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Temporal Trends over a Decade of Defibrillator Therapy for Primary Prevention in Community Practice

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Background – Technology and clinical practice surrounding the use of the primary prevention implantable cardioverter defibrillator (ICD) are in a state of constant evolution.

The purpose of the study was to test the hypothesis of significant temporal trends in characteristics and outcomes over a decade of ICD therapy.

Methods – Between 2002-2012, 5,539 consecutive patients (age 62.5 ± 11 years, 84.9% male), with ischemic or non-ischemic cardiomyopathy, implanted with a primary prevention ICD from 12 centres in France were included. Information on characteristics and outcomes (including causes of death) were evaluated over a median follow-up of 994 days [466-1,667].

Results – In addition to a shift in the type of devices implanted with a significant increase in cardiac resynchronization therapy-defibrillator (CRT-D) over time (43.6 to 60.4%, $P=0.0001$), an increase in mean age (from 61.5 ± 11.6 to 63.2 ± 10.9 years, $P=0.0016$), proportion of non-ischaemic cardiomyopathy (31.0 to 44.7%, $P<0.0001$) and women recipients (11.4 to 15.8%, $P=0.004$) was observed. A total of 1,181 patients (22.3%) received ≥ 1 appropriate therapy, inappropriate therapies occurred in 355 patients (6.7%) and 826 patients (15.2%) died, mainly from cardiovascular causes (49.3%). Annual mortality incidence (5.4% to 4.3%, $P=0.05$), as well as incidence of appropriate therapy (10.4% to 7.1%, $P=0.0004$), significantly decreased over the decade. By contrast, incidence of ICD-related late (>30 days after implant) complications significantly increased (4.6 to 7.6%, $P=0.003$).

Conclusion – Our findings demonstrate significant changes in patterns of use and outcomes in primary prevention ICD over the last decade with reductions in mortality and appropriate therapies, counterbalanced by an increase in complications.

Key Words: Sudden cardiac death; sudden death prevention; implantable cardioverter defibrillator

Introduction

Over the last decade, use of implantable cardioverter defibrillators (ICDs) for primary prevention of sudden cardiac death (SCD) has become an important part of the management of high-risk patients with severe left ventricular (LV) systolic dysfunction as evidenced by a depressed ejection fraction (EF).¹ This therapy is now recommended as a Class I indication with the highest level of evidence in the practice guidelines issued by the European and American Heart Associations.^{2, 3, 4}

Technology and clinical practice surrounding the primary prevention ICD has continually evolved and real-world data evaluating temporal trends in outcomes with ICD therapy, especially in Europe are scarce. This is particularly important both in terms of understanding the impact of the ICD in current clinical practice, as well as to identify potential areas for improvement. Data available on temporal trends in North America have relied on large administrative databases and claims data, which, while valuable, have some inherent limitations as opposed to direct access to patient medical records and physician-guided adjudication of outcomes.⁵ In addition, to the best of our knowledge, temporal trends for appropriate therapies, and specific causes of death of primary prevention ICD patients have not been addressed so far.⁶⁻⁸

For these purposes, the DAI-PP registry was specially developed in order to provide a large national database precisely describing the epidemiological data and outcomes (including causes of death) in a well-defined population of patients treated with a primary prevention ICDs, within a well-established network for the treatment of cardiac arrhythmias in France.

Methods

The DAI-PP study (Défibrillateur Automatique Implantable–Prévention Primaire,) was a retrospective analysis of all subjects with ischaemic or non-ischaemic cardiomyopathy implanted with a primary prevention ICD, between 2002 and 2012 in 12 French centres.⁹⁻¹¹

The data were collected according to a standardised and homogeneous process, using a similar electronic form. The study was funded by public sources, including the French Institute of Health and Medical Research (INSERM) and the French Society of Cardiology, and was coordinated by Clinique Pasteur, Toulouse and the Paris Cardiovascular Research Center, European Georges Pompidou Hospital, Paris. The study was also approved by the Institutional Review Board of each participating hospital, registered on ClinicalTrials.gov (NCT01992458), and the data file of the DAI-PP study was declared to and authorized by the French data protection committee (Commission Nationale Informatique et Liberté, CNIL, N°913203).

