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Impact of pacemaker longevity on expected device replacement rates: results from computer simulations based on a Multicenter Registry (ESSENTIAL)

Giuseppe Boriani[1,2], MD, PhD, Matteo Bertini[3], MD, PhD, Davide Saporito[4], MD, Giuseppina Belotti[5], MD, Fabio Quartieri[6], MD, Corrado Tomasi[7],MD, Angelo Pucci[8], MD, Giulio Boggian[9], MD, Gian Franco Mazzocca[10], MD, Davide Giorgi[11], MD, Paolo Diotallevi[12], MD, Biagio Sassone[9, 13], MD, Diego Grassini[14], EEng, Alessio Gargaro[14], MSc, Mauro Biffi[2] , MD, on behalf of ESSENTIAL Investigators*

*Complete list in the Appendix

1 Cardiology Division, Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia, Policlinico di Modena, Modena, Italy.

2 Institute of Cardiology, S.Orsola University Hospital, University of Bologna, bologna, Italy.

3 Arcispedale S. Anna-Cona, Università di Ferrara, Ferrara, Italy.

4 Ospedale degli Infermi, Rimini, Italy.

5 Ospedale Treviglio-Caravaggio, Treviglio, Italy.

6 Ospedale S. Maria Nuova, IRCCS, Reggio Emilia, Italy.

7 Ospedale S. Maria delle Croci, Ravenna, Italy.

8 Ospedale di Carrara, Carrara, Italy.

9 Ospedale di Bentivoglio, Bentivoglio, Italy.

10 Ospedale Civile, Cecina, Italy.

11 Ospedale San Luca, Lucca, Italy.

12 Clinica Città di Alessandria, Alessandria, Italy.

13 Ospedale SS Annunziata Cento (FE), Italy.

14 Biotronik Italia spa, Milan

Correspondence to: Prof. Giuseppe Boriani, MD, PhD, FESC, FEHRA.
Cardiology Division, Department of Diagnostics, Clinical and Public Health Medicine
University of Modena and Reggio Emilia, Policlinico di Modena; Via del Pozzo, 71, 41124 Modena, Italy. Phone +39-059-4225836; Fax: +39-059-4224498
E-mail: *giuseppe.boriani@unimore.it*

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Conflict of interest

G Boriani reported speaker'sfees from Boston, Biotronik and Medtronic; M Biffi has held educational activity and received speaker's bureau on behalf of Boston Scientific, Biotronik, and Medtronic; M Ziacchi has held educational activity and received speaker's bureau on behalf of Medtronic and Biotronik; D Grassini and A Gargaro are employees of Biotronik Italia; C Tomasi consulted for minor fees Biotronik and Boston Scientific.

No other potential conflict of interest exists.

Abstract

Aims. We estimated the probability of device replacement in an unselected population of pacemaker recipients, with automatic management of atrial and ventricular pacing output.

Methods. We considered a cohort of 542 pacemaker patients (age 78±9 years, 60% male, 71% de-novo implants) and combined 1-month projected device longevity with survival data and late complication rate in a 3-state Markov model tested in several Monte Carlo computer simulations. Predetermined subgroups were: age < or ≥ 70; gender; primary indication to cardiac pacing.

Results. At the 1-month follow-up the reported projected device longevity was 153±45 months. With these values the proportion of patients expected to undergo a device replacement due to battery depletion was higher in patients aged <70 49.9%, range 32.1%-61.9%) than in age ≥70 (24.5%,19.9%-28.8%); in women (39.9%, (30.8%-48.1%) than in men (32.0%,24.7%-37.5%); in sinus node dysfunction (41.5% 30.2%-53.0%) than in atrio-ventricular block (33.5%, 27.1-38.8%) or atrial fibrillation with bradycardia (27.9%, 18.5%-37.0%). The expected replacement rate was inversely related to the assumed device longevity and depended on age class: a 50% increase in battery longevity implied a 5% reduction of replacement rates in patients aged ≥80.

