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Published in:
Scandinavian cardiovascular journal : SCJ

DOI:
[10.1080/14017431.2016.1260768](https://doi.org/10.1080/14017431.2016.1260768)

2017

Document Version:
Peer reviewed version (aka post-print)

[Link to publication](#)

Citation for published version (APA):
Jacobsson, J., Platonov, P. G., Reitan, C., Carlsson, J., & Borgquist, R. (2017). Atrial high rate episodes predict clinical outcome in patients with cardiac resynchronization therapy. *Scandinavian cardiovascular journal : SCJ*, 51(2), 74-81. <https://doi.org/10.1080/14017431.2016.1260768>

Total number of authors:
5

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Atrial high rate episodes predict clinical outcome in patients with cardiac resynchronization therapy

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Short title: Atrial high rate episodes predict outcome in CRT

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Funding Sources: This work was supported by grants from the Swedish Heart and Lung foundation, and by governmental funding of clinical research within the Swedish National Health Service.

Conflicts of interest: None

Abstract**Objectives**

Up to 50 % of patients qualified for cardiac resynchronization therapy (CRT) have documented atrial fibrillation (AF) prior to CRT-implantation. This finding is associated with worse prognosis but few studies have evaluated the importance of post-implant device-detected AF. This study aimed to assess the prognostic impact of device-detected atrial high rate episodes (AHRE), as a surrogate for atrial fibrillation (AF).

Design

Data was retrospectively obtained from consecutive patients receiving CRT. Baseline clinical data and data from CRT device-interrogations, performed at a median of 12.2 months after CRT-implantation, were evaluated with regard to prediction of the composite endpoint of death, heart transplant or appropriate shock therapy. Median follow-up time was 51 months post-implant.

Results

The study included 377 patients. Preoperative AF was present in 49 % and associated with worse outcome. The cumulative burden of AHRE at 12 months post-implant was an independent predictor of the primary endpoint. During the first 12 months after CRT-implantation, AHRE were detected in 25 % of the patients with no preoperative diagnosis of AF. This finding was not associated with worse outcome.

Conclusions

In CRT recipients, the cumulative burden of AHRE during first year of follow-up was associated with worse long-term clinical outcome. Prospective trials are needed to determine if a rhythm control strategy is to be preferred in patients with CRT.

Keywords: *cardiac resynchronization therapy, atrial fibrillation, atrial high rate episodes, device-diagnostics, long-term prognosis, mortality*

Introduction

Cardiac resynchronization therapy (CRT) is a well-validated treatment option for patients with congestive heart failure (HF), widened QRS-complex and signs of electrical dyssynchrony during sinus rhythm (SR).[1, 2, 3] However, atrial fibrillation (AF) is a common comorbidity to HF, and up to 50 % of HF patients qualified for CRT have some documented AF prior to CRT-implantation.[4] This finding is associated with worse prognosis [5, 6] but the prognostic impact of post-implant device-detected AF is more uncertain in a CRT population.[7, 8, 9, 10, 11, 12]

Automatic mode switching (AMS) algorithms, designed to prevent tracking of rapidly occurring signals sensed by atrial channels to the ventricles, can be used for the detection of atrial tachyarrhythmias. Such algorithms have been found to be reliable surrogate markers for atrial high rate episodes (AHRE) with a high sensitivity and specificity for AF[13]. As CRT devices are capable of detecting and storing any, even short-lasting AHRE and AMS-events during follow-up, the prognostic impact of post-implant device-detected AF can be studied in patients treated with CRT.

We hypothesized that a higher burden of device-detected AHRE early after device implantation is associated with worse clinical outcomes in CRT patients. The primary objective of the study was to assess the prognostic impact of AF in HF patients treated with CRT using a composite of death, heart transplant or appropriate shock therapy (whichever came first) as the primary endpoint. The secondary objective was to assess the 1-year AF incidence in patients treated with

CRT and no documented AF prior to implantation and to evaluate if new-onset AF could be associated with an adverse clinical outcome.

Materials and Methods

Study population

Data was retrospectively obtained from consecutive patients receiving CRT-P or CRT-D at a large volume tertiary care center in Sweden from 1999 to May 2008. Baseline clinical data as well as data from the follow-up CRT device-interrogations were evaluated with regard to prediction of the composite primary endpoint. Patients fulfilling guideline indications for CRT[14], with a successfully implanted device were included (Figure 1). The local ethics committee approved the study.

Previous history of AF

The preoperative rhythm diagnosis (no AF, non-permanent AF or Permanent AF) was obtained by record linkage with The Swedish National Patient Register and by reviewing medical records. The Swedish National Patient Register is administered by the Swedish National Board of Health and Welfare and includes data on main and secondary diagnoses at discharge from all public hospitals in Sweden starting in the year 1987. It also includes information about outpatient visits to hospitals. The register uses International Classification of Disease (ICD) codes, with the 9th edition (ICD-9) used between 1987 and 1996, and the 10th edition (ICD-10) used from 1997 and until today. AF was defined as the presence of any of the following ICD codes: 427D for ICD-9 and I48 for ICD-10. Patients were considered as having AF history if it was documented by either The Swedish National Patient Register or by medical records at any time prior to CRT-implantation. The Swedish National Patient Register has previously been validated regarding

diagnostic accuracy for atrial fibrillation.[15][16]

Assessment of post-operative AF incidence and burden of AHRE

For the purpose of the analysis regarding post-operative AF incidence, AMS episodes retrieved from device diagnostics were considered as equivalents of AF. When a device turned into AMS mode this was considered as an episode of AF and patients with no history of AF prior to implantation were considered as having new-onset AF.

The cumulative burden of AHRE during the first year of follow-up was obtained from routine device-interrogations performed at a median of 12.2 months (IQR 8.9-15.2 months) after CRT-implantation. Only patients who had available device-detected data after 3 months from CRT-implantation were included in the analyses regarding 1-year incidence of AF and the prognostic impact of the cumulative burden of AHRE during the first year post-implant. Manufacturer-specific nominal settings for detection of AMS and AHRE were used as default.