The Cardiovascular Epidemiology Unit from the Paris Cardiovascular Research Center (INSERM Unit 970) was in charge of quality control and storage of all data as well as the statistical analyses, which had been planned and approved by the Steering Committee (appendix).

Study population

Consecutive patients with ischaemic or non-ischaemic dilated cardiomyopathy implanted with single, double or triple chamber ICD for primary prevention between 2002 and 2012 were enrolled.

To qualify for the study, patients had to be at least 18 years-old at the time of ICD implantation. Overall, all patients with ischaemic or non-ischaemic cardiomyopathy, implanted with an ICD (single, double or triple chamber) in the setting of primary prevention were considered and enrolled in the DAI-PP follow-up program. Ischaemic cardiomyopathy was

defined as presence of depressed LVEF due to a previous myocardial infarction, or developed in the setting of significant coronary artery disease with or without history of angioplasty or bypass graft surgery performed ≥ 3 months before device implantation. All other patients were classified as suffering from non-ischaemic cardiomyopathy. Primary prevention was defined as no prior documented history of sudden cardiac arrest and/or ventricular tachycardia/fibrillation. Exclusion criteria encompassed patients < 18 years of age, those with an ICD implant for secondary prevention or for primary prevention without structural heart disease (including Brugada, long QT syndrome among others) or structural heart disease other than ischaemic or non-ischaemic cardiomyopathy (hypertrophic cardiomyopathy, non-compaction cardiomyopathy and arrhythmogenic right ventricular dysplasia).

Patients were characterised at the time of ICD implantation. All variables at the time of the procedure were defined and categorized according to the literature or common practice. In addition to the New York Heart Association (NYHA) functional class, we noted the aetiology of the underlying heart disease (ischaemic or non-ischaemic cardiomyopathy). Glomerular filtration rate (GFR), was estimated with the Cockcroft–Gault formula and categorized in two categories (≥ 60 and < 60 mL/min); QRS duration was categorized as < 120 and ≥ 120 ms. Atrial fibrillation (AF) was defined as a history of AF (paroxysmal or persistent), documented on ECG or 24-hour Holter monitoring. Co-morbidities were systematically collected: cancer, chronic obstructive pulmonary disease, chronic renal failure, chronic liver disease, history of transient ischaemic neurological attack, and others (including diabetes mellitus). The type of implanted ICD device (biventricular, single chamber or dual chamber —without manufacturer information) was recorded, and device programming was left at the treating physician's discretion. Except specific clinical situations, the use of 2 zones with high rate (VT > 180 bpm; VF above 220 bpm) programming were encouraged according to the Cardiac Arrhythmias Group of the French Society of Cardiology internal

consensus at this time. Information on medication at hospital discharge was collected, including beta-blockers, amiodarone, Ic class anti-arrhythmics, sotalol, digoxin, calcium blockers, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, diuretics, anti-platelets, and vitamin K antagonists.

Patient follow-up, clinical outcomes and study endpoints

Follow-up information was obtained from regular appointments every 4 to 6 month for device evaluation.^{12,13} The different endpoints were: occurrence of appropriate therapies, inappropriate therapies and other complications, as well as overall and specific mortalities. Device interrogation printouts were checked by the lead-investigator at each site for appropriate and inappropriate ICD therapy. Based on this follow-up information, the long-term clinical endpoints of this study included i) mortality and specific causes of death, ii) delivery of appropriate therapies, and iii) ICD-related late (defined as occurring >30 days after implant) adverse effects including inappropriate shock(s).

The vital status was ascertained by review of the patients' medical files from the hospital or by communication with primary physicians and finally corroborated with the French vital status database of the National Institute of Economic Statistics. In case of death, the specific cause(s) was collected from the patients' files, complemented by information from the national database available at the French Centre on Medical Causes of Death (Centre d'Epidémiologie sur les Causes Médicales de Décès – CépiDc, Inserm). Each death was reviewed by two investigators and, whenever possible, classified as sudden arrhythmic or non-arrhythmic, end stage heart failure, ICD-related, or from another cardiovascular, or non-cardiovascular cause.