Conclusions. With current device technology 1/4 of pacemaker recipients aged ≥70 are expected to receive a second device in their life. Replacement rate depends on age, gender and primary indication owing to differences in patients' survival expectancy. Additional improvements in device service time may modestly impact expected replacement rates especially in patients ≥80 years.

Key Words: life expectancy, pacemaker longevity, complications, computer simulation

Introduction

The prevalence of cardiac pacemakers increases with age . Extending device battery longevity in an ageing population should reduce surgical interventions for device replacements, prevent related complications, including infections, and ultimately decrease healthcare costs[1,2].

Technologic improvements in hardware and in automated algorithms have significantly improved device longevity in the past 20 years[3],despite the changes of patients' medical conditions and of pacing parameters.[4,5-6]

Basing on the indications to cardiac stimulation and on life expectancy of contemporary pacemaker recipients, it is speculative whether device longevity meets patients' expected survival or further improvement of longevity is necessary. This question has important implications for the allocation of research resources and for the direction of future technological developments.

We investigated this aspect in the ESSENTIAL Registry [6], a prospective non-interventional study assessing the performance of specific algorithms designed to automatically control and safely minimize pacing outputs in routine medical practice. In particular, we sought to estimate the proportion of patients expected to undergo a device replacement at the end of the projected device service life. Estimations were obtained with Monte Carlo simulations based on a 3-state Markov model combining estimated patient survival and system-related complications with individual device longevity collected in the ESSENTIAL cohort. Several series of simulations were generated by arbitrarily varying the assumed device longevity with respect to the actual values, in order to obtain the corresponding variation of the expected replacement rate.

Methods

Study cohort

We interrogated the database of the ESSENTIAL Registry, a multicenter, prospective, non-interventional study investigating the performance of atrial and ventricular Automatic Capture Control (ACC) algorithms and their effect on the projected device longevity.

Ventricular ACC algorithm is based on detection of the evoked response and adaptation of pacing output at the measured threshold plus a programmable safety margin. Capture is automatically verified on a beat-to-beat basis. Atrial ACC is based on detection of atrial sensed events: threshold is measured periodically and pacing output is adapted according to the programmed safety margin. Capture verification occurs only at the scheduled threshold measurements.

Study endpoints were ACC success rate in automatically detecting atrial and ventricular pacing thresholds at 1 and 12 months from implant, under specific operational conditions (maximum output voltage that allowed automatic adaptation). The study was approved by the competent Ethics Committee. Patients with conventional indications to single or dual-chamber pacemaker implantation (either de-novo or replacement) were eligible in the study. Biventricular pacemakers were excluded as ACC algorithms were not available in these devices at the time of study enrolment. All the included devices were manufactured by BIOTRONIK SE & Co. KG (Berlin, Germany) and equipped with ACC functions systematically activated during the study. Patients who gave written informed consent were visited 1 and 12 months after implant to evaluate pacing system functioning, test ACC algorithms and collect diagnostic information including projected longevity. Projections estimates of device service life are based on battery characteristics and on several system and pacing parameters including intrinsic current drain, pacing output, amount of pacing, frequency of pacing delivery, etc. We included the projected longevities collected at the 1-month follow-up.

Simulation model

A 3-state Markov model with two absorbing states was implemented as shown in the figure S1 (online supplementary material). Individual patients were assumed to remain in a 'health' (H) state until switching to one of the two absorbing states: 'death' (D) or 'implant-revision' (R).

With a cycle length of 1 month, simulations were run for each subject assigning transition probabilities based on individual patient age with a total number of cycles (simulated duration) equal to the projected device longevity reported in the ESSENTIAL database. The output was the rate of survivors at the end of the simulation period (device end of service), and therefore expected to undergo device replacement.

Simulations were repeated with different assumptions on device longevity. Longevity of individual devices was arbitrarily reduced or increased in 10%-steps (from -50% to + 50%) in order to evaluate the corresponding changes in the rate of patients expected to undergo a device replacement. Effects on costs were estimated in the healthcare provider perspective (National Health Care System) basing on the Diagnosis-Related Group (DRG) coded tariffs. For pacemaker replacements current average DRG tariff in the regions of the ESSENTIAL investigational clinics is EUR 2,619.51. Costs are reported per 1.000 patients.