Statistics

SPSS Statistics for Macintosh, version 22.0 (IBM Corp. Armonk, NY) was used for all statistical analyses. The Kolmogorov-Smirnov Test, as well as visualization of histograms, was used to evaluate if continuous data were distributed normally or not. Continuous, normally distributed variables were reported as mean \pm standard deviation (SD). Non-continuous and continuous variables not normally distributed were reported as median \pm quartiles. The Kruskal-Wallis test was used to evaluate if the distribution of New York Heart Association Classification of heart failure (NYHA Class), ECG morphology, type of CRT manufacturer and mortality-cause were the same across groups. The Pearson chi-square test or Fisher's exact test were used to compare categorical variables. A univariate as well as a multivariate Cox-regression analysis was

performed to calculate possible predictors of the composite primary endpoint. Parameters with p-values < 0.1 in the univariate analysis were used in the multivariate analysis with stepwise backward conditional elimination in order to identify independent predictors. Kaplan Meier plots and log-rank tests were used to compare survival over time between groups.

Study outcome

The primary endpoint was a composite of death, heart transplant and appropriate shock therapy during follow-up (whichever came first).

Information regarding death dates was retrieved from the Swedish Death and Hospital Discharge Registries. Information regarding heart transplants was obtained by record linkage with The Swedish National Patient Register and from medical records, and information regarding appropriate shock therapies from device-interrogations in medical records. Patients were followed from the time of CRT-implantation until they reached the primary endpoint, or until 25th of May 2013 when data were retrieved from the National Patient Registries.

Results

Study population and data availability

The study included 377 consecutive patients from a large real-world population with CRT-treatment (n=377, median age 71 years, 85 % male, 62 % LBBB, 170 ms median QRS, 22 % LVEF, 57 % ischemic etiology). The percentage of CRT without defibrillator (CRT-P) was high (74 %). Median follow-up time was 51 months (IQR 17-83) from CRT-implantation.

Patient characteristics in regard to pre-implant AF

The baseline characteristics of the patients (Table 1) were similar for those with and without a

known AF diagnosis prior to implant. The differences were that patients with a history of permanent AF (PmAF) were slightly older (71 vs. 69 years, p-value 0.001), more symptomatic (more commonly in NYHA-class III or IV than I or II, p-value 0.02) and more often men (91 % vs. 81 %, p-value 0.02), compared to patients with no diagnosis of AF prior to implantation. As expected, antiarrhythmic drugs were most frequently used in patients with non-permanent AF (non-PmAF) prior to implantation, however these patients used significantly less angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) compared to patients with no diagnosis of AF (88 % vs. 96 %, p-value 0.003). Seventy-one percent of the patients had a CRT-device from the manufacturer Medtronic (Medtronic, Dublin, Leinster, Ireland), 17 % from St. Jude Medical (St. Jude Medical Inc, Saint Paul, Minnesota, USA) and 12 % from Biotronik (Biotronik SE & Co. KG, Berlin, Berlin, Germany).

During the first year of follow-up, the median percentage of achieved BiVP was significantly lower among patients with a history of PmAF compared to patients with no pre-implant AF and those with a history of non-PmAF, however even in the PmAF group the median BiVP was high. No significant difference regarding achieved BiVP was found when comparing patients with no diagnosis of AF before CRT implantation with patients with a history of non-PmAF.

Prognostic impact of the pre-implant AF history

A preoperative diagnosis of AF was found in 183 (49 %) patients and this was associated with a worse outcome (Figure 2, p-value < 0.001). No significant difference regarding outcome was found when comparing patients with a history of non-PmAF with patients with a history of PmAF (Figure 2, p-value 0.64). Patients with a history of PmAF, as well as patients with non-Pm AF preoperatively, had a significantly worse outcome compared to patients with no diagnosis of AF preoperatively (Figure 2, p-values 0.001 and 0.02 respectively). No difference was found

regarding mortality causes between groups. Heart failure was the most common mortality cause in all the preoperative rhythm diagnoses (Table 4).

Prognostic impact of new-onset AF during the first year after CRT-implantation

Among the 194 patients without a preoperative AF diagnosis, 132 patients qualified for the analysis of the new-onset AF first year post-implant due to the device interrogation data availability and did not reach the primary endpoint before the control device-interrogation (10 received appropriate shock therapy prior to the chosen ICD control and were excluded from the analysis). The definition of AMS did not differ among the different manufacturers and the distribution of manufacturers did not differ between the different categories of preoperative rhythm diagnosis (Kruskal-Wallis test, p-value 0.66). Thirty-three (25 %) of the included 132 patients had one or more AMS events during first year of follow-up and were considered as having new-onset AF during the first year post-implant. The patients with no preoperative diagnosis of AF who did not have documented AF during the first year post-implant did not have a superior outcome compared to those who had new-onset AF detected during the first year post-implant (Figure 3, p-value 0.67). Among these 33 patients with new-onset AF, the total burden of AHRE during the first year post-implant was low, ranging from seconds up to 1 % of the total time. Nine of these 33 patients had clinically recognized AF during follow-up.

If only mortality and heart transplant were considered as endpoint, 142 patients were included in the analysis and 36 (25 %) were, based on AMS events, considered as having new-onset AF during the first year post-implant. These patients did not have an inferior outcome compared to those who did not have new-onset AF (p-value 0.54). Among the 36 patients with new-onset AF, the total burden of AHRE was relatively low, ranging from seconds up to 5 % of the total time.

Device-derived data from the first year after CRT-implantation

A total of 220 patients were included in the analysis of the effect of the cumulative burden of AHRE on the outcome (Figure 1). The median burden of AHRE during the first year is presented in Table 1.

In the multivariate Cox regression analysis, the cumulative burden of AHRE during the first year of follow-up was an independent predictor of the composite primary endpoint; HR 1.1 for each 10 % increase in post-implant burden of AHRE (Table 3). Other independent predictors were LVEF before CRT-implantation and ischemic etiology of HF. None of the other parameters significantly differing among the preoperative rhythm diagnoses turned out as independent predictors of the composite primary outcome.

Discussion

In HF patients treated with CRT a preoperative diagnosis of AF was associated with a worse long-term outcome, thus supporting earlier observations. [4, 5, 6, 17, 18] New-onset AF during the first year post-implant was found in 25 % of the patients with no previous history of AF before CRT-implantation. New-onset AF was not related to an inferior outcome, and the prognostic impact of the short device-detected AHRE first observed *after* device implantation remains unclear. However, in patients treated with CRT, cumulative burden of AHRE during the first year of follow-up rather than mere presence of pre-implant AF history may improve risk stratification.

