ORIGINAL RESEARCH ARTICLE

Cardiovascular Autonomic Neuropathy in Non-Diabetic Stage 5 Chronic Kidney Disease: Comparison of Maintenance Dialysis and Conservative Management

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Abstract: Background: Cardiovascular autonomic neuropathy (CAN) is an important complication of advanced chronic kidney disease (CKD). This study compared CAN among non-diabetic stage 5 CKD patients receiving maintenance dialysis and those managed conservatively.**Methods:** In this comparative cross-sectional study, 80 adults with stage 5 CKD were included: 40 on maintenance dialysis and 40 receiving conservative management. Cardiovascular autonomic function was assessed using five standard reflex tests, and CAN severity was graded using the Bellavere scoring system.**Results:** CAN was present in 87.5% of participants. Its prevalence was significantly lower in the dialysis group than in the conservative group (77.5% vs 97.5%; p=0.014). Severe CAN occurred in 2.5% and 87.5% of patients, respectively. Mean total CAN score was lower with dialysis (2.62±1.41 vs 5.85±1.31; p<0.001). All five autonomic test subscores were significantly lower in the dialysis group. Dialysis duration correlated inversely with CAN score (r=−0.502; p=0.001). **Conclusion:** CAN was highly prevalent in non-diabetic stage 5 CKD but was substantially less severe among patients receiving maintenance dialysis.

Keywords: Chronic kidney disease; Cardiovascular autonomic neuropathy; Hemodialysis; Autonomic dysfunction; Stage 5 CKD

Received:28.09.2026 | Revised:26.10.2026 | Accepted:02.11.2026 | Published:19.11.2026

Citation: Dr. Sangeetha Somakumar *et al* (2026). Cardiovascular Autonomic Neuropathy in Non-Diabetic Stage 5 Chronic Kidney Disease: Comparison of Maintenance Dialysis and Conservative Management. STEMed, 7(2): 137-143.

Introduction

Cardiovascular morbidity and mortality are significant in chronic kidney disease (CKD), especially at advanced stages. In addition to structural cardiac disease and conventional cardiovascular risk factors, impaired autonomic regulation has been identified as an important aspect of uraemia. Abnormalities can include cardiovascular control, both parasympathetic and sympathetic, and baroreflex function, which can lead to orthostatic hypotension, haemodynamic instability, arrhythmias and adverse cardiovascular events [1]. In a few preliminary studies, non-invasive cardiovascular reflex testing (CVRT) has been used to show that there is autonomic dysfunction in patients with chronic renal failure, such as abnormal responses to the Valsalva manoeuvre and sustained handgrip [2].

While diabetes is known to be a cause of cardiovascular autonomic neuropathy (CAN), autonomic dysfunction is also present in renal failure patients without diabetes. Heidbreder et al. showed that uraemia is able to cause autonomic abnormalities in non-diabetic patients with chronic renal insufficiency [3]. Malik et al. subsequently reported parasympathetic abnormalities in about 65% of patients with chronic renal failure, and further sympathetic dysfunction in about one-quarter of patients [4], using a standardized battery of cardiovascular reflex tests. From these observations it may be inferred that there is relatively early involvement of parasympathetic function, while more extensive autonomic damage may be associated with advanced uraemia.

The effects of renal replacement therapy on autonomic dysfunction are unclear. The parasympathetic and baroreflex responses were found to be very abnormal in non-dialysed chronic

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renal failure, and there was minimal recovery in the short term after haemodialysis, compared to renal transplantation, which showed more obvious recovery [5]. On the other hand, some autonomic dysfunctions have been found to improve following dialysis [3] in studies that have compared non-diabetic predialysis and dialysis patients. Dynamic changes in sympathovagal regulation have also been demonstrated during haemodialysis, suggesting that dialysis could alter autonomic regulation without necessarily restoring normal function [6].

Abnormal physiological testing is not the only clinical significance of autonomic impairment. Among the Chronic Renal Insufficiency Cohort, changes in HRV were associated with worse renal function and mortality risk for all-cause mortality [7]. CAN has also been reported to be associated with increased cardiovascular and overall mortality, including an increased incidence of sudden cardiac death, in patients with end-stage renal disease on maintenance haemodialysis [8]. These findings support the possible utility of autonomic assessment as a marker of cardiovascular vulnerability in advanced CKD.