Transition probabilities

Transition probabilities from H to D was derived from Brunner M. et al.[7] who reported survival rate in a general population of about 6,500 pacemaker recipients cumulatively followed up for almost 31,000 patient-years and stratified in several subgroups.

We followed a graphical approach to generate survival probabilities at the individual patient level from the published Kaplan-Meier curves [8]. We assumed a Weibull distribution for the survival curves and a log-log transformation was applied to fit the series of the available data points and estimate the Weibull's shape and scale distribution parameters.

Strata with available survival curves were: age (≥ or <70), sex, primary indication to cardiac pacing (sick sinus dysfunction or atrio-ventricular (AV) block), prior atrial fibrillation (AF). We repeated our simulations to obtain the relative expected replacement rate in each subgroup.

Transition probabilities from the H to R states were derived from Eberhardt F. et al [9] who reported an annual rate of complications requiring surgical revision of 0.5%/year. The complication rate was assumed constant throughout the follow-up and was included in a linear model for free-complication rates. As a further conservative assumption, late complications (occurring >3 months post-implant) was supposed to always require a device replacement, while early complications were ignored for the purpose of our analysis.

Sensitivity analysis

A one-way sensitivity analysis was performed in each subgroup to test stability of simulation outputs.[10] Our model essentially depended on the assumed survival functions and late complication rate. Parameters were varied one at a time within the range -10% to +10% and simulations were repeated each time. Ten percent variation of the Weibull distribution parameters corresponded to 4% to 18% variations in assumed survival. Estimated probabilities of device replacement associated to input variations were recorded and graphically displayed in each subgroup.

Estimation of device replacement per patient age class

Finally, in order to investigate the association between age and expected replacement rate in more detail, we tried to combine survival functions reported by Brunner M et al.[7] and available life tables of a global population. To this purpose, we used the 2015 Life Table of resident population provided by the annual report of the Italian National Institute of Statistics, reporting the probability of death per 5-year age classes.[11] Survival of the Brunner's cohort (mean age 72.1) was associated to the 70-74 age class. The survival function of patients in other age classes was derived by applying a correction based on the national Life Tables. After a log-log transformation, the entity of correction to the survival curves was proportional to the variation of surviving fraction in the national Life Table changing from one age class to another (online supplementary material, figure s3).

Statistics

Ordinary descriptive statistics was used to report population baseline characteristics, using average ± standard deviation for continuous variables and percentages for binary variables. Mutilvariable linear regression models were implemented to evaluate the effect of heart rate, pacing percentage and threshold on the projected longevity. Estimates of regression coefficients were reported along with their standard errors. Unpaired Student's T test was used for some between-groups comparisons. We used STATA SE 11.0 (StataCorp, Texas, US). Codes for Monte Carlo simulations were edited in VB. Each simulation run consisted of 250 iterations, reporting the average of the variable of interest along with the minimum and maximum returned values.

Results

The ESSENTIAL cohort consisted of 542 patients (60% male) who received a de-novo pacemaker implantation (382, 70.5%) or a replacement (160, 29.5%) due to standard indications in sinus node dysfunction (123, 22.7%), AV block (410, 75.6%) and reflex syncope (23, 4.2%), between January 2012 and March 2013. The average age at implant was 78±9 years, with 10^{th}, 25^{th}, 75^{th} and 90^{th} centiles of 66, 73, 85, and 88, respectively. The main reported comorbidities were hypertension (65.9%), history of atrial fibrillation (26.9%), valvular disease (21.4%), coronary artery disease (20.5%), diabetes mellitus (18.1%) and renal insufficiency (9.4%).