Incidence of AF during the first year after CRT-implantation

As a diagnosis of AF may alter treatment, AF is important to diagnose, especially in patients with high CHA₂DS₂-VASc scores and thus high risk of stroke. In our study, AF was detected in 25 %

of patients with no diagnosis of AF prior to CRT-implantation and in total 57 % of all patients had documented AF by the end of the first year of follow-up.

Prior to this study, several have studied device-detected data to assess the incidence and/or the clinical importance of AF in CRT-patients[7, 8, 9, 10, 11, 12]. However, the monitoring periods, as well as the definitions of AF have varied, why it is difficult to make comparisons and conclusions.

There is a strong correlation between the prevalence of AF and the severity of HF[19]. In patients with less advanced HF, the incidence of AF has been found to be lower compared to the results of our study. In the MADIT-CRT sub-study only including patients in NYHA class I or II, AF incidence ranged from 3 to 9 %, within an average of 2.9 years of monitoring[20]. As 90 % of the patients included in our study were in NYHA class III or IV, it is not surprising that we found a higher AF incidence. Another study on patients in NYHA Class II-IV and mean LVEF of 23 %, new-onset AF was found in 25 % within 32 months of follow-up.[12] Even though the baseline characteristics of these patients did not differ greatly from ours, the AF incidence was lower, which may reflect the difference between patients in randomized trials such as the MADIT-CRT being less affected by comorbidity compared to an all-comer population such as the patients in our registry based study cohort.

New-onset AF has been associated with more cardiac adverse events and worse echocardiographic response to CRT [9, 12]. In our study patients with new-onset AF did not have an inferior outcome compared to those where no AF was found during the first year of follow-up, but the cumulative burden of AHRE was very low in general. It remains unclear whether short episodes of device-detected AHRE should be considered to be of clinical importance and if such

detections should alter treatment strategies. Only nine of the 33 patients with AHRE during first year of follow-up had clinically recognized AF during follow-up, according to medical records, suggesting that most patients were asymptomatic and that short episodes of AHRE seldom result in AF as a diagnosis.

A recently published prospective study demonstrated that short episodes of device-detected AF were not associated with a higher risk of clinical events, such as heart failure, stroke, hospitalization, or mortality over the course of two years of follow-up[21]. These findings are in line with our results, suggesting that clinicians should not overreact to short device-detected episodes of AF. However, the study only included patients with conventional pacemakers with or without ICD: s, and it is important to recognize that demographics differed significantly from a typical CRT-population such as ours.

The prognostic aspect of the device-detected burden of AHRE

Our findings provide further insights into the clinical importance of device-detected AHRE in CRT recipients and show that the cumulative burden of AHRE during the first year of follow-up turned out as an independent predictor in the multivariate analysis.

The reason for the negative impact of AF on prognosis in patients receiving CRT-therapy is believed, at least in part, to be related to the reduction of the time in biventricular pacing (BiVP). In our study, however, BiVP did not qualify as a predictor of the composite primary outcome in neither uni- nor multivariate analysis. The reason for that could be that even though we observed differences in regard to BiVP between AF groups, the percent of BiVP was very high in all groups thus fulfilling minimal requirements for the BiVP to be effective contributor for improving the outcome in HF.

Current AF guidelines regarding rate- vs. rhythm-control are to a great extent based on multicenter, randomized studies with patients differing significantly from a normal CRT-population.[22, 23, 24, 25]. These studies have not shown any advantage of a rhythm-control strategy.

Patients fulfilling standard CRT-indications represent a special population and one may speculate if CRT recipients could benefit from a rhythm-strategy after all. It is also important to recognize CRT-implantation as an intervention that potentially changes hemodynamics. Changed hemodynamics can result in myocardial remodeling over time,[26] making it very difficult to compare patients treated with CRT to others. As a diagnosis of AF is very frequent among patients qualified for CRT it is crucial to assess if this very special category of patients could benefit from spending less time in AF.

The cumulative burden of device-detected AHRE post-implant has previously been found to have an independent and prognostic rule in patients treated with CRT.[8] Lenarczyk et al. recently studied device-collected data on AF episodes during 24 months and found that for each additional per-cent of time spent in AF mortality increased by 5 %. Even though Lenarczyk et. al's study population was younger at CRT-implantation and only 13 % had a preoperative diagnosis of AF vs. 49 % in this study, the etiology of HF, median LVEF and QRS-duration were similar to the population we studied.

As a dichotomized variable, the AHRE burden in pacemaker patients has been identified to increase the risk of death or stroke.[11, 27, 28] Yet, pre-specified cut-points as well as the analyzed variables differed. Our data show that the relative risk of reaching the composite primary endpoint is elevated by 10 % for each additional 10 % of time with AHRE during first

year after CRT-implantation.

AF in patients with advanced HF may be a marker of a more severe disease or the co-morbidity that directly worsens prognosis. Even though plausible, the causality link between AF burden and poor outcome has not been proven. The strong association of AF burden with poor clinical outcome justifies further research aimed at assessing the effect of aggressive rhythm-control strategies in patients with advanced HF and recurrent AF. Anti-arrhythmic drugs are associated with adverse effects and may not be suitable for all patients. For CRT recipients with systolic HF, the availability of indicated anti-arrhythmic drug options is limited to amiodarone, the use of which is associated with significant side-effects, thus making rhythm-control in this patient category challenging.[23]

More studies are required to assess if rhythm-control could improve clinical outcome in patients treated with CRT. Device-diagnostics are easily assessable but until now published studies in this area have differed considerably regarding study-design. It is appealing that data from standard device-interrogations at regular follow-up visits may add prognostic value but an issue is that it is not yet established what time-duration of AHRE is needed to significantly have an effect on the outcome.

Limitations

This study was an observational, single-center retrospective study, with the inherent risk of bias in patient selection. All patients were covered by the Swedish state health insurance and all cases were referred to the same clinic, making a socio-economic bias unlikely. There was no standardized way in which physicians record kept device-stored data and we did not study intra-cardiac electrograms why some documented AHRE might be false and not represent true AF. The

study would have been more robust if intra-cardiac electrograms had been reviewed especially as short device-detected AHRE have been found to be more unreliable[29]. However, AMS algorithms and AHRE detected by CRT-devices have in general been found to be trustworthy surrogate markers for atrial tachyarrhythmias with a high sensitivity and specificity for AF[13, 30].