Appropriate ICD therapy was defined as the successful termination of an episode of sustained VT or VF by single or multiple shocks, antitachycardia pacing, or both. The date of first appropriate ICD therapy and the number of appropriate therapies delivered during follow-up were recorded.

ICD-related, non-fatal, late adverse events included infections, lead dislodgement or dysfunction and inappropriate therapies.

Statistical analysis

Data from the DAI-PP registry were used for analyses of clinical characteristics, and outcomes for all implanted patients. In addition, in order to identify temporal trends during the period 2002 -2012, we arbitrarily decided to cut it in three periods (2002-2005; 2006-2009; 2010-2012) in order to provide comparison results between ancient and more recent periods of implantation and all these data were carefully analysed through these 3 time periods of implantation. The results are presented as means \pm standard deviation, medians [interquartile ranges] or counts and percentages. Time to event for different outcomes being available, annual incidence rates could be calculated based on the exact number of person-years of follow-up. The chi-square test was used to compare categorical variables and Student's *t*-test to compare continuous variables. Levene's test was used to verify the homogeneity of variance. Equivalent, non-parametric tests were used when the Kolmogorov-Smirnov test indicated an absence of normal distribution. A Cox regression analysis was used to identify risk factors for different outcomes, with competing risk analysis option for ICD therapy endpoints (competing with death), with corresponding hazard-ratios (HR) and 95% confidence intervals (CI). Preliminary proportional hazards assumption was validated for the Cox model after checking in univariate analysis that time dependent covariates included in the Cox model by creating interactions of the predictors and a function of survival time were not significant. All covariates that reached $P < 0.02$ significance level in univariate analysis were then included in an initial multivariable regression model. A backward stepwise selection was applied to obtain final model that included covariates with $P < 0.05$. In all risk analysis, potential impact of clustering of patients within hospitals was tested by adding hospital (into four categories, according to public/private as well as volume of activity per

year) as a variable in models. The reported p-values are two-sided. P-values <0.05 were considered statistically significant. All data were analysed using the SAS program v9.4 (SAS Institute Inc., Cary, NC).

Results

Patients' characteristics

A total of 5,539 patients implanted between 2002 and 2012 were included in the DAI-PP program (Table 1). Mean age was 62.5 years (SD 11.2 years), 84.9% were men and 60.2% presented with ischaemic heart disease. A history of AF was confirmed in 24.0% of the sample, 48.8% were in New York Heart Association (NYHA) functional class III or IV, moderate to severe renal dysfunction was present in nearly 40% of patients, including 280 (8.7%) of patients who had a GFR less than 30 mL/Min. Beta-adrenergic blockers and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers were both prescribed in over 80% of patients. Single-chamber ICDs were implanted in 1,258 (22.9%), dual-chamber in 1,280 (23.3%) and CRT-Ds in 2,952 (53.8%) patients.

The patients' baseline characteristics and temporal trends over the 3 time periods are presented in Table 1. The mean age of implanted patients significantly increased from 2002 to 2012 (61.5 ± 11.6 vs. 63.2 ± 10.9 years, $P=0.0016$). The relative proportion of women (11.4 vs. 15.8%, $P=0.0038$) as well as that of non-ischaemic cardiomyopathy (31.0 vs. 44.7%, $P<0.0001$) increased. A significant increase was observed in the proportion of CRT-Ds implanted over the 10 years of the registry (44.1 vs. 60.1%, $P<0.0001$), representing >50% of all devices implanted after year 2008 (Figure 1). The proportion of patients prescribed with appropriate guideline-directed heart failure therapy, including beta-adrenergic blockers (78.8 vs. 87.2%, $P<0.0005$) and angiotensin converting enzyme inhibitors /angiotensin II receptor blockers (76.4 vs. 88.0%, $P=0.01$) increased over time. Diuretics (57.6 vs. 71.3%, $P=0.002$)

and antiplatelet use (50.9 vs. 60.7%, $P=0.01$), also increased, while rates of vitamin K antagonists ($P=0.32$), amiodarone ($P=0.81$), digoxin ($P=0.86$), and spironolactone ($P=0.98$) remained relatively stable. Performance of defibrillation testing during implantation significantly decreased over the decade (from 78.0 to 64.1%, $P<0.0001$).

