



Impact of chronic kidney disease on mortality in older adults treated with pacemaker implantation

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Abstract

Objective To investigate whether chronic kidney disease could negatively impact survival in older adults needing pacemaker implantation after admission for bradyarrhythmias. **Methods** This retrospective observational study considered 538 older adults consecutively admitted, who had been followed-up for 31 ± 20 months. Subjects with poor short-term prognosis were excluded. Charlson comorbidity index (CCI) and estimated glomerular filtration rate (eGFR) was calculated, along with the independent relationship between all-cause mortality and clinical data. Hazard Ratio (HR) was calculated by Cox regression analysis. **Results** Mean age of the population was 85 ± 3.7 years, and causes for implantation were atrioventricular block in 51.9% and other bradyarrhythmias in 48.1% of cases. Mean eGFR was 58.3 ± 24 mL/min per 1.73 m^2 , and mean CCI was 3.65 ± 2.28 . Death for all-causes was recorded in 213 subjects. Deceased patients were older, had lower eGFR, higher comorbidity, higher prevalence of myocardial infarction, congestive heart failure, cerebrovascular disease, dementia and chronic pulmonary disease. Age (HR: 1.081, 95% CI: 1.044–1.119; $P < 001$), CCI (HR: 1.651, 95% CI: 1.286–2.121, $P < 001$) and $\text{eGFR} \leq 45$ mL/min per 1.73 m^2 (HR: 1.360, 95% CI: 1.024–1.806; $P = 0.033$) were predictors of death. **Conclusions** Renal dysfunction, as well as comorbidity, impacts negatively survival of older adults treated with pacemaker implantation because of bradyarrhythmias.

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1 Introduction

Bradyarrhythmias are the most common arrhythmias in older adults.^[1] In the elderly population, bradyarrhythmia is caused by sinus node dysfunction and atrioventricular block. Progressive fibrosis in both the sinus node and atrioventricular conduction system is the main pathophysiologic alteration. In order to treat this condition, implantation of a permanent pacemaker is required, especially if bradycardia is symptomatic. In the case that damage involves mainly sinus node, pacing modes that preserve atrioventricular synchrony are required reducing incidence of atrial fibrillation and improving quality of life.^[2]

It has been reported that in patients with advanced renal

dysfunction suffering sudden cardiac death (SCD), more than 20% were due to asystole.^[3] Permanent pacing is the therapy of choice for treating high-degree atrioventricular block and bradycardia. On the other hand, increased life expectancy and health care expenditures have led to questions concerning the routine use of electrotherapy in very elderly patients with multi-morbidity.

Chronic kidney disease (CKD) is a frequent condition in developed countries, its median prevalence in the general population has been estimated to be 7.2% in persons aged 30 years or older and 23.4%–35.8% in persons aged 64 years or older.^[4] In Italy, subjects suspected to be affected by CKD are between 2.5 and 3 millions.^[5] CKD and comorbidity are independent predictors of all-cause mortality in different conditions requiring hospitalization such as myocardial infarction, stroke, and chronic obstructive pulmonary disease.^[6–8]

Shastri, *et al.*^[9] demonstrated that comorbidity including age, diabetes, peripheral vascular disease, ischemic heart disease, serum creatinine, and alkaline phosphatase were independent predictors of SCD. The pattern and prevalence of serious bradyarrhythmias and tachyarrhythmias in sub-

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jects with CKD is still a matter of debate. Studies investigating the relationship between CKD and survival after pacemaker implantation are lacking. Therefore, the aim of this study was to evaluate whether presence of CKD could impact survival of older subjects with comorbidity and admission because of bradyarrhythmias undergoing pacemaker implantation.

2 Method

This retrospective observational study was conducted in agreement with the Declaration of Helsinki and with the approval of the local Ethic committee. It included a cohort of Caucasian older adults consecutively admitted in the geriatric ward, who underwent pacemaker implantation because of bradyarrhythmia. Type of pacemaker (single chamber or dual chamber) was decided by cardiologists based on clinical conditions. Exclusion criteria were the following: patients with bad prognosis due to poor clinical conditions (i.e., subjects with metastatic cancer or those with life expectancy lower than 8 weeks) and those who underwent implantable cardioverter defibrillator (ICD). The study started on January 1st 2010 and finished on October 31st 2014. University Hospital St. Anna is a 626-bed teaching hospital with all facilities, excluding only cardiothoracic surgery. The majority of admissions derive from the province of Ferrara (about 350,000 inhabitants), in which the hospital serves as the hub center. In the province of Ferrara, there are other two second-level smaller hospitals. The annual flow of patients by the emergency department (ED) is approximately 80,000, mainly elderly subjects due to the fact that the area is characterized by a high percentage of older adults (26% are older than 65 years), and approximately 3000 subjects are aged more than 90 years. Geriatric ward consists of 30 beds (24/24 hours and 7/7 days open to the ED admissions), admitting around 1300 patients during the year. Admitted patients are usually subjects older than 80 years, presenting at ED with acute diseases. The great majority of medical and nursing staff is permanent, covering also festive days or holidays. Patient information, laboratory results, and medication use at the time of pacemaker implantation were extracted from clinical records. Comorbidities were defined as conditions diagnosed prior to pacemaker implantation.