Conclusions

In patients treated with CRT, the incidence of AF is high and a preoperative diagnosis of AF is associated with worse long-term clinical outcome. In patients with no preoperative history of AF, the clinical consequence of new-onset device-detected AF episodes remains uncertain but the results of this study corresponds well to recent findings and implies that such episodes are of minor importance. In our cohort, the cumulative burden of AHRE during first year of follow-up was an independent predictor of the composite primary outcome and our findings suggest that the burden of AHRE during early follow-up, rather than mere presence of pre-implant AF history, may improve risk stratification. However, it remains debatable if AF simply is a marker of a more severe disease or if patients with CRT treatment could benefit from spending less time in AF and prospective trials are needed to determine if a rhythm control strategy is to be preferred in this group of patients.

References

1. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA, 3rd, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, American College of Cardiology F, American Heart Association Task Force on Practice G, Heart Rhythm S. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2013;127:e283-352.
2. Moss AJ, Hall WJ, Cannom DS, Klein H, Brown MW, Daubert JP, Estes NA, 3rd, Foster E, Greenberg H, Higgins SL, Pfeffer MA, Solomon SD, Wilber D, Zareba W, Investigators M-CT. Cardiac-resynchronization therapy for the prevention of heart-failure events. *N Engl J Med*. 2009;361:1329-38.
3. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L, Cardiac Resynchronization-Heart Failure Study I. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med*. 2005;352:1539-49.
4. Brignole M, Auricchio A, Baron-Esquivias G, Bordachar P, Boriani G, Breithardt OA, Cleland J, Deharo JC, Delgado V, Elliott PM, Gorenek B, Israel CW, Leclercq C, Linde C, Mont L, Padeletti L, Sutton R, Vardas PE, Guidelines ESCCfP, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendra M, Torbicki A, Wijns W, Windecker S, Document R, Kirchhof P, Blomstrom-Lundqvist C, Badano LP, Aliyev F, Bansch D,

Baumgartner H, Bsata W, Buser P, Charron P, Daubert JC, Dobreanu D, Faerestrand S, Hasdai D, Hoes AW, Le Heuzey JY, Mavrakis H, McDonagh T, Merino JL, Nawar MM, Nielsen JC, Pieske B, Poposka L, Ruschitzka F, Tendera M, Van Gelder IC, Wilson CM. 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: the Task Force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). *Eur Heart J*. 2013;34:2281-329. Epub 2013/06/27.

5. Lopes C, Pereira T, Barra S. Cardiac resynchronization therapy in patients with atrial fibrillation: a meta-analysis. *Rev Port Cardiol*. 2014;33:717-25. Epub 2014/12/03.

6. Wilton SB, Leung AA, Ghali WA, Faris P, Exner DV. Outcomes of cardiac resynchronization therapy in patients with versus those without atrial fibrillation: a systematic review and meta-analysis. *Heart Rhythm*. 2011;8:1088-94. Epub 2011/02/23.

7. Witt CT, Kronborg MB, Nohr EA, Mortensen PT, Gerdes C, Nielsen JC. Early detection of atrial high rate episodes predicts atrial fibrillation and thromboembolic events in patients with cardiac resynchronization therapy. *Heart Rhythm*. 2015.

8. Lenarczyk R, Jedrzejczyk-Patej E, Szulik M, Mazurek M, Podolecki T, Kowalczyk J, Kowalski O, Sredniawa B, Kalarus Z. Atrial fibrillation in cardiac resynchronization recipients with and without prior arrhythmic history. How much of arrhythmia is too much? *Cardiol J*. 2015. Epub 2015/01/08.

9. Shanmugam N, Boerdlein A, Proff J, Ong P, Valencia O, Maier SK, Bauer WR, Paul V, Sack S. Detection of atrial high-rate events by continuous home monitoring: clinical significance in the heart failure-cardiac resynchronization therapy population. *Europace*. 2012;14:230-7.

10. Santini M, Gasparini M, Landolina M, Lunati M, Proclemer A, Padeletti L, Catanzariti D, Molon G, Botto GL, La Rocca L, Grammatico A, Boriani G, cardiological centers participating in ClinicalService P. Device-detected atrial tachyarrhythmias predict adverse outcome in real-world patients with implantable biventricular defibrillators. *J Am Coll Cardiol.* 2011;57:167-72.
11. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, Investigators A. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med.* 2012;366:120-9.
12. Borleffs CJ, Ypenburg C, van Bommel RJ, Delgado V, van Erven L, Schalij MJ, Bax JJ. Clinical importance of new-onset atrial fibrillation after cardiac resynchronization therapy. *Heart Rhythm.* 2009;6:305-10. Epub 2009/03/03.
13. Passman RS, Weinberg KM, Freher M, Denes P, Schaechter A, Goldberger JJ, Kadish AH. Accuracy of mode switch algorithms for detection of atrial tachyarrhythmias. *J Cardiovasc Electrophysiol.* 2004;15:773-7.
14. Vardas PE, Auricchio A, Blanc JJ, Daubert JC, Drexler H, Ector H, Gasparini M, Linde C, Morgado FB, Oto A, Sutton R, Trusz-Gluza M, European Society of C, European Heart Rhythm A. Guidelines for cardiac pacing and cardiac resynchronization therapy. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in collaboration with the European Heart Rhythm Association. *Europace.* 2007;9:959-98.
15. Baturova MA, Lindgren A, Carlson J, Shubik YV, Bertil Olsson S, Platonov PG. Atrial fibrillation in patients with ischaemic stroke in the Swedish national patient registers: how much do we miss? *Europace.* 2014;16:1714-9.