Overall and specific mortalities, appropriate therapies, and complications

Among the 5,539 patients, median follow-up was 994 days, IQR [466 – 1,667], based on median value of observation times distribution (difference between the date of death or last follow-up and the date of implantation), corresponding to 16,788 person-years of follow-up data.

Overall, 826 patients died (15.2%), corresponding to an annual incidence of 4.9% (95% CI 4.5-5.2). The multivariate Cox analysis of overall mortality showed a significant association with history of AF (HR 1.41, 95% CI 1.13-1.77, $P=0.003$), NYHA functional class \geq III (HR 2.25, 95% CI 1.81-2.79, $P<0.001$), LVEF $<30\%$ (HR 1.50, 95% CI 1.21-1.86, $P<0.001$) at the time of device implantation, ischaemic cardiomyopathy (HR 1.66, 95% CI 1.34-2.00, $P<0.001$), and a GFR ≤ 60 ml/min (HR 2.31, 95% CI 1.88-2.84, $P<0.001$) (Table 2). A specific cause of death was ultimately identified in 682 out of 826 deceased patients (82.6 %). End-stage heart failure was the main cause of death accounting for 357 deaths (52.3%), corresponding to an annual incidence of 2.4 % (95% CI 2.2-2.7). Annual mortality rate decreased over time, from 5.4% (95% CI 4.5-6.3) in 2002-2005, to 4.4% (95% CI 3.8-5.0) in 2006-2009, and 4.3% (95% CI 3.4-5.3) in 2009-2012 ($P=0.05$). This decrease in total mortality was mainly the result of a decrease in cardiovascular mortality (especially end-stage heart failure), from an annual incidence rate of 2.9% (95% CI 2.4-3.4) in 2002-2005, 2.3% (95% CI 2.0-2.6) in 2006-2009, to 1.9% (95% CI 1.3-2.5) in 2009-2012 ($P=0.01$).

Sudden cardiac death unresponsive to ICD, ICD-related fatal complications, as well as non-cardiovascular mortality remained unchanged over time.

At least one appropriate therapy was delivered in 1,181 patients (22.3%), with a median time to first appropriate therapy of 804 days [327-1,420], giving an average annual incidence of appropriate therapy over the entire time period (2002-2012) of 7.7% (95% CI 7.2-8.2). Over time, a highly significant decrease in the annual rate of appropriate therapies was observed from 10.4% (95% CI 7.2-8.2) in 2002-2005, to 8.7% (95% CI 7.8-9.7) in 2006-2009, and 7.1% (95% CI 5.8-8.4) in 2009-2012 ($P=0.0004$) (Figure 2).

A total of 824 (15.5%) patients presented with at least one late complication. Overall, inappropriate therapies were observed in 355 patients, giving an annual incidence of 2.1 (95%CI 1.8-2.6) per 100-patient-years. Over the three time periods, the overall late complication annual rate increased significantly ($P=0.003$), from 4.6 (95% CI 3.9-5.2) in 2002-2006, to 7.6% (95% CI 6.4-8.9) in 2009-2012. This was mainly a result of an increase in lead dysfunction (2.3 to 5.2, $P=0.0001$), whereas the incidence of inappropriate therapies remained stable (1.9 to 2.2%, $P=0.23$). No significant differences in inappropriate therapies ($P=0.23$) as well as appropriate therapies rates ($P=0.12$) between centres were observed. When analysed separately, the subset of CRT-D patients had higher cardiovascular mortality during follow-up (HR 1.7, 95%CI 1.4-2.2, $P<0.0001$), were less likely to have inappropriate therapy (HR 0.7, 95%CI 0.5-0.8, $P=0.02$), but had similar appropriate therapy rates (HR 0.9, 95%CI 0.8-1.1, $P=0.12$), compared to patients implanted with only an single/dual ICD.

