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Asystole episodes and bradycardia in patients with end-stage renal disease

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ABSTRACT

Background. Knowledge of arrhythmias in patients with end-stage renal disease (ESRD) is mainly based on ambulatory electrocardiography (ECG) studies and observations during haemodialysis. We used insertable cardiac monitors to define the prevalence of arrhythmias, focusing on bradyarrhythmias, in ESRD patients treated with several dialysis modes including home therapies. Moreover, we assessed whether these arrhythmias were detected in baseline or ambulatory ECG recordings.

Methods. Seventy-one patients with a subcutaneously insertable cardiac monitor were followed for up to three years. Asystole (≥4.0 secs) and bradycardia (heart rate <30 bpm for ≥4 beats) episodes, ventricular tachyarrhythmias and atrial fibrillation were collected and
verified visually. A baseline ECG and a 24-48-hour ambulatory ECG were recorded at recruitment and once a year thereafter.

**Results.** At recruitment, forty-four patients were treated in in-center haemodialysis, 12 in home haemodialysis and 15 in peritoneal dialysis. During a median follow-up of 34.4 months, 18 (25.4 %) patients had either an asystolic or a bradycardic episode. The median length of each patient’s longest asystole was 6.6 seconds and that of a bradycardia 13.5 seconds.

Ventricular tachyarrhythmias were detected in 16 (23%) patients, and atrial fibrillation in 34 (51%) patients. In-center haemodialysis and type II diabetes were significantly more frequent among those with bradyarrhythmias whereas no bradyarrhythmias were found in home haemodialysis. No bradyarrhythmias were evident in baseline or ambulatory ECG recordings.

**Conclusions.** Remarkably many patients with ESRD had bradycardia or asystolic episodes, but these arrhythmias were not detected by baseline or ambulatory ECG.

**Keywords:** cardiovascular, chronic kidney insufficiency, clinical trial, haemodialysis, peritoneal dialysis
KEY LEARNING POINTS

What is already known about the subject?

- Arrhythmias and cardiac arrest account for 25-28% of total and 67% of cardiovascular mortality in patients with end-stage renal disease, and bradycardic and asystolic arrhythmias are suggested to be the predominant mechanism of sudden cardiac death dialysis patients.
- The information on the prevalence of arrhythmias is currently based mainly on ambulatory ECG recordings or observational studies during dialysis treatments, and the few studies made with insertable cardiac monitors have concentrated mainly on patients treated with in-center haemodialysis.
- We used insertable cardiac monitors to detect the actual prevalence of remarkable arrhythmic episodes in different dialysis modalities, including home therapies, over the follow-up time up to three years, making this one of the largest prospective studies looking into bradyarrhythmias in patients with end-stage renal disease.

What this study adds?

- As many as 25% of the patients had a bradycardic or asystolic episode during the follow-up, showing that bradyarrhythmias are remarkably common in dialysis patients.
- Ambulatory ECG recordings are an inefficient way to detect arrhythmias in patients with end-stage renal disease, as no arrhythmia was found in ambulatory ECG recordings up to 144 hours per patient.
• We found that many diabetic patients and patients treated with in-center hemodialysis (29%) experienced significant bradyarrhythmia episodes, but no bradyarrhythmias were found in home haemodialysis.

What impact this may have on practice or policy?

• The possibility of bradyarrhythmias should always be considered if patients with end-stage renal disease present with symptoms that could be caused by these arrhythmias, such as syncope or dizziness.
• Avoiding long interdialytic intervals might prevent bradyarrhythmias, as all but one of the most severe bradycardia or asystolic episodes in our study occurred during the last day of the interdialytic period.
• If bradyarrhythmias are suspected in patients with end-stage renal disease, ambulatory ECG recordings might be of low value, and the use of an insertable cardiac monitor should be considered.
INTRODUCTION

Arrhythmias and cardiac arrest account for 25-28% of the total and 67% of cardiovascular (CV) mortality in patients with end-stage renal disease (ESRD)\(^1\). The arrhythmic risk is already elevated in the early stages of kidney disease and rises sharply as kidney function deteriorates, being highest in ESRD\(^1-3\).

The knowledge of arrhythmias in this patient group is currently based mainly on ambulatory ECG studies and on studies investigating arrhythmias during haemodialysis (HD) or immediately thereafter. A major part of these studies have focused on ventricular arrhythmias, which have been demonstrated to be common in ambulatory ECG recordings, but bradycardic and asystolic events have not been generally reported \(^4-7\). In recent studies using insertable cardiac monitors, the incidence of bradyarrhythmias in HD patients has varied widely between 10-25% \(^8-11\). Wong et al reported the incidence of bradycardia and asystole as high as 30% and 28%, respectively \(^12\). However, as these earlier studies have concentrated on in-center HD patients, the information about the prevalence of bradyarrhythmias in peritoneal or home-based haemodialysis (HHD) has thus far been very limited.