16. Smith JG, Platonov PG, Hedblad B, Engstrom G, Melander O. Atrial fibrillation in the Malmo Diet and Cancer study: a study of occurrence, risk factors and diagnostic validity. *European journal of epidemiology*. 2010;25:95-102.
17. Upadhyay GA, Choudhry NK, Auricchio A, Ruskin J, Singh JP. Cardiac resynchronization in patients with atrial fibrillation: a meta-analysis of prospective cohort studies. *J Am Coll Cardiol*. 2008;52:1239-46. Epub 2008/10/18.
18. Wilton SB, Kavanagh KM, Aggarwal SG, Philippon F, Yee R, Cowan K, Exner DV. Association of rate-controlled persistent atrial fibrillation with clinical outcome and ventricular remodelling in recipients of cardiac resynchronization therapy. *Can J Cardiol*. 2011;27:787-93. Epub 2011/09/13.
19. Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. *Am J Cardiol*. 2003;91:2D-8D.
20. Brenyo A, Link MS, Barsheshet A, Moss AJ, Zareba W, Wang PJ, McNitt S, Huang D, Foster E, Estes M, 3rd, Solomon SD, Goldenberg I. Cardiac resynchronization therapy reduces left atrial volume and the risk of atrial tachyarrhythmias in MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy). *J Am Coll Cardiol*. 2011;58:1682-9.
21. Swiryn S, Orlov MV, Benditt DG, DiMarco JP, Lloyd-Jones DM, Karst E, Qu F, Slawsky MT, Turkel M, Waldo AL, Investigators RR. Clinical Implications of Brief Device-Detected Atrial Tachyarrhythmias in a Cardiac Rhythm Management Device Population: Results from the Registry of Atrial Tachycardia and Atrial Fibrillation Episodes. *Circulation*. 2016;134:1130-40.
22. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, Kellen JC, Greene HL, Mickel MC, Dalquist JE, Corley SD, Atrial Fibrillation Follow-up

Investigation of Rhythm Management I. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347:1825-33. Epub 2002/12/06.

23. European Heart Rhythm A, European Association for Cardio-Thoracic S, Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J.* 2010;31:2369-429. Epub 2010/08/31.

24. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Kober L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Ronnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Guidelines ESCCfP. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J.* 2012;33:1787-847. Epub 2012/05/23.

25. Hagens VE, Crijns HJ, Van Veldhuisen DJ, Van Den Berg MP, Rienstra M, Ranchar AV, Bosker HA, Kamp O, Tijssen JG, Veeger NJ, Van Gelder IC, group RACvEcfpafs. Rate control versus rhythm control for patients with persistent atrial fibrillation with mild to moderate heart failure: results from the RAtE Control versus Electrical cardioversion (RACE) study. *Am Heart J.* 2005;149:1106-11. Epub 2005/06/25.

26. Daubert C, Gold MR, Abraham WT, Ghio S, Hassager C, Goode G, Szili-Torok T, Linde C, Group RS. Prevention of disease progression by cardiac resynchronization therapy in

patients with asymptomatic or mildly symptomatic left ventricular dysfunction: insights from the European cohort of the REVERSE (Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction) trial. *J Am Coll Cardiol.* 2009;54:1837-46.

27. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C, Miller C, Qi D, Ziegler PD. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circulation Arrhythmia and electrophysiology.* 2009;2:474-80.

28. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, Cook J, Paraschos A, Love J, Radoslovich G, Lee KL, Lamas GA, Investigators M. Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). *Circulation.* 2003;107:1614-9.

29. Kaufman ES, Israel CW, Nair GM, Armaganijan L, Divakaramenon S, Mairesse GH, Brandes A, Crystal E, Costantini O, Sandhu RK, Parkash R, Connolly SJ, Hohnloser SH, Healey JS, Committee AS, Investigators. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT. *Heart Rhythm.* 2012;9:1241-6.

30. Purerfellner H, Gillis AM, Holbrook R, Hettrick DA. Accuracy of atrial tachyarrhythmia detection in implantable devices with arrhythmia therapies. *Pacing Clin Electrophysiol.* 2004;27:983-92.

Tables and figures

Table 1. Baseline characteristics of the patients stratified for known rhythm diagnosis preoperatively.

| Parameter | All (n=377) | No AF (n=194) | Non-pm AF (n=70) | Pm AF (n=113) | No AF vs. Non-pm AF | No AF vs. Pm AF | Non-pm vs. Pm AF |
|--|---------------|---------------|------------------|-----------------|---------------------|------------------|------------------|
| Male | 321 (85 %) | 158 (81 %) | 60 (86 %) | 103 (91 %) | 0.42 | 0.02 | 0.25 |
| Age (years, median, IQR) | 71 (63-76) | 69 (60-75) | 70 (65-76) | 71 (67-77) | 0.07 | 0.001 | 0.38 |
| NYHA Class | | | | | | | |
| Class I | 3 (0.9 %) | 3 (1.8 %) | 0 (0 %) | 0 (0 %) | 0.14 | 0.02 | 0.81 |
| Class II | 29 (8.9 %) | 19 (11 %) | 6 (10 %) | 4 (4.0 %) | | | |
| Class III | 262 (80 %) | 133 (79 %) | 45 (75 %) | 84 (85 %) | | | |
| Class IV | 33 (10 %) | 13 (7.7 %) | 9 (15 %) | 11 (11 %) | | | |
| QRS duration ms (IQR) | 170 (154-184) | 168 (154-184) | 171 (156-184) | 168 (150-185) | 0.66 | 0.95 | 0.69 |
| LVEF (IQR) | 22 (20-25) | 24 (20-25) | 22 (17-25) | 22 (20-25) | 0.56 | 0.80 | 0.70 |
| Ischemic etiology | 216 (57 %) | 109 (56 %) | 46 (66 %) | 61 (54 %) | 0.17 | 0.81 | 0.53 |
| ECG Morphology | | | | | | | |
| LBBB | 232 (62 %) | 135 (70 %) | 42 (61 %) | 55 (49 %) | 0.15 | <0.001 | 0.09 |
| RBBB | 4 (1.1 %) | 2 (1.0 %) | 1 (1.4 %) | 1 (0.9 %) | | | |
| Atypical | 49 (13 %) | 23 (12 %) | 9 (13 %) | 17 (15 %) | | | |
| Paced | 90 (24 %) | 33 (17 %) | 17 (25 %) | 40 (35 %) | | | |
| ACEi or ARB use | 345 (94 %) | 182 (96 %) | 59 (88 %) | 104 (95 %) | 0.01 | 0.47 | 0.12 |
| β-Blocker use | 301 (82 %) | 155 (82 %) | 56 (82 %) | 90 (82 %) | 0.95 | 0.97 | 0.93 |
| Loop diuretic use | 337 (93 %) | 173 (92 %) | 63 (94 %) | 101 (93 %) | 0.59 | 0.84 | 0.73 |
| Class I or III antiarrhythmic use | 52 (14 %) | 20 (11 %) | 17 (25 %) | 15 (14 %) | 0.003 | 0.42 | 0.05 |
| Hypertension | 134 (36 %) | 71 (37 %) | 22 (31 %) | 41 (36 %) | 0.44 | 0.96 | 0.50 |
| Diabetes | 128 (34 %) | 67 (35 %) | 18 (26 %) | 43 (38 %) | 0.18 | 0.54 | 0.09 |
| Digoxin use | 129 (35 %) | 54 (29 %) | 26 (38 %) | 49 (45 %) | 0.15 | 0.005 | 0.38 |
| CRT-Pacemaker | 278 (74 %) | 142 (73 %) | 45 (64 %) | 91 (81 %) | 0.18 | 0.14 | 0.02 |
| Creatinine (g/L) (IQR) | 110 (90-138) | 110 (89-136) | 114 (91-150) | 114 (89-140) | 0.63 | 0.95 | 0.70 |
| Hemoglobin (g/L) (SD) | 134 (17) | 135(17) | 132 (17) | 133 (120 & 147) | 0.27 | 0.73 | 0.51 |
| Median BiVP first year (IQR) | 99 (97-100) | 100 (98-100) | 99 (97-100) | 97 (88-100) | 0.56 | <0.001 | 0.03 |
| Median burden of AHRE first year (IQR) | 0 (0-100) | 0 (0-0) | 0 (0-98) | 100 (100-100) | <0.001 | <0.001 | <0.001 |