Charlson comorbidity index (CCI)^[10] was evaluated in order to summarize comorbidity. For score calculation, the following diseases were considered: hypertension, obesity, diabetes mellitus, cardiac and peripheral vascular diseases, cerebrovascular disease, hematological and solid neoplasms, and liver disease. Since original CCI incorporates also CKD,

to limit the possible influencing effect of renal dysfunction, the index modified excluding CKD was also calculated. Age and sex were the other variables considered. All patients underwent echocardiography and ejection fraction was calculated.

Estimated glomerular filtration rate (eGFR) was calculated using the following Modification of Diet in Renal Diseases (MDRD) equation.

$$eGFR = 175 \times SCr^{-1.154} \times \text{age}^{-0.203} \times 0.742 \text{ (if female)} \times 1.212 \text{ (if Black)}$$

where eGFR is measured in mL/min per 1.73 m², serum creatinine (SCr) is measured in mg/dL, and age is measured in years.

Renal dysfunction was defined by decreasing glomerular filtration below 60 mL/min per 1.73 m² in agreement with guidelines of National Kidney Foundation.^[11–13] SCr was assayed using Jaffe method on a Hitachi Modular (Roche Diagnostics, Mannheim, Germany).

Follow-up was performed at University Hospital St. Anna after discharge at intervals of 3–6 months. Outcome of the study was all-cause mortality, and information from medical records was combined with data obtained from institutional databases. Moreover complications related to pacemaker implantation were collected.

We performed a descriptive analysis and data were expressed as absolute numbers, percentages, and means \pm SD. Univariate analysis was performed to define the difference between survivors and deceased subjects. Statistical analysis was conducted using the χ^2 , Student *t*-tests and Mann Whitney test as appropriate. Also, in order to assess the independent parameters associated with all-cause mortality, the latter was considered as a dependent variable in a logistic regression analysis, and the age, eGFR < 60 mL/min per 1.73 m², eGFR \leq 45 mL/min per 1.73 m² and logarithm of corrected CCI were considered as independent ones. Odds ratios (ORs) and their 95% confidence intervals (95% CI) were reported. SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, 2004) was used for statistical analyzes.

3 Results

In this retrospective observational study, 538 patients (52.6% males) aged 85 ± 3.7 years, were implanted with a pacemaker (9 procedures/month). Duration of follow-up was 31 ± 20 months. Reasons for pacemaker implantation were severe atrioventricular block in 279 subjects (51.9%) while different types of bradyarrhythmias in 259 cases (48.1%). Single chamber pacing was prescribed in 250 subjects (46.5%) and dual chamber pacing in 288 (53.5%). At the

time of implantation, 53% of patients were on renin-angiotensin inhibitors and diuretics, 45% on aspirin, 32% on β -blockers, 23% on statins, 24% on oral anticoagulants, 20% on low molecular weight heparin and 14% on clopidogrel.

CCI was 3.65 ± 2.28 and after correction for CKD 3.13 ± 2.07 (LnCCI: 1.1 ± 0.59). Mean eGFR was 58.3 ± 24 mL/min per 1.73 m^2 , eGFR < 60 mL/min per 1.73 m^2 was calculated in 282 patients (52.4%) and eGFR < 45 mL/min per 1.73 m^2 in 172 (32%). Short-term complications after pacemaker implantation (< 30 days) were pocket haematoma in 15 patients (2.8%), leads dislodgment in 14 (2.6%), pericardial effusion in 9 (1.7%) and pneumothorax in 6 (1.1%). Long-term complications after pacemaker implantation (> 30 days) were pocket infections in 5 (0.9%) and endocarditis in 1 (0.2%). During follow-up, admissions due to congestive heart failure were recorded in 163 patients (30%). Main clinical characteristics of the patients are reported in Table 1.