As the prevalence of chronic kidney disease is rapidly growing due to the aging of the population as well as rise in the incidence of diabetes, hypertension and obesity,\(^1\) it is increasingly important to study severe arrhythmias in these patients with methods beyond ambulatory ECGs. It has also been suggested that bradycardic and asystolic arrhythmias are the predominant mechanism of sudden cardiac death in this patient group \(^13\). This multi-center, prospective study aimed to determine the incidence of arrhythmic episodes, mainly bradycardia and asystole by using ICM for the definite assessment of arrhythmias. To our knowledge, we estimated for the first time, whether an ICM is more useful in detecting these arrhythmias than yearly repeated ambulatory ECG recordings.
MATERIALS AND METHODS

Patients were recruited from dialysis and pre-dialysis units from five hospitals in Finland: the Päijät-Häme Central Hospital (n=40), Helsinki University Central Hospital (n=25), Central Finland Central Hospital (n=5), Satakunta Central Hospital (n=5) and Vaasa Central Hospital (n=5). The inclusion criteria were stage 4 (glomerular filtration rate [eGFR] 15-29 ml/min/1.73m$^2$) or stage 5 (eGFR <15 ml/min/1.73m$^2$ or on dialysis) renal disease. Patients under 18 or over 75 years of age were excluded, as were those with a non-cardiovascular or non-renal disease limiting the expected lifespan to less than one year. The expected follow-up time was up to three years. Patients with pre-existing arrhythmic conditions were not excluded.

A total of 80 patients were recruited. One patient died, two received a kidney transplant and three withdrew before the ICM implantation and were not included in the study. One patient remained in pre-dialytic stage during the whole follow-up, and was also excluded from the final analysis. In addition, two patients with unsuccessful implantation were withdrawn from the study. None of the patients presented with later complications of ICM implantation.

Altogether, 71 patients were accepted into the final analysis, 44 of whom were treated by in-center HD, 12 by home HD (HHD) and 15 by (PD) (Fig. 1). PD patients were treated by either continuous ambulatory PD (CAPD, n= 7) or by automated PD (APD, n= 8). The study protocol was approved by the Ethics Committee of the Pirkanmaa Hospital District, Tampere, Finland (IRB approval number R11138 / 2011), and all patients gave informed consent as stipulated in the Declaration of Helsinki. The trial has been registered, Trial ID ISRCTN10855079.

The following data was collected at baseline: detailed medical history including information on renal disease, dialysis and potential kidney transplantations, medication, anthropometric
data, 12-lead ECG as well as pre- and post-dialytic blood pressures. All patients underwent an echocardiogram performed by a cardiologist.

Each patient underwent a 24-48-hour ambulatory ECG recording at the beginning of the study and once a year thereafter. The recordings were analysed with the MARS Ambulatory ECG Analysis System (GE Healthcare, CA, USA).

ICMs were implanted subcutaneously in the left side of the chest using local anaesthesia. The devices used in the study were Reveal XT (44 patients), Reveal LINQ (27 patients) or Reveal DX (3 patients) (Medtronic Inc, Minneapolis, MN, USA). Data retrieval from Reveal XT and DX was performed noninvasively via an induction link when the patients visited the hospital for dialysis or for a routine nephrologic check-up. The data retrieval from the Reveal LINQ was automatic via a home-based radiofrequency link. The ICMs were set to detect all asystole episodes of at least 3.0 seconds in duration. However, in this particular study, an asystole episode was defined as a cardiac arrest of at least 4.0 seconds in duration. Bradycardia was defined as a heart rate of less than 30 beats per minute in at least 4 consecutive beats. All the ICMs captured ventricular tachyarrhythmias, and Reveal XT and Reveal LINQ also atrial fibrillation (AF). Reveal DX is not able to detect AF. Ventricular tachycardia (VT) was defined as heart rate > 167 beats per minute (R-R-time < 360 ms) for >16 beats. AF was detected by analyzing the irregularity of ventricular rhythm using an automatic algorithm.

The ICM-recorded arrhythmias were verified visually from the electrocardiograms by two experienced cardiologists. Each ICM could store up to 27 minutes of ECG. If the available memory for detected episodes became full between data retrievals, a new ECG recording overwrote the oldest stored ECG recording. The system would only overwrite a recording if at least 3 episodes of the same type remained in memory. Only text entry of the overwritten
episodes was available for the researchers. Episodes with visual ECG verification as a true arrhythmia were utilized in the analysis.

Statistical analyses were performed using SPSS 22.0 for Mac (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation or as median with interquartile range (IQR), as appropriate. The t test for independent samples was used to compare the continuous normally distributed variables and categorical variables and a chi-square test to compare the categorical variables between groups with and without bradycardic or asystolic episodes. The associations between categorical variables and continuous non-normally distributed variables were analysed by Mann-Whitney U-test. Odds ratios and 95 % confidence intervals were computed using logistic regression analyses. The variables included in logistic regression analyses were recorded bradyarrhythmias, dialysis modality, age, sex, presence of type II diabetes and history of myocardial infarction. A two-sided p value of < 0.05 was considered as statistically significant.
RESULTS

At recruitment, the mean age of the 71 patients (49 males) was 59.8±9.3 years, and the median time on dialysis was 17.6 months (IQR 6.0–37.5 months). No patient had previously known severe bradyarrhythmic episodes or ventricular tachyarrhythmias at recruitment. 14 (20%) patients were known to have AF prior to entering the study, six of which had permanent and eight paroxysmal AF. No patient had a pacemaker at the beginning of the study.