Abbreviations: ACEi=Angiotensin Converting Enzyme inhibitor, AF=Atrial Fibrillation, AHRE=Atrial High Rate Episodes, ARB=Angiotensin II Receptor Blocker, BiVP=Biventricular Pacing, CRT-Pacemaker=Cardiac Resynchronization Therapy without implantable cardioverter defibrillator, ECG=Electrocardiography, ICD=Implantable Defibrillator, LBBB=Left Bundle Branch Block, LVEF=Left Ventricular Ejection Fraction, NYHA=New York Heart Association classification of heart failure, Pm=Permanent atrial fibrillation, RBBB=Right Bundle Branch Block, SR=Sinus Rhythm.

Table 2. Univariate Cox-regression analysis.

| Parameter | n=377 | p-value | HR | CI |
|--|--------------|----------------|-----------|-----------|
| Male | 341 | 0.28 | 0.81 | 0.56-1.2 |
| Age, median years | 341 | < 0.001 | 1.0 | 1.0-1.0 |
| Ischemic etiology or not | 341 | < 0.001 | 1.6 | 1.2-2.1 |
| NYHA Class I-II compared to III-IV | 287 | 0.22 | 0.71 | 0.41-1.2 |
| QRS Duration, ms | 333 | 0.40 | 1.0 | 1.0-1.0 |
| Myocardial infarction | 336 | 0.001 | 1.6 | 1.2-2.1 |
| Hypertension | 341 | 0.53 | 1.1 | 0.83-1.4 |
| Diabetes | 341 | 0.32 | 1.1 | 0.88-1.5 |
| LVEF | 330 | 0.002 | 0.97 | 0.95-0.99 |
| β-Blocker use | 333 | 0.27 | 0.83 | 0.60-1.2 |
| ACEi or ARB use | 332 | 0.29 | 0.76 | 0.46-1.3 |
| Loop diuretic use | 330 | 0.08 | 1.7 | 0.93-3.0 |
| Class I or III antiarrhythmic use | 330 | 0.14 | 1.3 | 0.91-1.9 |
| Digoxin use | 331 | 0.17 | 1.2 | 0.92-1.6 |
| Anticoagulant use | 338 | 0.02 | 1.4 | 1.0-1.8 |
| LBBB on ECG | 339 | 0.06 | 0.77 | 0.59-1.0 |
| Creatinine (g/L) | 252 | 0.29 | 1.0 | 1.0-1.0 |
| Haemoglobin (g/L) | 236 | 0.42 | 1.0 | 0.99-1.0 |
| AF diagnosis before CRT-implantation | 341 | < 0.001 | 1.6 | 1.2-2.1 |
| Previous pacemaker or ICD | 338 | 0.10 | 1.3 | 1.0-1.7 |
| CRT-P compared to CRT-D | 341 | 0.68 | 0.93 | 0.67-1.3 |
| Cumulative burden of AHRE per 10 % during the first year | 220 | 0.007 | 1.1 | 1.0-1.1 |
| Achieved BiVP during the first year | 219 | 0.10 | 0.99 | 0.97-1.0 |

Abbreviations: ACEi=Angiotensin Converting Enzyme inhibitor, AF=Atrial Fibrillation, AHRE=Atrial High Rate Episodes, ARB=Angiotensin II Receptor Blocker, BiVP=Biventricular pacing, ECG=Electrocardiography, ICD=Implantable Cardioverter Defibrillator, LBBB=Left Bundle Branch Block, LVEF=Left Ventricular Ejection Fraction, NYHA=New York Heart Association classification of heart failure.

Table 3. *Multivariate Cox-regression analysis. Independent predictors of the primary outcome.*

| Parameter | p-value | HR | CI |
|--|----------------|-----------|-----------|
| Cumulative burden of AHRE per 10 % during the first year | 0.003 | 1.1 | 1.0-1.1 |
| Ischemic etiology | < 0.001 | 2.0 | 1.4-3.0 |
| LVEF | 0.01 | 0.97 | 0.94-0.99 |

Abbreviations: AHRE=Atrial High Rate Episodes, LVEF=Left Ventricular Ejection Fraction.