Discussion

Using a large, nationwide, multicentre registry with direct evaluation of patient data and physician-adjudication, we highlight important trends in ICD therapy and outcomes over the

past decade. These results can be useful to guide future policy and identify areas for improvement.

We found significant changes in patient characteristics with older and relatively greater proportion of female and/or non-ischaemic cardiomyopathy patients being implanted. The latter is an interesting finding, considering the very recent published data from DANISH trial.¹⁴ Indeed, this trial suggests the lack of efficiency for mortality prevention in non-ischemic cardiomyopathy patients implanted for primary prevention.¹⁴ The characteristics of the patients in our registry are broadly concordant with those patients included in previously published reports of “real world” national registries.^{15,16} Compared to one of the largest North American primary prevention registries,⁷ the mean age of our patients was somewhat lower (63 vs. 68 years), potentially suggesting a more conservative selection of candidates for primary prevention by French cardiologists in the early years of the registry. It is however noteworthy that the mean age, as well as comorbidity burden, of the ICD recipients increased over the ten-year duration of the registry, likely reflecting an improvement of physician’s judgment of benefit and confidence related to the primary prevention ICD.^{17,18} The proportion of women implanted increased over time, though it still remains relatively low compared to men, in concordance with recent data from Italy showing a five-fold higher implantation rates among men.¹⁵ In similar fashion to randomized controlled trials and other registries of ICD recipients in daily clinical practice, women account for only a minority of our cohort, possibly caused by lower rates of referral of women to this therapy.¹⁹⁻²³ Similarly, recent analysis of trends in the US suggest persisting sex disparities;²⁴ clearly there is a need to better understand factors underlying these differences so that appropriate measures can be instituted to optimize ICD use in all subgroups. With regard to device types, the proportion of CRT-D increased significantly, reaching over 60% in the last three years of the study; a change consistent with the on-going expansion of CRT indications,²⁵ and also a significant

switch from CRT-P to CRT-D in elderly patients. Encouragingly, rates of appropriate heart failure medical therapy have increased over time, as in the US.²⁴⁻²⁶

The overall death rate observed over a median follow-up of 3 years in our study (4.9%) is concordant with the findings of ICD-treatment arms of the large randomized trials MADIT II and SCDHeFT,^{27,28} and with recently updated data from a US registry.⁷ Adjusted annual overall mortality declined over the past decade, in line with the trend of declining death rates in the heart failure population in Europe and other parts of the world. To the best of our knowledge, we have provided the first data on temporal changes in specific mortalities in an unselected population of primary prevention ICD recipients. ICD-unresponsive sudden mortality remains low and relatively more progressive heart failure deaths were noted, highlighting the issue of competing risks for mortality.

The average annual incidence of appropriate therapies decreased significantly over the time course of this study. While this may partly relate to extension of primary prevention to potentially lower risk-profile candidates (at probably lower risk of VT/VF), this is also likely to be related to improvements in medical management of heart failure over time and improvement in programming towards less aggressive therapies and longer detection times, which may help reduce mortality as well.¹⁶

Device complications, including infection and lead-related problems, increased over the period of this study. Infections in particular, have been a source of concern with some studies from the US showing rise in infection rates disproportionate to the increase in number of devices implanted.²⁹ Increase of lead-related problems seems also logical as the rate of CRT-D devices increased dramatically over time in the registry. Inappropriate therapies, did not significantly change over time. This information is reassuring, as inappropriate shocks are not only unpleasant but known to be associated with higher mortality and healthcare costs.^{16,30} Two large randomized trials have reported reduced rates of delivery of

inappropriate therapies by thoughtful programming of devices.^{31,32} In recent years, several reports have emerged that have highlighted the strong association between ICD therapies and increased mortality.³³ In prior analyses of both the MADIT II and SCD-HeFT trials, ICD therapies (mostly shocks) were associated with a greater than 3-fold increase in all-cause mortality.^{34,35} Considering both together shocks and ATP in our study (ATP for which the association with mortality is still unclear) may have participated to the lack of association after multiple adjustment. It is still not certain whether this association indicates a direct harmful effect of ICD therapy, or whether ICD therapies act as a marker for more severe underlying cardiac disease. Although appropriate shocks have consistently been shown to be associated with a significantly worse outcome, the same is less clear for inappropriate shocks. Analyses from both SCD-HeFT and MADIT II trials showed that inappropriate shocks were associated with an approximate 2-fold increase in all-cause mortality.^{34,35} In contrast, 3 other studies found no association between inappropriate shocks and increased mortality.³⁶⁻³⁹

