real world practice

In our analysis, among the Reactive ATP patients the incidence of AF >7 days was similar to that found in the DDDRP+MVP MINERVA group, and significantly lower from that found in the MINERVA Control DDDR and MVP groups (Figure 1).

In particular, these new results confirm the hypothesis, suggested by Padeletti et al [6], that the key pacing feature in delaying AF disease progression is Reactive ATP. Indeed, in our research, preventive pacing algorithms were not used, and Reactive ATP was associated with the same capability to prevent progression to persistent AF as found in the MINERVA trial. [5-6] Interestingly, also history of syncope has been associated to reduction in AF >7 days occurrence both in univariate and multivariate analysis. This may be due to the fact that all the MINERVA patients, except for those in the MVP group, and most of patients in the Reactive ATP group had the sensor-driven rate response algorithm turned ON. This feature provides periodic instances of competitive atrial pacing, due to the sensor-triggered rate response, and this may prevent the onset of bradycardia episodes triggering AF.***New insights on Reactive ATP clinical benefit***

The MINERVA trial results mostly apply to sinus node disease patients, since persistent III-degree AV block was an exclusion criterium. [5-6] The results of our comparative study suggest the hypothesis that Reactive ATP is able to prevent progression to persistent AF also in patients with complete AV block. The fact that Reactive ATP may be associated with significant lower risk of long-lasting persistent AF independently from the device type (pacemaker, defibrillator, or resynchronization device) has been shown by Crossley et al. [7] in an observational study that did not make comparisons with MINERVA in view of the different setting (ICD, CRT devices). Our data confirm and extend those findings since in the analyses reported by Crossley et al. the information about bradycardia pacing indication or about AV conduction was not available.

We evaluated the clinical benefit of Reactive ATP in real-world practice of Italian and Japanese cardiology centres; Reactive ATP emerged as a predictor of AF progression prevention regardless of patients' origin. To date, the only other evidence available on Reactive ATP efficacy among Japanese patients was the very recent analysis from Ueda et al. [8] demonstrating a successful and safe reduction of AF burden by Reactive ATP, that was also associated with a lower incidence of HF hospitalization in patients implanted with CRT devices.

Clinical implications

The results of the MINERVA randomized controlled trial [5-6] together with real world data on patients wearing pacemaker, defibrillators and CRT devices [7-8] and together with our findings provide convincing evidence about the benefit of Reactive ATP, based on the intervention of this pacing algorithm when AF becomes slower or more regular. [6] Since safety of Reactive ATP has been fully proven [5], all these evidences may suggest to consider Reactive ATP algorithm enabling in patients wearing cardiac implantable devices.

A recent sub-analysis of the MINERVA trial has suggested that the prevention of persistent/permanent AF is not only a matter of programming Reactive ATP, but it is also associated with an appropriate choice of pacing mode according to patient characteristics. [9] Indeed, in that analysis the risk of AF > 7 days was lower (HR=0.58, 95%CI 0.34-0.99; p = 0.047) in patients with normal PR if programmed in MVP mode compared with DDDR mode, and it was lower (HR=0.65, 95%CI 0.43–0.99; p = 0.049) in patients with prolonged AV conduction if programmed in DDDR mode compared with MVP. [9] These results, on one hand, confirm previous findings [10-15] about right apical pacing deleterious effects and association with increased risk of developing AF, and on the other hand suggest the importance of left heart AV synchrony. According to the model by Chirife et al. [16] right apical pacing delays left ventricular contraction due to interventricular conduction time and may cause too short left heart AV intervals. Conversely delaying ventricular pacing aiming for spontaneous AV conduction may cause too long left heart intervals, in patients with prolonged AV conduction. In conclusion Reactive ATP should be considered as a useful tool to be programmed on top of optimal pacing mode, either DDD/DDDR in patients with AV block or MVP in patients with normal AV conduction. [17-19] In this perspectives all the current possibilities of advanced device programming should be integrated in a clinically-oriented

approach to pacemakers use, also in relationship to possible changes over time of arrhythmic patterns. [20-24]

Limitations

The present analysis compared data belonging to a randomized clinical trial and data from a real-world prospective data collection of patients followed according to clinical practice. This implies that the two patients' populations were not randomized and slightly heterogeneous. We attempted to reduce the possible biases by adjusting through propensity score models and sensitivity analyses.
We did not consider permanent AF in view of the difficulties in an observational collection of data.
This analysis provides additional insights to previous knowledge on the role of Reactive ATP in reducing the incidence of persistent AF among patients implanted with a pacemaker. However, due to its observational nature, it must be considered as an explanatory study, and a future randomized study may be needed to further support these observations.