In fact, direct comparisons of CAN between non-diabetic stage 5 CKD patients on maintenance dialysis and those managed conservatively are still limited, and diabetes is often a confounder in previous studies. The present study thus sought to identify and compare the prevalence and severity of cardiovascular autonomic neuropathy (CAN) in non-diabetic stage 5 CKD patients undergoing maintenance dialysis and conservative management by applying standardized cardiovascular autonomic reflex testing.

Methods

Study design and participants

The study was a comparative cross-sectional study carried out in the Department of Nephrology, Government Medical College, Kottayam, from June 2014 to May 2015. Patients were included if they were adults (18–70 years) with stage 5 chronic kidney disease (CKD), as defined by the National Kidney Foundation-KDOQI criteria. The patients were divided into two groups: 40 on maintenance dialysis and 40 conservatively managed. Patients with diabetes mellitus, neurological disorders with autonomic dysfunction, cardiac or respiratory failure, and those taking drugs known to affect autonomic function were excluded.

Cardiovascular autonomic function assessment

Cardiovascular autonomic function was assessed by five standard non-invasive reflex tests: Valsalva ratio, heart-rate response to deep breathing, 30:15 ratio on standing, blood-pressure response to standing and blood-pressure response to sustained handgrip. The first three predominantly measured parasympathetic function and the latter two sympathetic function.

During the Valsalva manoeuvre, the subjects held an expiratory pressure of 40 mmHg for 15 seconds, and continuous ECG was recorded. The test was repeated three times and the mean Valsalva ratio was used. The effect of deep breathing on the heart rate was examined at 6 breaths per minute. The 30:15 ratio was determined by using the longest R-R interval around the 30th beat and the shortest R-R interval around the 15th beat following standing. In the postural blood-pressure response, systolic blood pressure was measured after 15 minutes in the supine position and during the first three minutes of standing. Participants held the handgrip for 4 minutes at 30% of maximal voluntary contraction and the rise in diastolic blood pressure was measured.

The Bellavere scoring system was used, with each test considered normal (0), borderline (1), or abnormal (2). The total cardiovascular autonomic neuropathy (CAN) score was obtained by adding the scores of the five tests. A score of 0–1 was defined as no CAN, 2–4 as early CAN and ≥5 as severe CAN, and a score ≥2 was taken as a diagnosis of CAN.

Outcomes and statistical analysis

The main outcomes were the prevalence and severity of CAN and the comparison of the two groups (maintenance-dialysis and conservative-management). Secondary outcomes were differences in total CAN score, individual autonomic test subscale scores and relationships between CAN score and age, CKD duration and dialysis duration.

Data for continuous variables were presented as mean ± standard deviation and data for categorical variables were presented as frequencies and percentages. Fisher's exact test was used to compare the prevalence of CAN between groups and the Mann–Whitney U test was used to compare the severity categories. Welch's independent-samples t-test was used to compare the scores on the total CAN and individual test subscale scores between the groups, and the results were reported as mean differences with 95% confidence intervals. For multiple comparisons, Holm adjustment was used for the five component scores. Pearson's correlation coefficient was used to evaluate the association of CAN score with age, dialysis duration and CKD duration. A p value of <0.05 was taken as statistically significant.

Ethics

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The study was approved by the Scientific Review Committee and Institutional Review Board of Government Medical College, Kottayam. All participants provided written informed consent prior to enrollment.

RESULTS

Study population

A total of 80 patients with stage 5 chronic kidney disease (CKD) were included in the study, comprising 40 patients receiving maintenance dialysis and 40 patients managed conservatively. Patients with diabetes mellitus were excluded according to the study eligibility criteria.

The mean age was 53.42 ± 7.01 years in the maintenance-dialysis group and 54.05 ± 8.67 years in the conservative-management group. The mean between-group difference in age was −0.63 years (95% CI −4.14 to 2.88; p=0.722). Both groups had identical sex distributions, with 38 men (95.0%) and two women (5.0%) in each group (Table 1).