A vast majority of implanted devices were dual-chamber, with only 63 (11.6%) single-chamber devices. The average projected device longevities at 1 and 12 months were 153±45 and 141±44 months, respectively. There were significant differences between dual- and single-chamber devices: at the 1-month follow-up, 174±51 months in single-chamber as compared to 150±43 in dual-chamber devices (p=0.0001), which respectively turned into 156±52 and 137±42 months (p=0.0025) at the 12-month follow-up. As expected, projected longevity was negatively associated to average heart rate, pacing threshold and pacing percentage. The effect of heart rate was modest after adjusting for pacing percentage and threshold, with an estimated 2.22 (0.93) month longevity reduction every 5 bpm increase in mean heart rate in dual chamber models (p=0.018).

Results of simulations

Figure 1 shows the results of a first set of simulations for the subgroups of patients aged <70 or ≥70. With an average projected longevity of 153 months the expected proportion of patients requiring device replacement at the end of the device service time was higher in age <70 than in age ≥70: 49.9% (32.1%-61.9%) versus 24.5% (19.9%-28.8%). The plot also shows how the replacement rate is expected to trend as a function of progressive 10%-step increase or decrease of the projected longevity. The replacement rate increased with reduced device longevity and decreased with an increased device longevity, the trend being well described by a quadratic fit (R^2 = 0.99). Estimations at the edges of the explored device longevity range were as follows: in patients aged <70, 70.2% (56.0%-83.3%) with a 50% device longevity decrease, and 35.1% (21.4%-50.0%) with 50% longevity increase; in patients aged ≥70, 51.2% (42.8%-57.4%) with 50% longevity decrease, and 12.3% (8.7%-15.3%) with a 50% longevity increase.

It is worth noting that trends are not symmetrical with respect to device longevity variations. Although only 1.2 out of ten over-70 patients are expected to undergo device replacement with a 50% longevity increase, more than 1 out of two would need a device replacement should device longevity be 50% lower than its current value. In terms of projected costs to National Health, device longevity of 153 months corresponds to about EUR 745.000 per 1000 implants within 12 years. Each 10%-decrease in device longevity would cost EUR 135.000 more in the national budget, with an overall cost of about 1.4 million in 6 years with 50% decrease in longevity. On the other hand, 10%-increase in device longevity would generate an average saving of EUR 66.000 every 1000 implants in the next 18 years.

Results of simulations conducted in pre-specified subgroups are displayed in Figure 2. By combining current device longevities with survival rates in each subgroup (as reported in Brunner M. et al.[7]) we obtained the following estimates of device replacement rates: 32.0% (24.7%-37.5%) in men as compared to 39.9% (30.8%-48.1%) in women; 27.9% (18.5%-37.0%) in with bradycardia and atrial fibrillation, 33.5% (27.1-38.8%) in AV block, 41.5% (30.2%-53.0%) in sick sinus dysfunction. Similar quadratic trends were obtained varying the assumed projected longevities form -50% to +50%.

As a result of the performed one-way sensitivity analysis, Figure S2 shows ranges of variation of the estimated probability of device replacement for -50%, 0%, +50% variation of projected longevity, obtained by varying each simulation parameter. Analysis was repeated in each subgroup. The results of such analysis showed that ±10% variation of input parameters would produce 15% or less variation in the simulation outputs. Uncertainty on late complication rate minimally affected outputs.

Estimation of replacement rates per age class

Monte Carlo simulations were finally repeated for twelve 5-year age classes from <45 up to 95-99 years. Figure 3 shows the results for 6 age classes from 60-64 to 90-94. As expected the estimates of replacement rates decreased with increasing age. It is worth noting that the dependence of replacement rates on device longevity varied with age, being almost constant in 60-64 and 90-94. This is more clearly evident in Figure 4 where the amplitude of replacement rate variation is displayed for ±50% longevity change in each age class. We may note that increasing or decreasing device longevity by 50%, the respective variation of replacements rates depended on class age, reaching the maximum increase in the 70-80 age range in case of longevity reduction, and the maximum reduction at 65-75 for longevity increase. A reduction of device longevity implied higher increase of replacement rate than an equivalent increase reduced it. Extending device longevities up to +50% minimally affected replacement rate in >80 patients.