During the median follow-up time of 34.4 months (IQR 23.2 36.9 months), 18 (25.4%) patients had either an asystolic or a bradycardic episode (Tables 1-2, Fig. 1). Three (4.2% of the total population) of them had only an asystole, seven (9.9%) had only an episode of bradycardia, and eight (11.3%) had both. The median duration of the longest asystole within each patient was 6.6 seconds (IQR 5.2–8.3 secs). The median heart rate during a bradycardia episode was 27.5 bpm (IQR 24.2–29.0 bpm), and the median duration of the episode was 13.5 seconds (IQR 8.9–35.0 secs).

Type II diabetes was more prevalent among those with asystolic and bradycardic episodes, however, the prevalence of type 1 diabetes or diabetic kidney disease was not different (Table 1). Those with bradyarrhythmia did not use beta-adrenergic blockers more often than others. Interestingly, in 11 of the 12 in-center HD patients with bradyarrhythmias, the most severe bradycardic episode occurred within 24 hours before the next HD session, while only one was detected on the same day the patient had had his/her dialysis treatment. Mean time from the previous HD to a bradycardic event was 44.3 hours and to an asystolic event 28.4 hours.

Dialysis mode and bradyarrhythmias

Bradyarrhythmias were especially common in in-center HD patients. Of the 44 patients treated with in-center HD at the beginning of the study, 15 (34%) had at least one major
asystolic or bradycardic episode. 12 of these patients (27% of all HD patients) had their first detected episode while still in HD (Table 1), while three had undergone renal transplantation before bradyarrhythmias occurred. No bradyarrhythmia was found in HHD patients (p=0.036). Three out of 15 PD patients (20.0%) had bradyarrhythmia. The patients in HHD were younger (53.3±10.1 years) than those in in-center HD (61.9±7.6 years), but otherwise there were not significant differences in morbidities (Table 3).

12-lead ECG, ambulatory ECG and echocardiography

There were no bradycardia or asystole in the 10-second baseline ECGs. The patients with bradyarrhythmic episodes had significantly longer PR interval and longer maximal R-R interval (Table 1). In the 24-48-hour ambulatory ECG recordings taken at the beginning of the study and during the follow-up, no patient had asystole ≥ 3.0 seconds or bradycardia < 30 beats per minute. Patients with a bradycardic or asystolic episode had significantly lower minimum and average heart rate and longer maximal R-R interval – albeit all being within normal ranges – in their ambulatory ECG recordings compared to the patients without bradyarrhythmia. Ambulatory ECG recording was taken once a year for each patient, therefore some patients had a total recording time of up to 144 hours.

In echocardiograms at the beginning of the study, the left ventricular mass index was mildly elevated in patients without bradyarrhythmias (122±38 g/m²) and moderately elevated in those with these arrhythmias (145±61 g/m², p=0.117).

Laboratory parameters and residual renal function

Electrolytes as well as several other laboratory parameters were measured at the beginning of the study (K⁺, Na⁺, Mg²⁺, haemoglobin, creatinine, ionized calcium, urea). None of the measured electrolytes was linked to incidence of bradyarrhythmias, most notably, the level of
potassium (p= 0.499) or ionized calcium (p=0.09). Nor was the level of haemoglobin (p=0.856). There was no difference in urine excretion between the patients with or without bradyarrhythmic episodes (839±745 ml and 913±799 ml, respectively, p=0.759).

Association of other arrhythmias to bradycardia and asystole

During the follow-up, 16 patients (23%) had at least one episode of VT or ventricular fibrillation. AF was captured in 34 (50%) of the 68 patients with an ICM with AF capability. There was no association with the prevalence of bradyarrhythmias and VT (Table 1). AF was remarkably common in patients with bradyarrhythmias, as 13 of the 16 patients (81%) with bradyarrhythmias also had AF.

Mortality, pacemaker implantation and kidney transplantation

Fourteen patients (19.7%) died during the follow-up, one of which was in PD, three in HDD and ten in in-center-HD. Mortality was similar in patients with or without bradyarrhythmias (17% and 21%, respectively). The annual mortality rate during the follow up was 6.9%. When considering only the time in dialysis treatment before possible transplantation (23.6±12.1 months), the mortality rate was 10.0%/year. ICM documented three sudden cardiac deaths, two of which were caused by ventricular fibrillation and one by severe bradyarrhythmia. In addition, two patients had sudden cardiac death based on clinical information; unfortunately, their ICM was not interrogated after the death. Six of the deaths were due to septic infections: three of them after a major surgical operation and three originating from diabetic or other wounds. In one of these cases, the patient had marked bradyarrhythmias before the death. Three patients died of acute myocardial infarction.

During the follow-up one patient got a pacemaker due to sick sinus syndrome and six patients due to bradycardia detected by ICM. In two patients, the asystolic episode was detected for
the first time shortly before their death. For the others, the follow-up was continued closely after the recorded bradyarrhythmia with medication adjustments.

As many as 21 patients (29.6%) received a kidney transplant. Three of them had a bradycardic or asystolic event before the transplantation, while none of these had another event post-transplant. On the other hand, three patients without prior bradyarrhythmia had an event after the kidney transplantation. All of these three patients had been treated with in-center HD before transplantation.
DISCUSSION

To our knowledge this is one of the largest studies on bradyarrhythmias in ESRD patients with ICMs. As many as one in four ESRD patients had a clinically noteworthy asystolic episode or bradycardia during a median follow-up of almost three years.