Table 1. Demographic characteristics of the study population

Characteristic	Maintenance dialysis (n=40)	Conservative management (n=40)	Between-group comparison
Age, years	53.42 ± 7.01	54.05 ± 8.67	MD −0.63 (95% CI −4.14 to 2.88); p=0.722
Male sex	38 (95.0%)	38 (95.0%)	—
Female sex	2 (5.0%)	2 (5.0%)	—

Data are presented as mean ± SD or n (%). MD, mean difference.

Prevalenceof cardiovascular autonomic neuropathy

Overall, 70 of 80 patients (87.5%; 95% CI 78.5%–93.1%) had cardiovascular autonomic neuropathy (CAN), while 10 patients (12.5%) had no CAN.

CAN was present in 31 of 40 patients (77.5%; 95% CI 62.5%–87.7%) receiving maintenance dialysis and 39 of 40 patients (97.5%; 95% CI 87.1%–99.6%) receiving conservative management (Table 2). The absolute difference in CAN prevalence between the groups was −20.0 percentage points, and the prevalence ratio for dialysis versus conservative management was 0.79 (95% CI 0.67–0.95). The difference was statistically significant (Fisher's exact p=0.014).

Severity of cardiovascular autonomic neuropathy

The distribution of CAN severity differed markedly between the two treatment groups (Table 2; Figure 1). Among patients receiving maintenance dialysis, 9 (22.5%) had no CAN, 30 (75.0%) had early CAN, and only 1 (2.5%) had severe CAN. In contrast, among patients receiving conservative management, 1 (2.5%) had no CAN, 4 (10.0%) had early CAN, and 35 (87.5%) had severe CAN.

Overall, 34 patients (42.5%) had early CAN and 36 (45.0%) had severe CAN, in addition to the 10 patients (12.5%) without CAN. The ordered distribution of CAN severity was significantly different between the two groups (Mann–Whitney U=117; p<0.001).

Among patients with CAN, 30 of 31 patients in the dialysis group (96.8%) had early CAN and 1 (3.2%) had severe CAN. By comparison, among the 39 CAN-positive patients receiving conservative management, 4 (10.3%) had early CAN and 35 (89.7%) had severe CAN.

Table 2. Prevalence and severity of cardiovascular autonomic neuropathy

CAN category	Maintenance dialysis (n=40)	Conservative management (n=40)	Overall (N=80)
No CAN	9 (22.5%)	1 (2.5%)	10 (12.5%)
Any CAN	31 (77.5%)	39 (97.5%)	70 (87.5%)
Early CAN	30 (75.0%)	4 (10.0%)	34 (42.5%)
Severe CAN	1 (2.5%)	35 (87.5%)	36 (45.0%)

CAN, cardiovascular autonomic neuropathy. CAN was defined as a total CAN score ≥2. Scores of 2–4 were classified as early CAN and scores ≥5 as severe CAN.

Total cardiovascular autonomic neuropathy score

The mean total CAN score was significantly lower among patients receiving maintenance dialysis than among those managed conservatively (2.62 ± 1.41 vs 5.85 ± 1.31, respectively) (Table 3; Figure 2). The mean between-group difference was −3.23 points (95% CI −3.84 to −2.62; p<0.001).

This difference indicates substantially lower cardiovascular autonomic neuropathy scores among patients receiving maintenance dialysis.

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Individual cardiovascular autonomic function test scores

Mean Bellavere subscores for all five cardiovascular autonomic reflex tests were lower among patients receiving maintenance dialysis than among patients receiving conservative management (Table 3).

The mean Valsalva subscore was 0.88 ± 0.69 in the dialysis group compared with 1.28 ± 0.55 in the conservative-management group. The corresponding values for the heart-rate response to deep breathing were 0.95 ± 0.71 and 1.60 ± 0.55, respectively. The mean 30:15 ratio subscores were 0.52 ± 0.68 and 0.90 ± 0.78, respectively.