Conclusions

This multicenter multinational real-world research suggests that in patients with AF, device algorithms allow to reduce device-detected AF of long duration (>7 days) as compared to control DDDR and that this positive effect is due to use of reactive ATP, with a minor, if any, impact of preventive pacing algorithms.

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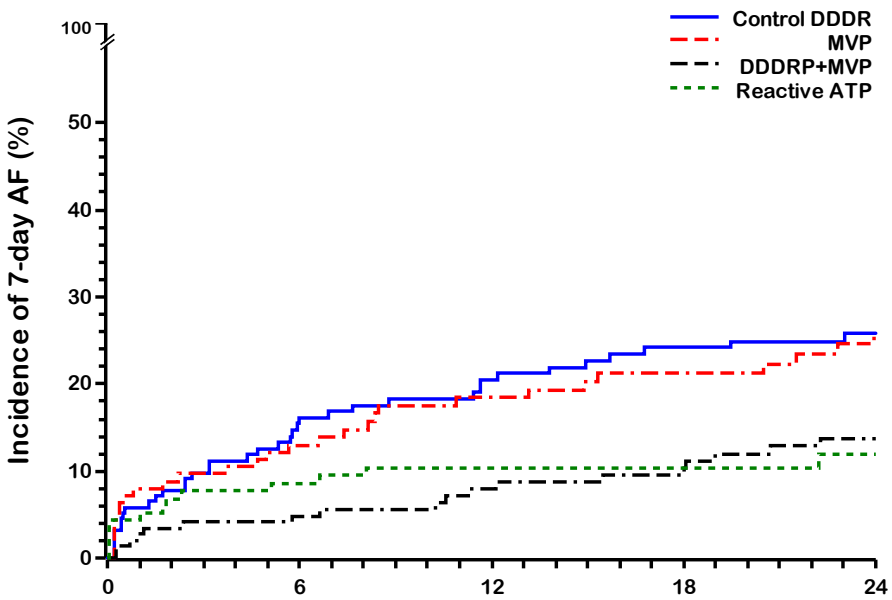
Figure legend

Figure 1 – Time to AF longer than 7 consecutive days

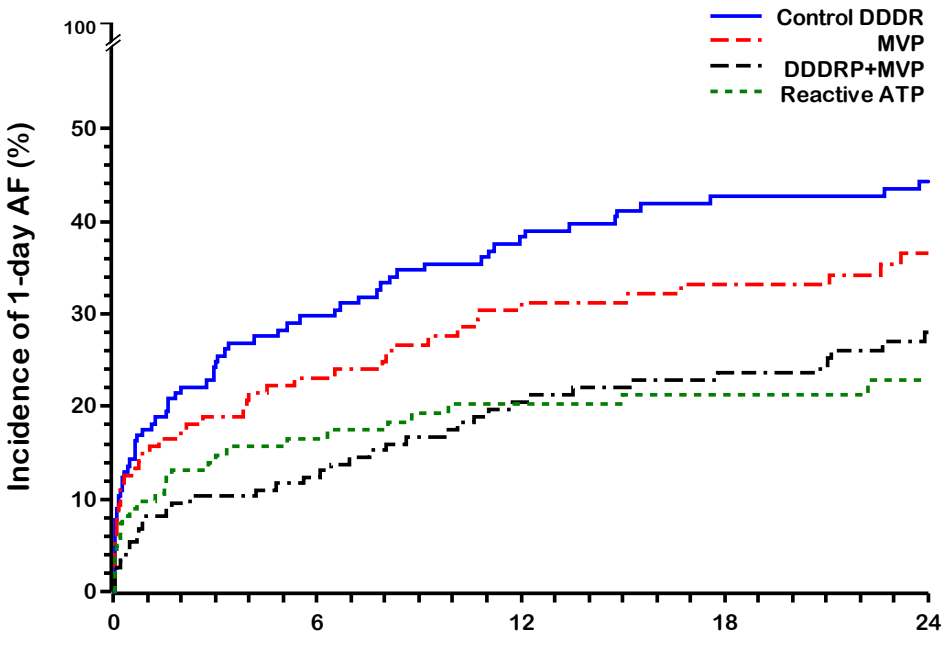
Figure 2 – Time to AF longer than 1 day

Figure 1 – Time to AF longer than 7 consecutive days



No. at Risk					
Control DDDR	156	118	109	99	82
MVP	132	100	87	79	54
DDDRP+MVP	150	131	117	110	78
Reactive ATP	146	102	89	69	48

Figure 2 – Time to AF longer than 1 day



No. at Risk					
Control DDDR	156	99	86	77	62
MVP	132	88	75	67	47
DDDRP+MVP	150	123	104	96	71
Reactive ATP	146	94	79	62	42