This registry is one of the first large-scale evaluations of primary ICD implantation in Europe; however it has some limitations. First, ICD programming was left to the discretion of individual physicians/centers and therefore could result in some variability. However, as previously explained, there exists a broad expert consensus among the senior investigators from each center in terms of ICD programming, namely use of generally high ventricular rates and fewer zones. Therefore we feel that major heterogeneity in programming type between centers is unlikely, as suggested by the absence of any significant differences centres. Second, while the median follow-up time (2.7 years) may appear relatively short, this is mainly related to a relatively greater number of patients were enrolled in the later stages of the study with shorter duration of follow-up till censure. This is in keeping with the dramatic increase in primary prevention ICD implantation rates in recent times. Third, because we did not collect data stratified by brands as well as details on single/dual coil implant, we were

unable to test any differences in outcomes, although previously reported.⁴⁰ Finally, the accurate identification and sub-classification of specific causes of death is a very difficult and challenging task, which remained undetermined in nearly 20% of our study population, in line with previously published prospective cohort studies.⁴¹

Conclusion

Real world data from a population of primary prevention ICD recipients over the past decade in France demonstrate favourable trends, with increase in CRT devices, declining rates of overall mortality and appropriate therapy.

Disclosures

Dr. Boveda has received consulting fees from Medtronic, Boston Scientific, and Sorin Group. Dr. Sadoul has received personal fees from Biotronik, Boston Scientific, Medtronic, Sorin Group, and St. Jude Medical. Dr. Piot has received consulting honoraria from Medtronic and St. Jude Medical and research grants from Medtronic and Boston Scientific. Dr. Klug has received consultant fees from St. Jude Medical, Medtronic, Sorin Group, Boston Scientific, and Biotronik. Dr. Babuty has received travel support and clinical study support from Biotronik, Boston Scientific, Medtronic, St. Jude Medical, and Sorin Group. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Appendix

The following investigators and institutions participated in the conception of the registry, and in the organisation, collection, storage and analysis of the data:

Co-principal Investigators: Serge Boveda, MD, Clinique Pasteur, Toulouse; Eloi Marijon, MD, PhD, Hôpital Européen Georges Pompidou, Paris, France. Conceived, designed and organized the registry in 2009.

Co-investigators in charge of the data collection and analysis at each medical centre:

Vincent Algalarrondo, MD, PhD, CHU Antoine Bécclère, Clamart; Dominique Babuty, MD, PhD, CHU Trousseau, Tours; Pierre Bordachar, MD, PhD, CHU Haut Lévêque, Bordeaux; Serge Boveda, MD, Rui Providencia, MD, MS, Clinique Pasteur, Toulouse; Pascal Defaye, MD, CHU Michallon, Grenoble; Daniel Gras, MD, Nouvelles Cliniques Nantaises, Nantes; Jean-Claude Deharo, MD, PhD, CHU La Timone, Marseille; Didier Klug, MD, PhD, CHRU Lille, Lille; Christophe Leclercq, MD, PhD, CHU Pontchaillou, Rennes; Eloi Marijon, MD, PhD; Hôpital Européen Georges Pompidou, Paris; Olivier Piot, MD, Centre Cardiologique du Nord, Saint Denis; Nicolas Sadoul, MD, PhD, CHU Brabois, Nancy.

Data storage, quality control, and statistical analyses: Frankie Beganton, MS, Marie-Cecile Perier, MS, Cardiovascular Epidemiology Unit, Paris Cardiovascular Research Center (INSERM Unit 970), Hôpital Européen Georges Pompidou, Paris.