Differences were also observed for the sympathetic-function tests. The mean blood-pressure response-to-standing subscore was 0.20 ± 0.46 in the dialysis group compared with 1.12 ± 0.65 in the conservative-management group. Similarly, the sustained-handgrip subscore was 0.08 ± 0.35 in the dialysis group and 0.95 ± 0.75 in the conservative-management group.

All five between-group differences remained statistically significant after Holm adjustment for multiple comparisons (Table 3).

Table 3. Total CAN score and individual cardiovascular autonomic test subscores

Outcome	Maintenance dialysis (n=40)	Conservative management (n=40)	Mean difference, dialysis − conservative (95% CI)	Holm-adjusted p value
Total CAN score	**2.62 ± 1.41**	**5.85 ± 1.31**	**−3.23 (−3.84 to −2.62)**	**<0.001**
Valsalva subscore	0.88 ± 0.69	1.28 ± 0.55	−0.40 (−0.68 to −0.12)	0.011
Deep-breathing subscore	0.95 ± 0.71	1.60 ± 0.55	−0.65 (−0.93 to −0.37)	<0.001
30:15 subscore	0.52 ± 0.68	0.90 ± 0.78	−0.38 (−0.71 to −0.05)	0.023
BP response-to-standing subscore	0.20 ± 0.46	1.12 ± 0.65	−0.92 (−1.17 to −0.67)	<0.001
Sustained-handgrip subscore	0.08 ± 0.35	0.95 ± 0.75	−0.87 (−1.13 to −0.61)	<0.001

Data are presented as mean ± SD. Lower scores indicate less severe autonomic dysfunction. BP, blood pressure; CAN, cardiovascular autonomic neuropathy.

Association of CAN score with age, duration of CKD, and duration of dialysis

Total CAN score showed no significant association with either age or overall duration of CKD (Table 4). The correlation between CAN score and age was negligible (r=0.034; p=0.765), while the correlation with duration of CKD was weak and not statistically significant (r=0.164; p=0.146).

Among the 40 patients receiving maintenance dialysis, however, duration of dialysis showed a moderate inverse correlation with total CAN score (r=−0.502; 95% CI −0.704 to −0.226; p=0.001) (Table 4). Thus, longer duration of dialysis was associated with lower CAN scores.

Table 4. Correlation of total cardiovascular autonomic neuropathy score with clinical variables

Variable	n	Pearson r	95% CI for r	p value
Age	80	0.034	−0.187 to 0.252	0.765
Duration of CKD	80	0.164	−0.058 to 0.370	0.146
Duration of dialysis*	40	**−0.502**	**−0.704 to −0.226**	**0.001**

*Evaluated among patients receiving maintenance dialysis.

Relationship between CKD duration and CAN among patients receiving dialysis

Among patients receiving maintenance dialysis, those with CAN had a longer mean duration of CKD than those without CAN (3.032 ± 2.280 years vs 1.722 ± 1.228 years, respectively). The estimated mean difference was 1.31 years (95% CI 0.12–2.50; p=0.032).

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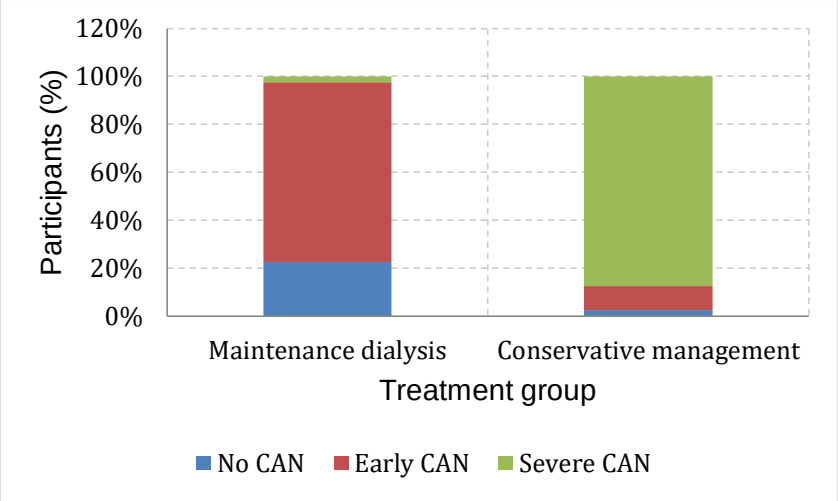


Figure 1. Distribution of cardiovascular autonomic neuropathy severity according to treatment group.