Discussion

Main results

Computer simulations showed that the pacemaker population selected in our analysis, implanted with devices equipped with automatic management of pacing output, had a 24.5% chance of undergoing a device replacement due to normal battery depletion if aged 70 or more and 49.9% if aged less than 70, given the sample device longevity (153-months on average) and current ordinary medical care level. However simulations could detect effects also related to gender and primary indications owing to differences in life expectancy among subgroups. More importantly, while lower device longevities were associated to considerable increases in replacement rates, extending service life beyond current values would not produce an equivalent reduction of expected replacements and related costs.

Implications for resource optimization

Pacemaker is a common therapy in the elderly and its use has increased with ageing population, it actually increased by 56% in US from 1993 to 2009.[12] More recent investigations have revealed that the overall use of pacemakers is still growing and demand for pacing services is likely to continue to grow in addition to burden of device replacement as equilibrium has probably not been reached.[1] Therefore minimizing the need of subsequent device replacement has straightforward implications in terms of reduction of surgical interventions, associated risks and, ultimately, related costs.

Implant surgical revision is a well-known risk factor for subsequent infection and in particular, device replacement has been often reported as an independent predictor.[14] Klug et al.[15] reported a rate of infection of about 1% in the replacement subgroup of a cohort of 6,319 consecutive recipients of implantable systems, with 2-fold increased risk as compared to de-novo implants. In consideration of the continuously increasing pacemaker use, these data have epidemiological and financial importance. A single life-long device would be the safest and most effective aid to prevent replacement-related complications with direct impact on quality of life, costs associated to: replacement procedure, new devices, treatment of related complications, and mortality.[16]

There are differences among reported estimates of annual pacemaker replacement rates. Nationwide registries and international surveys [17-18] have reported values in the 15%-35% range. These data may have some limitations. However it may be difficult to observe the effect of the progressive increase of device longevity on the replacement rate in a general pacemaker population, unless specifically designed, long-term follow-up studies are conducted. That is why computer simulations appear as an interesting tool to obtain at least rough estimations.

The ESSENTIAL study cohort included 29% replacements, rather in line with reported rates in Italy. [18-20] According to an annual report of pacemaker implantations in Italy,[20] it is estimated that about 45% of patients who received a pacemaker in 2015 were aged >80 and 21% were replacements of devices with a median service time of about 94 months. According to our projections, a patient aged >80 should have 10% or less chance of undergoing a replacement with devices ensuring on average 153 months of service, corresponding to potential halving of future replacements. As a rough estimation, this would produce a net saving for the national health care system of about 6.4mln EUR with the current DRG tariffs for pacemaker replacements.

Further source of savings would come from the cost of treatments of complications associated with device replacements, which may not be negligible. These may be less readily estimated, however it has been recently calculated that current costs for treatment of replacement-related infections are in the range of 26,200 to 36,500 EUR per infection incident at the current exchange rate.[16]

Implications for technological development

Pacemaker longevity has increased over last decades. In the cohort considered here 153 months were technically achievable with current battery technology and outputs optimized to reduce energy consumption, but at full diagnostic capabilities. In the ESSENTIAL study the 93%-97% reliability of the ACC function for managing pacing output may have significantly contributed to minimization of energy drain.[6] Although such longevity values are still not ideal and there is room for improvement, our projections showed that further increase of device service life are expected to have less effect on future replacement rate. A 10% increase in individual device longevity would translate in only a 2.3% absolute reduction in expected replacement rates in the 75-79 age class and 1.6% in the 80-84 age class. A 50% increase in device longevity, which probably requires a significant advancement in battery technology, would only reduce subsequent replacement rate by 13% in patients aged 70-74 and by 5% or less in ≥80.