Table 4. Mortality causes stratified for known rhythm diagnosis preoperatively.

| Mortality cause | No AF | Non-pm AF | Pm AF | No AF vs. non-pm AF | No AF vs. Pm AF | Non-pm AF vs. Pm AF |
|------------------------|--------------|------------------|--------------|----------------------------|------------------------|----------------------------|
| Heart failure | 41 (42 %) | 25 (61 %) | 33 (45 %) | 0.16 | 0.40 | 0.41 |
| Cardiac arrest | 19 (20 %) | 2 (5 %) | 20 (27 %) | | | |
| Other | 37 (38 %) | 14 (34 %) | 21 (28 %) | | | |

Abbreviations: AF=Atrial Fibrillation, Pm=Permanent

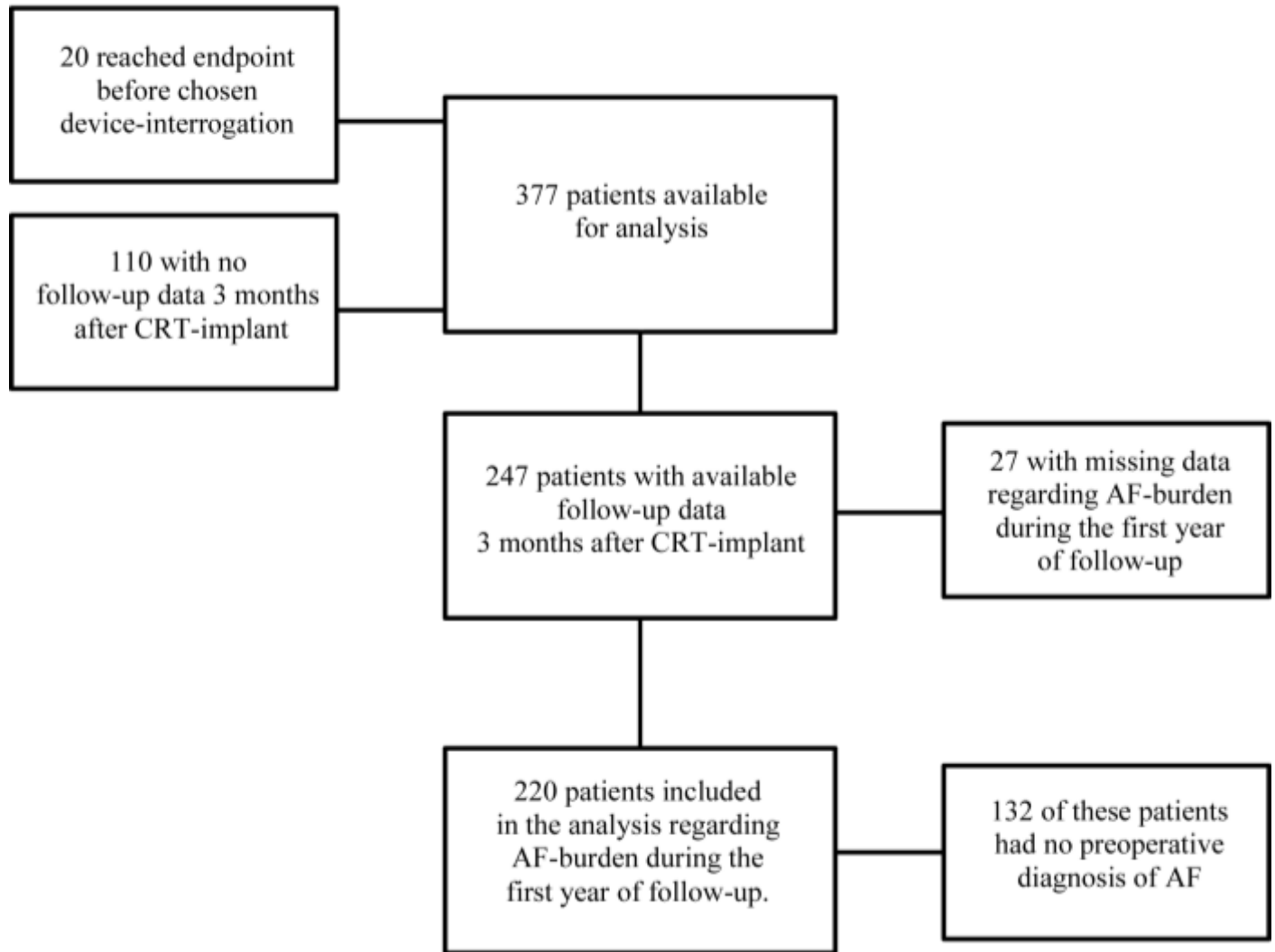


Figure 1: Flowchart of included patients.

Abbreviations: AHRE=Atrial High Rate Episodes, CRT= Cardiac Resynchronization Therapy.