The figure shows the percentage of patients with no CAN, early CAN, and severe CAN among patients receiving maintenance dialysis and those receiving conservative management. CAN severity differed significantly between the groups ($p<0.001$).

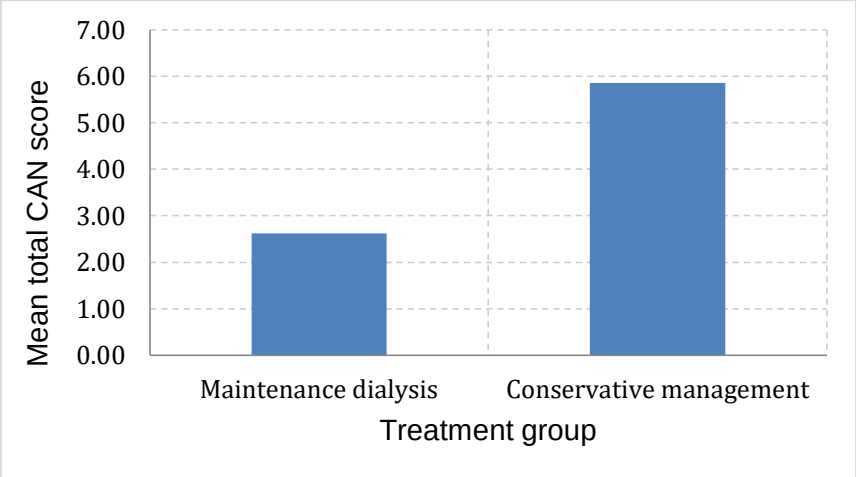


Figure 2. Mean total cardiovascular autonomic neuropathy score according to treatment group.

Mean total CAN score was lower among patients receiving maintenance dialysis than among patients receiving conservative management (2.62 ± 1.41 vs 5.85 ± 1.31; $p<0.001$). Error bars should represent 95% confidence intervals.

Discussion

The prevalence of cardiovascular autonomic neuropathy (CAN) was very high in non-diabetic patients with stage 5 chronic kidney disease (CKD), with 87.5% of the study population having CAN. The burden varied, however, depending on the treatment modality. In the patients who were treated with maintenance dialysis, 77.5% had CAN, and 2.5% had severe CAN, whereas 97.5% and 87.5% of the patients with conservative management had CAN and severe CAN, respectively. The mean total CAN score was also significantly lower in the dialysis group, and there was significantly less impairment in all five cardiovascular autonomic reflex-test scores.

The overall prevalence of autonomic dysfunction is similar to previous reports in advanced non-diabetic CKD. Sanya and Ogunniyi reported CAN in about 65% of non-diabetic patients with chronic renal failure, with abnormalities in both the heart-rate and blood-pressure responses [9]. Our cohort's even greater prevalence may be due to the fact that we included only patients with stage 5 CKD. Similarly, Oliveira et al. found that cardiac autonomic modulation was progressively altered with increasing CKD severity, with patients with advanced CKD having more altered sympathovagal balance than those with less advanced CKD [10]. The results are in keeping with the hypothesis that autonomic dysfunction is more evident with the worsening of renal function.

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Haemodialysis patients also frequently have autonomic abnormalities. Sahin et al. examined 40 non-diabetic haemodialysis patients and found that 87.5% had at least one abnormal cardiovascular reflex test, especially the deep-breathing and sustained-handgrip responses [11]. Likewise, Vita et al. showed marked autonomic dysfunction in haemodialysis patients, both by conventional cardiovascular testing and by heart-rate spectral analysis, especially in the parasympathetic domain [12]. Our dialysis group was thus still significantly impacted, but not quite as severely as the conservatively managed group.