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Figures and Tables

Figure 1: Changes in the types of devices implanted between 2002 and 2012

VVI = single chamber ICD; DDD = dual chamber ICD; CRT-D = cardiac resynchronization therapy with back-up defibrillator.

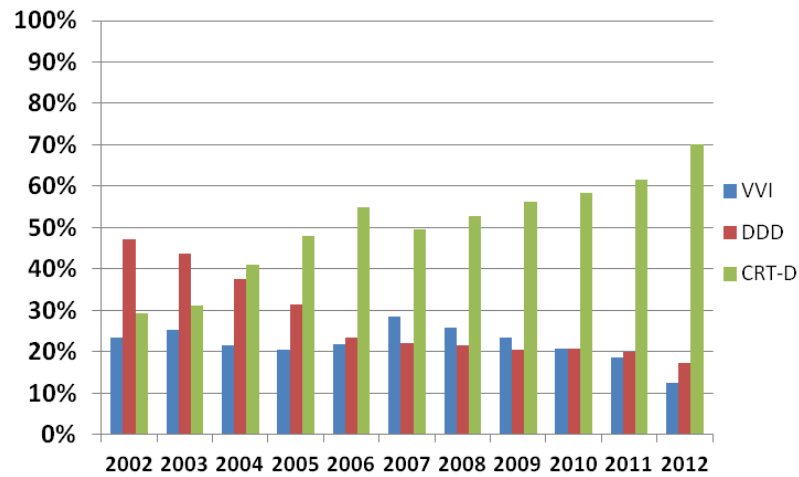
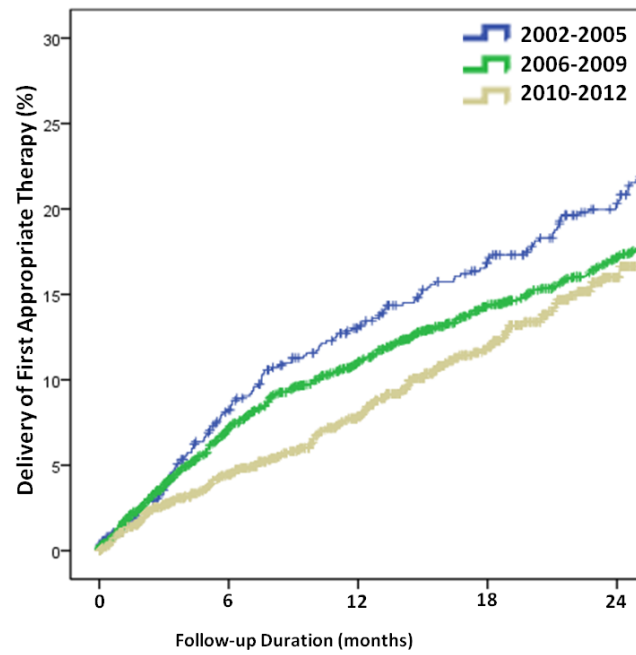


Figure 2: Baseline characteristics of the 5,539 implanted patients in the DAI-PP registry and according to the period of implantation 2002-2005, 2006-2009, 2010-2012.

In order to identify temporal trends during the period 2002 -2012, we arbitrarily decided to cut it in three periods (2002-2005; 2006-2009; 2010-2012) in order to provide comparison results between ancient and more recent periods of implantation and all these data were carefully analysed through these 3 time periods of implantation






Number at Risk	0	6	12	18	24
	847	741	677	630	579
	3019	2611	2386	2165	2005
	1421	1117	875	592	323

Table 1: Baseline characteristics and the 3 time periods temporal trends of the 5,539 participants in the DAI-PP registry