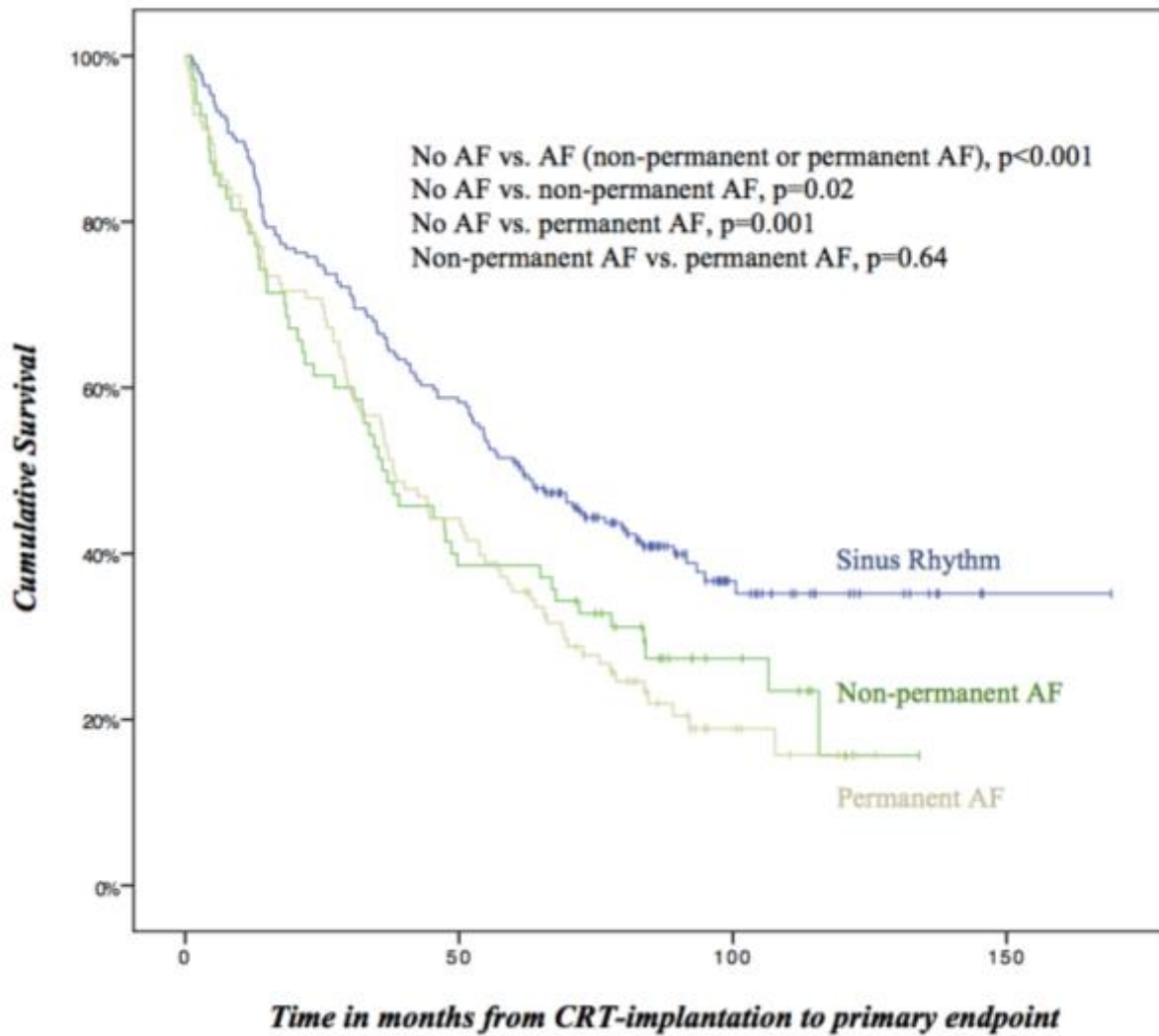


Figure 2. Kaplan Meier plot stratified for "AF diagnosis pre-operatively".

Abbreviations: AF=Atrial Fibrillation, CRT=Cardiac Resynchronization Therapy.

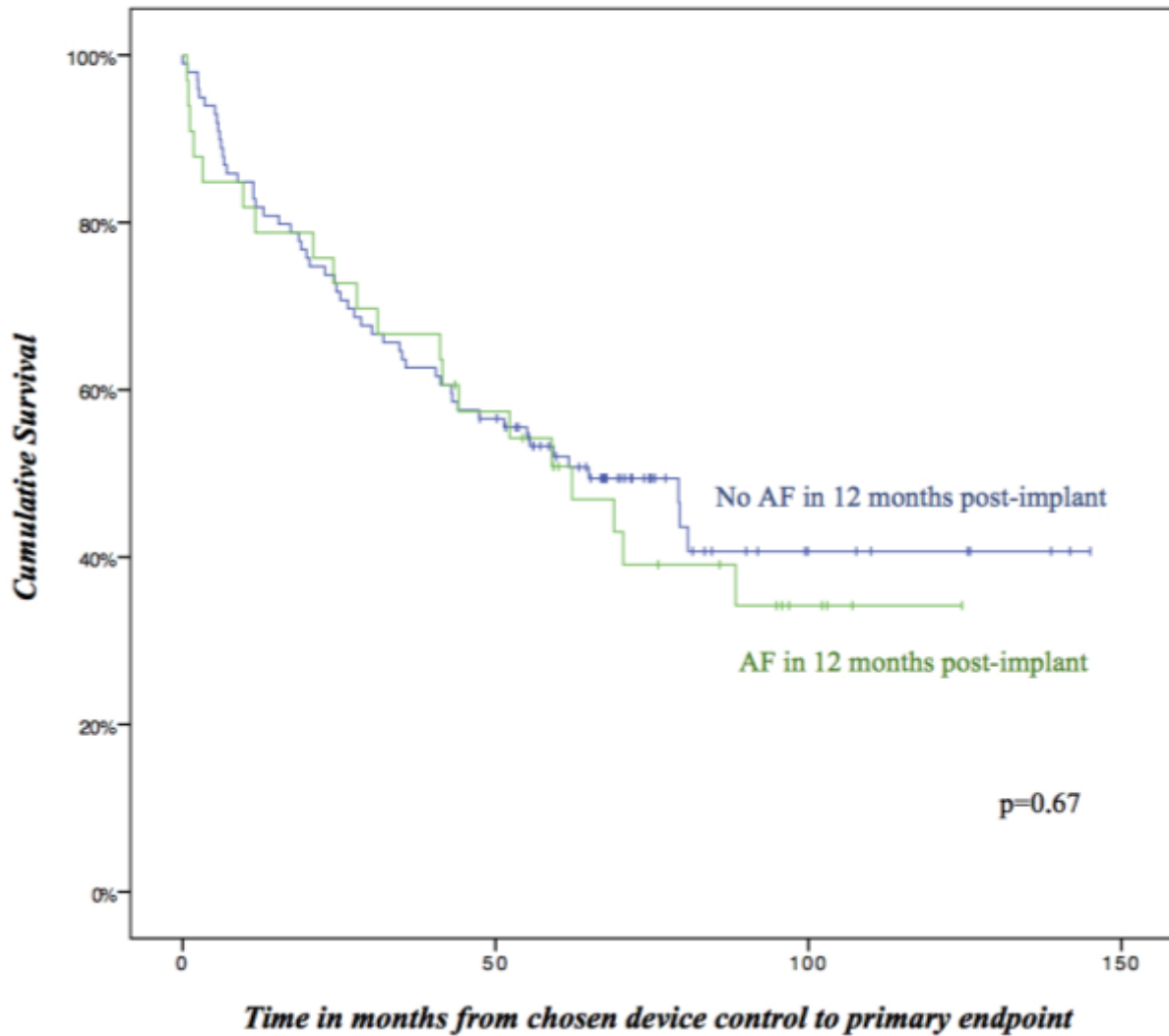


Figure 3. Kaplan Meier plot stratified for "new-onset AF or not within the first year after CRT-implantation". Only patients with available data from device-interrogations 3 months after CRT-implantation and no preoperative diagnosis of AF included.

Abbreviations: AF=Atrial Fibrillation, CRT=Cardiac Resynchronization Therapy.