Two hundred thirteen patients (39.6%) died after a follow up of 17 ± 14 months. Comparison between survivors and deceased subjects is reported in Table 2. Deceased patients were older, had lower eGFR, higher comorbidity,

Table 1 Clinical characteristics of the patients enrolled in the study ($n = 538$).

Females	255 (47.4%)
Age, yrs	85.1 ± 3.7
eGFR, mL/min per 1.73 m^2	58.3 ± 24
CCI correct for CKD	3.13 ± 2.07
Follow-up, months	31 ± 20
eGFR ≤ 45 mL/min per 1.73 m^2	172 (32%)
Ejection fraction	$56.1\% \pm 8.5\%$
Hypertension	470 (87.4%)
Moderate or severe renal disease	282 (52.4%)
Cerebrovascular disease	184 (34.2%)
Tumor without metastases	162 (30.1%)
Myocardial infarction	146 (27.1%)
Dementia	117 (21.7%)
Diabetes	115 (21.4%)
Congestive heart failure	101 (18.8%)
Chronic pulmonary disease	95 (17.7%)
Peripheral vascular disease	87 (16.2%)
Hemiplegia	81 (15.1%)
Peptic ulcer disease	51 (9.5%)
Connective tissue disease	19 (3.5%)
Deceased	213 (39.6%)

Data are presented as mean \pm SD or n (%). CCI: Charlson comorbidity index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

higher prevalence of myocardial infarction, congestive heart failure, cerebrovascular disease, dementia and chronic pulmonary disease.

Age, comorbidity and eGFR < 45 mL/min per 1.73 m^2 were predictors of death (Table 3). On the contrary, all the other parameters investigated which included ejection fraction and therapy were not related with mortality. Patients with eGFR ≤ 45 mL/min per 1.73 m^2 had lower survival than those with eGFR > 45 mL/min per 1.73 m^2 . On the contrary setting, a cut-off for eGFR at 60 mL/min per 1.73 m^2 could not allow detecting any difference in survival of the two groups (Figure 1).

Table 2. Comparison between survivors and deceased subjects.

	Survival ($n = 325$)	Deceased ($n = 213$)	<i>P</i>
Female	156 (48%)	99 (46.5%)	NS
Male	169 (52%)	114 (53.5%)	
Age, yrs	84.5 ± 3.3	86 ± 4.2	< 0.001
eGFR mL/min per 1.73 m^2	61.3 ± 23.3	53.8 ± 24.5	< 0.001
CCI correct for CKD	2.74 ± 1.98	3.72 ± 2.07	< 0.001
Follow-up, months	40.2 ± 17.6	17 ± 14	< 0.001
eGFR ≤ 45 mL/min per 1.73 m^2	128 (35%)	85 (49.4%)	0.001
Ejection fraction	$56.1\% \pm 8.3\%$	$56.1\% \pm 8.9\%$	NS
Hypertension	290 (89.2%)	180 (84.5%)	NS
Moderate or severe renal disease	150 (46.2%)	132 (62%)	< 0.001
Cerebrovascular disease	90 (27.7%)	94 (44.1%)	< 0.001
Tumor without metastases	91 (28%)	71 (33.3%)	NS
Myocardial infarction	78 (24%)	68 (31.9%)	0.043
Dementia	61 (18.8%)	56 (26.3%)	0.039
Diabetes	65 (20%)	50 (23.5%)	NS
Congestive heart failure	46 (14.2%)	55 (25.8%)	0.001
Chronic pulmonary disease	48 (14.8%)	47 (22.1%)	0.03
Peripheral vascular disease	47 (14.5%)	40 (18.8%)	NS
Hemiplegia	37 (11.4%)	44 (20.7%)	0.003
Peptic ulcer disease	37 (11.4%)	14 (6.6%)	NS
Connective tissue disease	13 (4%)	6 (2.8%)	NS

Data are presented as mean \pm SD or n (%). eGFR: estimated glomerular filtration rate; NS: not significant.

Table 3. Factors independently associated with mortality during follow-up.

	HR	95% CI	<i>P</i>
Age	1.081	1.044–1.119	< 0.001
LnCCI (corrected for CKD)	1.651	1.286–2.121	< 0.001
eGFR ≤ 45 mL/min per 1.73 m^2	1.360	1.024–1.806	0.033

CCI: Charlson comorbidity index; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate.