Date of implantation	2002-2012	2002-2005	2006-2009	2010-2012	<i>p-value</i>
Number of patients	5539	876	3155	1508	
Age, y	62.5±11.2	61.5±11.6	62.4±11.2	63.2±10.9	0.0016
Men	4,702 (84.9)	776 (88.6)	2,657 (84.2)	1,269 (84.2)	0.0038
Dilated cardiomyopathy					
Ischaemic	3,304 (60.2)	598 (69.0)	1877 (60.2)	829 (55.3)	<0.0001
Non-ischaemic	2,181 (39.8)	268 (31.0)	1242 (39.8)	671 (44.7)	
Left ventricular ejection Fraction, %	27±7	26±8	26±7	27±6	0.001
QRS duration, ms					
<120	1,183 (30.5)	169 (33.4)	680 (29.9)	334 (30.1)	0.32
120 – 150	1,368 (35.3)	163 (32.2)	830 (36.5)	375 (34.3)	
>150	1,322 (34.1)	174 (34.4)	765 (33.6)	383 (35.1)	
New York Heart Association functional class					
I or II	2,335 (51.2)	344 (50.6)	1320 (50.8)	671 (52.2)	0.68
III or IV	2,227 (48.8)	335 (49.3)	1278 (49.2)	614 (47.8)	
Atrial fibrillation	1,134 (24.0)	186 (26.2)	610 (22.8)	338 (25.1)	0.16
Concomitant illness(es)					
0	1,173 (28.0)	174 (28.2)	636 (26.9)	363 (30.0)	0.13
1	2,339 (55.9)	345 (56.0)	1338 (56.7)	656 (54.3)	
2	526 (12.6)	76 (12.3)	313 (13.3)	137 (11.3)	
≥3	147 (3.5)	21 (3.5)	73 (3.1)	53 (4.4)	
Device					
Single or dual chamber cardioverter defibrillator	2,538 (46.2)	485 (55.9)	1458 (46.8)	595 (39.9)	<0.0001
Cardiac resynchronization therapy with back-up defibrillator	2,952 (53.8)	375 (44.1)	1671 (53.2)	906 (60.1)	
Drug therapy					
Beta-adrenergic blocker	3,378 (84.9)	424 (78.8)	1,990 (85.2)	964 (87.2)	<0.0005
Angiotensin converting enzyme inhibitor/angiotensin II receptor blocker	3,265 (82.0)	411 (76.4)	1,877 (80.3)	975 (88.0)	0.019
Antiplatelet agent	2,278 (57.2)	374 (50.9)	1,333 (57.0)	671 (60.7)	0.016
Vitamin K antagonist	1,404 (35.3)	2,000 (37.2)	807 (34.5)	397 (35.9)	0.32
Amiodarone	902 (22.7)	122 (22.7)	545 (23.3)	235 (21.3)	0.81
Digoxin	225 (5.7)	35 (6.5)	146 (6.2)	44 (3.4)	0.86
Furosemide	2,709 (68.1)	310 (57.6)	1,611 (68.9)	788 (71.3)	0.002

Spironolactone 1,284 (32.3) 167 (31.0) 726 (31.1) 391 (35.3) 0.98

Values are means \pm SD, numbers (%) of observations or median [IQR]. The percentages were calculated on the basis of the total number of known observations

Table 2: Risk analysis for all-cause mortality

	Analysis					
	Single variable			Multiple variable		
	HR	95% CI	P	HR	95% CI	P
Female gender	0.85	0.69-1.04	0.120	-	-	-
History of atrial fibrillation	1.73	1.48-2.03	<0.001	1.41	1.13-1.77	0.003
Cardiac resynchronisation therapy	1.57	1.36-1.81	<0.001	-	-	-
Age >70 years	1.65	1.43-1.90	<0.001	-	-	-
New York Heart Association functional class \geq III	2.33	1.98-2.73	<0.001	2.25	1.81-2.79	<0.001
QRS >120 ms	1.31	1.09-1.57	0.003	-	-	-
Left ventricular ejection fraction <30%	1.50	1.29-1.74	<0.001	1.50	1.21-1.86	<0.001
Ischaemic heart disease	1.22	1.05-1.42	0.008	1.66	1.34-2.0	<0.001
Glomerular filtration rate \leq 60ml/min	2.45	2.05-2.93	<0.001	2.31	1.88-2.84	<0.001
Appropriate shock or antitachycardia pacing	0.94	0.80-1.10	0.444	-	-	-
Inappropriate shock	0.48	0.35-0.67	<0.001	-	-	-