By contrast, as a result of our analysis a decrease in device longevity with respect to current values was associated to a higher increase in the expected replacement rates. In the ≥70 age group replacement rates increased by 5% each 10% reduction in device longevity. From this point of view our estimations may be important in ordinary practice for manufacturer/model selection which may be based on patient's age, characteristics and device longevity as reported in user manuals. As long as the cohort selected in our analysis is a sufficiently reliable sample of current pacemaker recipients, our assumptions on device longevity may be used for estimating the chance of replacement at time of model selection. On average, patients with indication for sinus node dysfunction and advanced AV block had 13% and 9% respectively higher chance of device replacement as compared to patients with atrial fibrillation; women 3% higher than in men.

Limitations

Computer simulations cannot replace direct observations, irrespective of model accuracy. Epidemiologic changes may have occurred along decades owing to improved medical care, current pacemaker recipients being older but with better survival expectancy at midterm than in the Brunner's study that represents the basis of our model. Nevertheless the model appeared rather stable at a one-way sensitivity analysis with ±10% variation of model inputs. On the one hand, variations due to complication rates were negligible. On the other hand, variations of survival inputs, corresponding to 4%-18% variation at the end of the simulated period, always induced 15% or less variations of the estimated replacement rate. Finally we used projected device longevity as inputs of our analysis. Although some discrepancy may be observed between projections and real longevities,[yet projections suited the “what-if” purpose of our analysis providing estimations of future expected replacements, given the reported service times. Nevertheless longevity projections in the study devices has been proven sufficiently reliable at least in the 1-year term as 1-month projections fairly well predicted 12-month projections.[6]

Conclusions

By combining life expectancy, device-related complication rate and projected longevities of the pacemaker models included in the study, we estimated that about 1/4 of the selected population aged ≥70 will undergo a device replacement due to battery depletion. The proportion may vary depending on patient’s characteristics, being higher in women and in patients with sinus node dysfunctions. The sample average of projected device longevity was 153 months. While shorter service time would inevitably increase future replacements with a quadratic trend, further increase in longevity will have less effect. Further technology developments are still desirable but will progressively generate modest reductions of expected device replacement rates.

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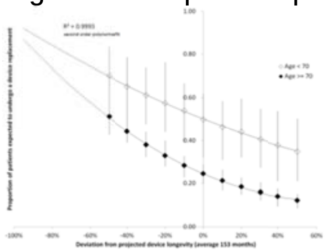
Figure 1: Expected pacemaker replacement rates.



Results of the Monte Carlo simulations for the estimation of replacement rates expected in age subgroups of the study population. The proportion of patients expected to undergo a device replacement due to battery depletion is reported as a function of 10%-deviations from projected longevity using automatic management of atrial and ventricular pacing output . Second-order polynomial fits are also displayed.

Figure 2: Expected device replacement rate in patient subgroups

Results of the Monte Carlo simulations for the estimation of replacement rates expected in patient subgroups according to varying % deviations from expected pacemaker longevity. Panel A, gender; Panel B, primary indication to cardiac pacing: sinus node dysfunction (SSS); atrio-ventricular block (AVB); atrial fibrillation with bradycardia (AF).

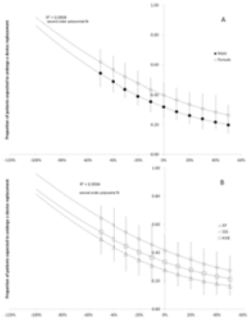


Figure 3: Expected device replacement rate per age class.
Results of simulations for 5-year age classes at implant, from 60 to 94. Survival in each class was obtained by applying a correction derived from the 2015 Life Tables of the National Institute for Statistics. [14]

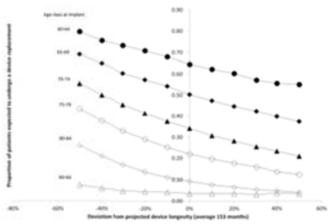


Figure 4: Expected variation of device replacement rate per age class
The bar graph shows the variation range of the expected device replacement rate in each age class obtained by varying the assumed device longevity by ±10%. The maximum increase (+21%) of replacement rates for a 50% reduction in longevity is expected in the 70-79 age classes; while the maximum decrease (-13%) for 50% increase in longevity is expected in the 65-74 age classes.