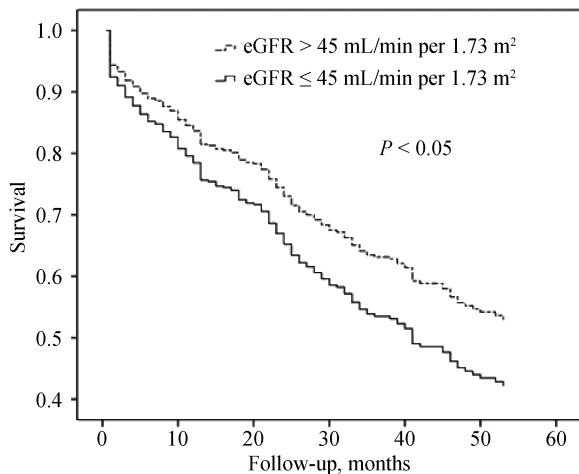


Figure 1. Survival of patients who underwent pacemaker implantation with eGFR > and ≤ 45 mL/min per 1.73 m^2 . eGFR: estimated glomerular filtration rate.

4 Discussion

This is the first study that evaluated relationship between renal dysfunction, comorbidity and bradyarrhythmias which were treated with pacemaker implantation in older adults. We found that age, comorbidity and eGFR ≤ 45 mL/min per 1.73 m^2 were determinants of all-cause mortality in older adults needing pace-maker implantation.

Cardiovascular disease represents the leading cause of death in Western countries and accounts for approximately 41% of the deaths among dialysis patients. Death from cardiovascular disease is far more common in patients with CKD than progression to end-stage renal disease. United States Renal Data System reports that cardiac arrest and ventricular arrhythmias are three times more frequent in patients with renal dysfunction than in those with normal renal function.^[14]

Risk for SCD has been established to be 17% higher for every 10 mL/min per 1.73 m^2 reduction in glomerular filtration rate.^[15] Moreover, risk of SCD is strongly associated with the severity of the renal disease in patients with coronary artery disease (CAD), each 10 mL/min per 1.73 m^2 decrement in eGFR increases the risk for SCD by 11%.^[16]

It has been reported that the rhythm most often recorded at the time of sudden cardiac arrest is ventricular fibrillation in 75%–80% of cases, whilst 15%–20% of SCDs are attributed to bradyarrhythmias, including advanced atrioventricular (AV) block and asystole.^[17]

Severe coronary stenosis is an important factor for the induction and lengthy persistence of ventricular arrhythmias during and after hemodialysis.^[18] Moreover, physicians should consider the following additional triggers commonly

encountered in patients with renal dysfunction: fluid and electrolytes disorders, autonomic neuropathy, anemia, valvular and vascular calcifications, and obstructive sleep apnea.^[19]

Ten years ago, Kestenbaum, *et al.*^[20] showed that eGFR lower than 60 mL/min per 1.73 m^2 was related to cardiac rhythm disturbances demonstrated by resting electrocardiography. Similar results were confirmed by Dobre, *et al.*^[21] reporting that first-degree atrioventricular block and ventricular conduction defect were more prevalent when GFR < 60 mL/min per 1.73 m^2 , especially if CAD was present. Both studies concluded that major ECG abnormalities were frequently diagnosed in CKD patients and predicted significantly higher risk for death and adverse cardiovascular outcomes.

In 2011, Raza, *et al.*^[22] evaluated long-term pacing and mortality outcomes examining patients undergoing pacemaker implantation for high-degree AV block and bradycardia, after cardiac surgery at the Minneapolis Veterans Administration Medical Center between 1987 and 2010. Age, diuretic use, cardiopulmonary bypass time, and valve surgery were independent predictors of pacemaker implantation. Patients who underwent the procedure had a higher long-term mortality. However, after adjusting for confounding factors pacemaker requirement was not anymore associated with mortality. The authors concluded that the majority of patients who require pacemaker after cardiac surgery were not exposed to high risk of long-term mortality.^[22]

To determine factors associated with survival, baseline characteristics of 6505 patients after pacemaker implantation were analyzed during a 30 years follow-up in a single center university hospital. All-cause mortality was the main outcome. Median survival was 101.9 months, with 44.8% of patients alive after 10 years and 21.4% alive after 20 years. In all subgroups, women had a significantly longer survival than men, despite being older at implantation. Multivariate analysis revealed that age, gender, decade of implantation, type of pacemaker, index arrhythmia and initial symptoms were predictors of survival.^[23]

In another study, more than 1500 patients aged ≥ 80 years who underwent pacemaker implantation between 1971 and 2000 were investigated. The authors identified decade of implantation, a history of pre-syncope and male sex as the prognostic factors. However, none of them could be recommended for estimating outcome or for guiding device selection. Pacemaker therapy was suggested as a clinically and economically effective therapeutic option to control bradyarrhythmia-related symptoms in older adults.^[24]

Relationship between renal dysfunction and comorbidity is not a novelty, because age, hypertension, diabetes, atherosclerosis, congestive heart failure are closely related.^[25]

However, data relating renal dysfunction and prognosis of patients with pacemaker are scarce, and we found that low eGFR reduces survival of such patients.