Recently, Wong et al reported that 30% of the in-center HD patients had bradycardia and 28% an asystolic event during the ICM follow-up of 18 months. In another ICM study with a follow-up of 6 months, the corresponding figures were 19.7% for the prevalence of bradycardia and 9.1% for asystolic episodes, respectively. While our main findings are in line with previous results, the present study also renders clearly novel perspectives. First, we applied stricter and clinically more meaningful criteria to define asystole and bradycardia, i.e., 4.0 seconds instead of 3.0 seconds as the limit for an asystolic episode, and a heart rate < 30 bpm instead of 40 bpm for at least 4 beats for bradycardia. Second, in addition to in-center HD patients, we also examined patients in home-based therapies, who are generally healthier and younger than patients in in-center HD. Third, we analysed repetitive ambulatory ECG as a comparison to the ICM findings.

The relatively young age and good health of our ESRD patients is manifested in the remarkably low mortality 19.7% during the entire follow-up or 10.0%/year in patients receiving dialysis treatment. More typically, reported annual mortality among ESRD patients has been as high as 16.5%. Consequently, as the arrhythmias are known to become more prevalent with age and co-morbidities, the prevalence of marked bradycardic and asystolic events may be even higher in overall clinical practice than what is demonstrated in our study.

One study investigated the incidence of arrhythmia in non-renal patients after a myocardial infarction using ICM and the same criteria for bradycardia and asystole as in our study. Both of these arrhythmias were more common in our ESRD patients than after a myocardial
infarction. This suggests that ESRD patients should be regarded as having at least the same risk for adverse bradyarrhythmias as patients after myocardial infarction.

Even though our in-center HD patients were highly susceptible to bradyarrhythmias, 29% had a bradycardic and 14% an asystolic episode, none of the patients in HHD had these arrhythmias. This is probably mostly explained by the patient selection: HDD patients were younger and with fewer comorbidities. However, we postulate that longer HD treatment times and slower shifts in electrolytes might also contribute to this finding. The majority of the in-center HD patients were treated 12 hours a week, while our HHD patients had treatment 15 hours a week. Heart rate variability (HRV) and other electrocardiographic parameters have been investigated in daily HD patients and in nocturnal HHD patients. Intensive HD improved the balance of autonomic nervous system as evidenced in an increase in HRV. Frequent and intermittent nocturnal HD decreased mean time between peak and end of the T wave as well as associated with improvements in QTc intervals, suggesting a lesser degree of heterogeneity of the repolarization phase. In aggregate, these findings may reflect slower shifts in electrolyte levels, less myocardial stunning or lesser degrees of neurohormonal activation with treatment times longer than in typical in-center HD.

Patients with type II diabetes were more likely to have bradycardic or asystolic episodes, but this was not the case with type I diabetes. The difference is probably explained by the fact that those with type II diabetes were older and had higher BMI compared to those with type I diabetes. Association between obesity and sudden cardiac death and arrhythmias, especially atrial fibrillation, has been reported before, and a recent study demonstrated that also bradyarrhythmias were more prevalent in obese patients. This topic needs to be scrutinised in future studies.

None of the bradyarrhythmias detected with ICMs were manifest in the baseline ECGs or in repetitive ambulatory ECG recordings. However, ambulatory ECG recordings are widely used...
when arrhythmias are suspected in the presence of dizziness, presyncope or syncope. These symptoms are common in patients with chronic kidney disease: 23% of patients in the predialytic stage suffered from severe dizziness or falling during one year. At the age of 70 years and above, as many as 70% of the patients undergoing in-center HD reported dizziness and 40% presyncope or syncope. As bradycardia and asystole may lie behind these symptoms, ICM could be a useful diagnostic approach for patients with unexplained and repeated bouts of syncope or presyncope.

Risk of sudden death is known to be highest during the longest intervals between dialysis sessions. In our data, 11 of the 12 in-center HD patients with bradyarrhythmias had their most severe bradyarrhythmic episode within the last day before the next dialysis. This corroborates the hypothesis that bradycardic events might well be culprits for a portion of sudden deaths within the long intervals. Further analysis would necessitate a larger pool of patients.

LIMITATIONS

There was a limited number of patients in our study, resulting in a relatively small amount of end-points. Therefore, we could not analyse the risk factors of bradycardia and asystolic events separately. Further research is needed to better understand the mechanisms behind the asystolic and bradycardic events in this patient group, including parameters for cardiac repolarization and autonomic nervous system, and to find out whether these arrhythmic events could be predicted or prevented.

We did not require the patients to report symptoms such as syncope, presyncope or dizziness, as we wanted to minimize the interference with daily life, and we cannot report if the detected arrhythmic episodes were symptomatic. In addition, we are not able report the exact amount of arrhythmic episodes for each patient because of the limited memory ECG storage capacity.
of the ICMs. This also hindered accurate investigation of the relation of each bradyarrhythmic episode to the dialysis procedures. Further studies are needed to investigate this subject further.