The significant difference in the severity of CAN between the two groups suggests that renal replacement therapy might have an effect on uraemia-associated autonomic dysfunction. Mylonopoulou et al. have shown that in patients with advanced CKD, several time-domain parameters of HRV improved after the commencement of haemodialysis, but not all autonomic parameters [13]. This partial recovery is consistent with our observation of significantly lower CAN scores in dialysis patients. However, since this study was cross-sectional, it is not possible to determine a cause-and-effect relationship between dialysis and the lower CAN scores observed.

The autonomic effects of haemodialysis are complex and may also vary during individual dialysis sessions. Galetta et al. showed that chronic uraemic patients had significantly lower HRV than healthy controls. Autonomic indices during dialysis were found to vary during the different stages of ultrafiltration and solute removal, indicating that both volume changes and dialysis-related physiological changes affect autonomic regulation [14]. As such, maintenance dialysis may have beneficial effects on the chronic uraemic milieu, but can also induce acute haemodynamic stresses.

The autonomic components in the present study were all significantly different between groups. The relatively large differences in the blood-pressure responses to standing and sustained handgrip suggest substantial sympathetic involvement in the conservatively managed group, while abnormalities across the remaining tests also indicate parasympathetic involvement. Vita et al. had previously reported that uraemic autonomic neuropathy is not limited to a single autonomic division and that spectral abnormalities can be detected even if the conventional reflex tests are less affected [12]. The three tests, which were mainly parasympathetic, and the two tests, which were mainly sympathetic, were used together in our study, thus giving a wider picture of autonomic dysfunction than would a single reflex test.

The other interesting result was that there was no significant relationship between total CAN score and age or total duration of CKD. In a group of chronic haemodialysis patients, Stamboulis et al. also did not observe any clear relationship between autonomic dysfunction and age, sex or dialysis duration [15]. However, the dialysis subgroup had a moderate negative correlation between dialysis duration and CAN score ($r=-0.502$), indicating that patients with longer dialysis duration had less severe autonomic dysfunction. This observation is potentially important but should be viewed with caution due to the possibility of survivor effects, variations in dialysis adequacy, volume control, residual renal function, nutritional status and choice of treatment.

The clinical significance of these abnormalities is substantial, as cardiovascular autonomic dysfunction may play a role in orthostatic intolerance, intradialytic haemodynamic instability, arrhythmogenesis and impaired cardiovascular adaptation. The predominance of severe CAN in the conservatively managed group therefore suggests a particularly vulnerable physiological state in untreated stage 5 CKD. On the other hand, the lower prevalence and much lower severity among dialysis-treated patients suggest that correction of uraemia and fluid-electrolyte disturbances might have beneficial effects on cardiovascular autonomic regulation.

There are a number of strengths of the present study. A significant source of confounding, diabetes mellitus, was excluded. The two groups were similar in age and sex distribution, and autonomic function was assessed by five standardized cardiovascular reflex tests covering both parasympathetic and sympathetic domains. The composite scoring system also allowed the measurement of the severity of the disease, not just whether or not autonomic dysfunction was present.

There are a number of caveats to be noted. It is not possible to determine from the cross-sectional design whether there was a direct impact of dialysis on autonomic function. The sample size was small and obtained from a single centre, and the sample was very male-dominated, which restricted generalizability. Potential influences such as residual renal function, dialysis adequacy, anaemia, nutritional status, electrolyte abnormalities, antihypertensive treatment and biochemical measures of uraemic burden were not included in the present analysis. It would therefore be useful to determine whether the differences noted represent a true treatment effect through a prospective longitudinal study before and after dialysis is initiated.

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Conclusion

Cardiovascular autonomic neuropathy was very common in non-diabetic patients with stage 5 CKD, and was significantly more common and more severe in those managed conservatively than in those treated with maintenance dialysis. Patients receiving dialysis exhibited lower total CAN scores and less impairment in both parasympathetic and sympathetic cardiovascular reflex tests. The inverse correlation between duration of dialysis and severity of CAN also indicates a potential beneficial effect of prolonged renal replacement therapy on autonomic dysfunction. Future longitudinal studies are needed to establish whether the initiation and maintenance of dialysis actually have an effect on cardiovascular autonomic function and whether improvements in cardiovascular autonomic function lead to improved cardiovascular outcomes.

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