Autonomic imbalance, altered myocardial structure, electrolytes imbalance, diabetes, left ventricular hypertrophy and dysfunction, repolarization abnormalities, inflammation, CAD and renal dysfunction *per se* are considered the main pathophysiological conditions involved in the genesis of arrhythmias in CKD patients.^[26] The previous reported conditions suggest that different mechanisms from atherosclerotic derangement and congestive heart failure could be responsible for triggering fatal arrhythmias in CKD patients.

Cuculich, *et al.*^[27] analyzed retrospectively patients who underwent ICD implantation for primary prevention of sudden death and found that CKD significantly reduced long-term survival, a 10 mL/min reduction in creatinine clearance was associated with a 55% increase in hazard of mortality. Bogdan, *et al.*^[28] examined outcomes associated with the severity of renal dysfunction investigating 2289 patients who were enrolled and prospectively followed up in the Israeli ICD registry. They found patients with eGFR < 30 mL/min per 1.73 m² were older, had higher prevalence of comorbidities, and more likely to suffer from congestive heart failure. The authors concluded that severe renal dysfunction increased risk for all-cause and cardiac mortality following device implantation, and risk for non-cardiac hospitalizations. These results were confirmed in a meta-analysis evaluating 11 observational studies enrolling 3010 patients, which indicated that CKD was associated with increased mortality in patients receiving ICD therapy.^[29]

As well as in our study, age plays a major role on benefits due to ICD therapy. Amin, *et al.*^[30] quantified the benefit of an ICD for primary prevention of SCD in patients with CKD depending on the patient's age and stage of kidney disease. In patients with stages 1 and 2 CKD, ICD implantation reduces mortality. On the other hand, in patients with more advanced stages of CKD, the benefit is less significant and age-dependent. ICD implantation is favored at ages < 80 years for stage 3, ages < 75 years for stage 4, and ages < 65 years for stage 5.^[30]

We found that survival of patients who needing cardiovascular implantable electronic devices (CIEDs) is affected by decreasing renal function. On the other hand, in our study we excluded subjects with ICD implantation as we decided to focus on bradyarrhythmias.

4.1 Limitations

The main limitation is that our study is a retrospective observational one, and no control group was included. On the other hand, we enrolled a significant number of elderly

patients admitted with an acute event associated with bradyarrhythmias and treated with pacemaker implantation. Renal dysfunction and bradyarrhythmias due to sinus node dysfunction are thought to be related to age, and age itself is a predictor for mortality. Thus, our observation may not be new findings. Relationship between pacemaker implantation, comorbidity and eGFR is still a matter of debate. It is more important to know whether pacemaker implantation improves mortality, CCI or preserves renal function in elderly patients with bradyarrhythmia and renal dysfunction, or the opposite way round.

It has been suggested that in order to evaluate the impact of CIEDs, it would be better to test the main outcome cardiac mortality instead of all-cause mortality.^[31] However CIEDs are costly, so all-cause mortality could be considered a better outcome, especially in the case of shortage of resources.

In our study, medications were not related to death, however their impact could not be detected due to retrospective study design. Cholinesterase inhibitors are commonly prescribed to treat dementia. However, in subjects treated with these drugs hospital visits for bradycardia, permanent pacemaker insertion, and hip fracture have been reported to be more frequent than in people non treated.^[32] On the other hand, polypharmacy is a common problem in older adults, increasing risk of drug interaction, especially if renal function is reduced, due to changes in medication pharmacokinetics and pharmacodynamics.^[33]

We did not evaluate precisely impact of renal dysfunction on complications due to pacemaker implantation. CKD represents a risk factor for cardiac implantable electronic device removal because of infection.^[34] However, the number of complications in our study could be considered low, especially if we consider the mean age of the population. A strong collaboration between physicians, care manager and patients, such as the team described in the project Leonardo,^[35] could even reduce complications.

4.2 Conclusions

We concluded that comorbidity and renal dysfunction, especially eGFR \leq 45 mL/min per 1.73 m², should be taken into consideration at the time of pacemaker implantation in older adults. Calculation of eGFR and CCI may help physicians in risk stratification of elderly patients who need pacemaker implantation.

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