CONCLUSION

Remarkably many patients with ESRD have major asystolic and bradycardic episodes. The possibility of these arrhythmic events should be considered in this patient group even though baseline ECG or ambulatory ECG recordings are normal.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST STATEMENT

Dr. Kerola reports non-financial support from St Jude Medical, Medtronic and Boston Scientific, outside the submitted work.

Dr. Koistinen reports participation in international congresses sponsored by St. Jude Medical, Medtronic, Biotronik and Boston Scientific.

AUTHORS’ CONTRIBUTIONS


T.K., T.N., O.A., J.K. and A.Y. implanted the ICMs and carried out the echocardiograms.

J.R., T.N., T.K. and K.K. analysed the data. J.R. and T.N. carried out the statistics and made
the figures and tables. J.R., T.K., K.K. and T.N. drafted the paper. All authors revised and
accepted the final version of the manuscript.

FUNDING

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Tuovinen Fund.
Table 1. Baseline characteristics of the patients with and without bradyarrhythmic episodes detected by an insertable cardiac monitor (ICM)

<table>
<thead>
<tr>
<th></th>
<th><strong>No bradycardia/asystole</strong> n = 53</th>
<th><strong>Bradycardia/asystole</strong> n = 18</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean or n  SD or %</td>
<td>Mean or n  SD or %</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>59.2 9.6</td>
<td>61.5 8.4</td>
<td>0.381</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>38 72%</td>
<td>11 61%</td>
<td>0.401</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>27.8 7.7</td>
<td>30.2 8.3</td>
<td>0.278</td>
</tr>
<tr>
<td>History of coronary heart disease</td>
<td>17 32%</td>
<td>8 44%</td>
<td>0.342</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>10 19%</td>
<td>6 33%</td>
<td>0.204</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>10 19%</td>
<td>4 22%</td>
<td>0.757</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>7 13%</td>
<td>4 22%</td>
<td>0.361</td>
</tr>
<tr>
<td>Diabetes type I</td>
<td>11 21%</td>
<td>4 22%</td>
<td>0.895</td>
</tr>
<tr>
<td>Diabetes type II</td>
<td>11 21%</td>
<td>8 44%</td>
<td><strong>0.050</strong></td>
</tr>
<tr>
<td>Sleep apnoea</td>
<td>5 9%</td>
<td>4 22%</td>
<td>0.159</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>147 23</td>
<td>152 28</td>
<td>0.524</td>
</tr>
<tr>
<td>Use of beta-blocker</td>
<td>32 60%</td>
<td>13 72%</td>
<td>0.367</td>
</tr>
</tbody>
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**Baseline 12-lead ECG**

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<tr>
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<th><strong>Mean or n  SD or %</strong></th>
<th><strong>p</strong></th>
</tr>
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<tbody>
<tr>
<td>Sinus rhythm</td>
<td>49 92%</td>
<td>17 94%</td>
<td>0.775</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>4 8%</td>
<td>1 6%</td>
<td>0.775</td>
</tr>
<tr>
<td>Heart rate (per minute)</td>
<td>74 14.7</td>
<td>67 8.7</td>
<td>0.173</td>
</tr>
<tr>
<td>QRS width (ms)*</td>
<td>96 15.9</td>
<td>106 26.4</td>
<td>0.169</td>
</tr>
<tr>
<td>PR interval (ms)**</td>
<td>168 25.7</td>
<td>193 35.4</td>
<td><strong>0.006</strong></td>
</tr>
<tr>
<td>Maximal R-R interval (s)***</td>
<td>0.86 0.20</td>
<td>0.98 0.21</td>
<td><strong>0.037</strong></td>
</tr>
</tbody>
</table>

**Ambulatory ECG recording**

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<th><strong>p</strong></th>
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<tbody>
<tr>
<td>Average heart rate (bpm)</td>
<td>76.6 10.4</td>
<td>72.2 11.9</td>
<td>0.197</td>
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<tr>
<td>Minimum heart rate (bpm)</td>
<td>55.2 7.6</td>
<td>48.6 8.0</td>
<td><strong>0.005</strong></td>
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<tr>
<td>Maximal R-R interval (s)***</td>
<td>1.44 0.40</td>
<td>1.71 0.40</td>
<td><strong>0.024</strong></td>
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**Echocardiogram**

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<th><strong>Mean or n  SD or %</strong></th>
<th><strong>Mean or n  SD or %</strong></th>
<th><strong>p</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricle diameter (mm)</td>
<td>48 14</td>
<td>46 18</td>
<td>0.718</td>
</tr>
<tr>
<td>Left atrium diameter (mm)</td>
<td>40 10</td>
<td>43 8</td>
<td>0.253</td>
</tr>
<tr>
<td>Left ventricle ejection fraction (%)</td>
<td>60   9</td>
<td>56 10</td>
<td>0.155</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>122 38</td>
<td>145 61</td>
<td>0.869</td>
</tr>
<tr>
<td>Left ventricular mass index (g/m²)</td>
<td>653 201</td>
<td>618 177</td>
<td>0.550</td>
</tr>
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</table>

**Baseline laboratory parameters**

<table>
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<tr>
<th></th>
<th><strong>Mean or n  SD or %</strong></th>
<th><strong>Mean or n  SD or %</strong></th>
<th><strong>p</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium (mmol/l)</td>
<td>4.6 0.8</td>
<td>4.4 0.5</td>
<td>0.499</td>
</tr>
<tr>
<td>Haemoglobin (g/l)</td>
<td>115 15</td>
<td>115 13</td>
<td>0.856</td>
</tr>
<tr>
<td>Creatinine (umol/l)</td>
<td>653 201</td>
<td>618 177</td>
<td>0.550</td>
</tr>
<tr>
<td>Ionized calcium (mmol/l)</td>
<td>1.17</td>
<td>0.11</td>
<td>1.12</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Sodium</td>
<td>138</td>
<td>4</td>
<td>138</td>
</tr>
</tbody>
</table>

**Other arrhythmias**

Ventricular tachycardias

<table>
<thead>
<tr>
<th>Atrial fibrillation</th>
<th>10</th>
<th>19%</th>
<th>6</th>
<th>33%</th>
<th>0.204</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22</td>
<td>42%</td>
<td>13</td>
<td>72%</td>
<td><strong>0.034</strong></td>
</tr>
</tbody>
</table>

**Dialysis mode**

Dialysis vintage (months)

| In-center HD | 40  | 69   | 22   | 24   | 0.359 |
|              | 29  | 55%  | 12   | 67%  | 0.077 |

- Weekly treatment time (hours)
  | 12.25 | 0.7  | 12.1 | 1.6  | 0.767 |

- HHD
  | 12    | 21%  | 0    | 0%   | **0.036** |

- Weekly treatment time (hours)
  | 15.3  | n.a. | n.a. | n.a. | n.a. |

PD

| Weekly treatment time (hours) | 12  | 23%  | 3    | 17%  | 0.741 |

Kidney transplant

| n.a. | n.a. | 3\(^a\) | n.a. | n.a. |

**Kidney disease**

- Diabetic
  | 17   | 32%  | 9    | 50%  | 0.121 |

- Polycystic
  | 11   | 21%  | 1    | 6%   | 0.157 |

- Glomerulonephritis
  | 13   | 25%  | 5    | 28%  | 0.689 |

- Nephrosclerosis
  | 0    | 0%   | 1    | 6%   | 0.075 |

- Other
  | 13   | 25%  | 3    | 17%  | 0.557 |

- Earlier kidney transplant
  | 17   | 32%  | 1    | 6%   | **0.039** |

HD, haemodialysis; HHD, home HD; PD, peritoneal dialysis

*reference for normal values: 80-100 ms

**reference for normal values: 120 – 200 ms

***reference for normal values: 0.6 – 1.2 s

n.a. = not applicable

\(^a\)all of these 3 patients were treated initially with in-center HD
Table 2. Electrocardiographic and insertable cardiac monitor (ICM) data on patients with bradycardic episodes detected in ICM. Information on the longest asystolic or bradycardic episode is shown for each patient

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Dialysis mode</th>
<th>Follow-up time (months)</th>
<th>Rhythm</th>
<th>HR (bpm)</th>
<th>QRS (ms)*</th>
<th>PR interval (ms)**</th>
<th>Total recording time</th>
<th>Average HR</th>
<th>Min HR</th>
<th>Max HR</th>
<th>Max RR interval (s)**</th>
<th>Asystole (sec)</th>
<th>HR in bradycardia</th>
<th>Length of bradycardia (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>60</td>
<td>female</td>
<td>HD</td>
<td>35.5</td>
<td>SR</td>
<td>57</td>
<td>114</td>
<td>208</td>
<td>96 h</td>
<td>58</td>
<td>48</td>
<td>75</td>
<td>1.58</td>
<td>6.0</td>
<td>27</td>
<td>150</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>male</td>
<td>HD</td>
<td>35.2</td>
<td>SR</td>
<td>56</td>
<td>74</td>
<td>164</td>
<td>96 h</td>
<td>68</td>
<td>46</td>
<td>122</td>
<td>1.64</td>
<td>-</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>3*</td>
<td>75</td>
<td>female</td>
<td>HD</td>
<td>15.5</td>
<td>SR</td>
<td>68</td>
<td>170</td>
<td>256</td>
<td>96 h</td>
<td>65</td>
<td>41</td>
<td>120</td>
<td>2.12</td>
<td>8.6</td>
<td>29</td>
<td>41</td>
</tr>
<tr>
<td>4*</td>
<td>63</td>
<td>male</td>
<td>HD</td>
<td>9.8</td>
<td>SR</td>
<td>66</td>
<td>92</td>
<td>192</td>
<td>48 h</td>
<td>69</td>
<td>55</td>
<td>114</td>
<td>1.48</td>
<td>5.0</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>male</td>
<td>transplant</td>
<td>36.1</td>
<td>SR</td>
<td>62</td>
<td>86</td>
<td>204</td>
<td>96 h</td>
<td>68</td>
<td>49</td>
<td>106</td>
<td>1.87</td>
<td>5.2</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>66</td>
<td>male</td>
<td>HD</td>
<td>18.4</td>
<td>SR</td>
<td>66</td>
<td>94</td>
<td>164</td>
<td>48 h</td>
<td>64</td>
<td>45</td>
<td>100</td>
<td>1.65</td>
<td>-</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>7</td>
<td>63</td>
<td>male</td>
<td>HD</td>
<td>27</td>
<td>SR</td>
<td>66</td>
<td>80</td>
<td>150</td>
<td>48 h</td>
<td>64</td>
<td>43</td>
<td>137</td>
<td>1.90</td>
<td>7.1</td>
<td>25</td>
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<tr>
<td>8*</td>
<td>59</td>
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<td>PD</td>
<td>22.1</td>
<td>SR</td>
<td>80</td>
<td>90</td>
<td>190</td>
<td>76 h</td>
<td>81</td>
<td>70</td>
<td>103</td>
<td>1.03</td>
<td>7.4</td>
<td>22</td>
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<tr>
<td>9*</td>
<td>54</td>
<td>female</td>
<td>HD</td>
<td>33.1</td>
<td>SR</td>
<td>77</td>
<td>86</td>
<td>160</td>
<td>48 h</td>
<td>96</td>
<td>45</td>
<td>140</td>
<td>1.71</td>
<td>8.8</td>
<td>29</td>
<td>8</td>
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<td>10</td>
<td>51</td>
<td>male</td>
<td>transplant</td>
<td>40.9</td>
<td>AF</td>
<td>71</td>
<td>86</td>
<td>-</td>
<td>47 h</td>
<td>76</td>
<td>40</td>
<td>149</td>
<td>2.75</td>
<td>4.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>67</td>
<td>female</td>
<td>HD</td>
<td>40.1</td>
<td>SR</td>
<td>51</td>
<td>118</td>
<td>236</td>
<td>47 h</td>
<td>58</td>
<td>40</td>
<td>90</td>
<td>1.98</td>
<td>5.9</td>
<td>28</td>
<td>8</td>
</tr>
<tr>
<td>12</td>
<td>64</td>
<td>male</td>
<td>HD</td>
<td>26.3</td>
<td>SR</td>
<td>76</td>
<td>112</td>
<td>250</td>
<td>48 h</td>
<td>65</td>
<td>52</td>
<td>88</td>
<td>1.63</td>
<td>-</td>
<td>21</td>
<td>8</td>
</tr>
<tr>
<td>13</td>
<td>36</td>
<td>male</td>
<td>PD</td>
<td>22.3</td>
<td>SR</td>
<td>78</td>
<td>108</td>
<td>164</td>
<td>86 h</td>
<td>97</td>
<td>57</td>
<td>150</td>
<td>1.40</td>
<td>7.2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14*</td>
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<td>male</td>
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<td>SR</td>
<td>65</td>
<td>96</td>
<td>230</td>
<td>86 h</td>
<td>63</td>
<td>38</td>
<td>81</td>
<td>2.03</td>
<td>-</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>15</td>
<td>66</td>
<td>male</td>
<td>transplant</td>
<td>35.6</td>
<td>SR</td>
<td>75</td>
<td>136</td>
<td>192</td>
<td>48 h</td>
<td>76</td>
<td>48</td>
<td>124</td>
<td>1.80</td>
<td>-</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td>16</td>
<td>58</td>
<td>female</td>
<td>HD</td>
<td>2.3</td>
<td>SR</td>
<td>73</td>
<td>98</td>
<td>150</td>
<td>48 h</td>
<td>75</td>
<td>55</td>
<td>105</td>
<td>1.32</td>
<td>-</td>
<td>27</td>
<td>11</td>
</tr>
<tr>
<td>17</td>
<td>67</td>
<td>male</td>
<td>HD</td>
<td>35.2</td>
<td>SR</td>
<td>84</td>
<td>98</td>
<td>164</td>
<td>96 h</td>
<td>90</td>
<td>54</td>
<td>135</td>
<td>1.23</td>
<td>27</td>
<td>9</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>59</td>
<td>female</td>
<td>PD</td>
<td>34.9</td>
<td>SR</td>
<td>59</td>
<td>154</td>
<td>166</td>
<td>96 h</td>
<td>68</td>
<td>56</td>
<td>98</td>
<td>1.46</td>
<td>5.9</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

HR, heart rate; SR, sinus rhythm; AF, atrial fibrillation; HD, in-center haemodialysis; PD, peritoneal dialysis
Patient received a pacemaker
*reference for normal values: 80 – 100 ms
** reference for normal values: 120 – 200 ms
***reference for normal values: 0.6 – 1.2 s

Table 3. Baseline characteristics of the patients treated with in-center haemodialysis and home haemodialysis. Patients with bradyarrhythmias detected for the first time after kidney transplantation excluded

<table>
<thead>
<tr>
<th></th>
<th>In-center HD patients n = 41</th>
<th>Home HD patients n = 12</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>61.9 ± 7.6</td>
<td>53.3 ± 10.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>27 (66%)</td>
<td>9 (75%)</td>
<td>0.550</td>
</tr>
<tr>
<td>Body-mass index</td>
<td>28.7 ± 9.2</td>
<td>28.1 ± 7.7</td>
<td>0.850</td>
</tr>
<tr>
<td>History of coronary heart disease</td>
<td>15 (37%)</td>
<td>3 (25%)</td>
<td>0.456</td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>9 (20%)</td>
<td>2 (17%)</td>
<td>0.691</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>9 (22%)</td>
<td>2 (17%)</td>
<td>0.691</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>10 (22%)</td>
<td>0 (0%)</td>
<td>0.068</td>
</tr>
<tr>
<td>Diabetes type I</td>
<td>10 (24%)</td>
<td>0 (0%)</td>
<td>0.058</td>
</tr>
<tr>
<td>Diabetes type II</td>
<td>15 (37%)</td>
<td>2 (17%)</td>
<td>0.194</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>150 ± 298</td>
<td>142 ± 13</td>
<td>0.381</td>
</tr>
<tr>
<td>Valvular disease in ECHO</td>
<td>7 (17%)</td>
<td>1 (8%)</td>
<td>0.318</td>
</tr>
<tr>
<td>Use of beta-blocker</td>
<td>26 (63%)</td>
<td>7 (58%)</td>
<td>0.749</td>
</tr>
<tr>
<td>Use of calcium channel blocker</td>
<td>19 (46%)</td>
<td>3 (25%)</td>
<td>0.187</td>
</tr>
</tbody>
</table>
**FIGURE 1:** Study flow diagram.

**FIGURE 2:** An example of an asystole episode of 8.6 seconds detected by the implantable cardiac monitor. The patient received a pacemaker.
REFERENCES


Patients recruited (n=80)

Excluded (n=6):
• Died (n=1)
• Withdrew consent (n=3)
• Kidney transplant before ICM insertion (n=2)

Medical history and pre-study examination (n=74)
• Physical examination
• Venous blood sample
• Baseline ECG
• Echocardiography

ICM inserted (n=74)

Excluded (n=2):
• ICM removed right after implantation due to irritation (n=1)
• ICM removed right after implantation due to infection (n=1)

Ambulatory ECG recording at the beginning and once a year thereafter

Excluded (n=1):
• Dialysis treatment not initiated

Patients entering follow-up and included in final analysis (n=71)
• iHD (n=44)
• HDD (n=12)
• PD (n=15)

Follow-up < 3 years (n=15):
• Died (n=14)
• ICM removal as safety measure as result of infection of unknown etiology (n=1)

Complete follow-up of 3 years (n=56)

Excluded (n=6):
• Died (n=1)
• Withdrew consent (n=3)
• Kidney transplant before ICM insertion (n=2)

Excluded (n=2):
• ICM removed right after implantation due to irritation (n=1)
• ICM removed right after implantation due to infection (n=1)

Excluded (n=1):
• Dialysis treatment not initiated
### Prospective cohort

#### Asystole episodes and bradycardia in patients with end-stage renal disease

**Background**
Arrhythmias and cardiac arrest account for 25–28% of total mortality in patients with end-stage renal disease. Bradycardia and asystolic arrhythmias are thought to be the predominant mechanism of sudden cardiac death in dialysis patients.

**Methods**
- Five centres in Finland
  - Patients on dialysis (N=71):
    - Home haemodialysis (HD) (n=12)
    - In-centre HD (n=44)
    - Peritoneal dialysis (n=15)
- Insertable cardiac monitor (ICM) inserted for up to 3 years
- At baseline and 1 year:
  - Electrocardiogram (ECG)
  - 24-48 h ambulatory ECG

**Results**
During the total period of follow-up (median 34.4 months):
- 9.9% only bradycardia
- 4.2% only asystole
- 25% asystole or bradycardia
- 13.5 seconds median length of bradycardia
- 6.6 seconds median asystolic pause
- No detected asystole or bradycardia
- ECG and 24-48 h ECG
- Mean time from HD to bradycardia
- 44.3 h bradycardia
- 28.4 h asystole
- 27% of HD patients had first detected episode while on HD

**Conclusion**
Bradyarrhythmias and asystolic episodes were common in patients with end-stage renal disease, but these arrhythmias were not detected by baseline or ambulatory ECG

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180x125mm (300 x 300 DPI)
Prospective cohort

Arrhythmias and cardiac arrest account for 25–28% of total mortality in patients with end-stage renal disease

Bradycardic and asystolic arrhythmias are thought to be the predominant mechanism of sudden cardiac death in dialysis patients

Methods

Five centres in Finland

Patients on dialysis (N=71):
• Home haemodialysis (HD) (n=12)
• In-centre HD (n=44)
• Peritoneal dialysis (n=15)

Insertable cardiac monitor (ICM) inserted for up to 3 years

At baseline and 1 year:
• Electrocardiogram (ECG)
• 24–48 h ambulatory ECG

Results

During the total period of follow-up (median 34.4 months):

<table>
<thead>
<tr>
<th>Bradycardia</th>
<th>Asystole</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.9%</td>
<td>4.2%</td>
</tr>
<tr>
<td>ICM for up to 3 years</td>
<td>25% asystole or bradycardia</td>
</tr>
<tr>
<td>13.5 seconds median length of bradycardia</td>
<td>6.6 seconds median asystolic pause</td>
</tr>
</tbody>
</table>

ECG and 24–48 h ECG

No detected asystole or bradycardia

Mean time from HD to bradyarrhythmia

44.3 h bradycardia
28.4 h asystole
27% of HD patients had first detected episode while on HD

Conclusion

Bradycardia and asystolic episodes were common in patients with end-stage renal disease, but these arrhythmias were not detected by baseline or ambulatory ECG

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