N-Terminal Pro–B-Type Natriuretic Peptide Variability in Stable Dialysis Patients

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Abstract

Background and objectives Monitoring N-terminal pro–B-type natriuretic peptide (NT-proBNP) may be useful for assessing cardiovascular risk in dialysis patients. However, its biologic variation is unknown, hindering the accurate interpretation of serial concentrations. The aims of this prospective cohort study were to estimate the within- and between-person coefficients of variation of NT-proBNP in stable dialysis patients, and derive the critical difference between measurements needed to exclude biologic and analytic variation.

Design, setting, participants, & measurements Fifty-five prevalent hemodialysis and peritoneal dialysis patients attending two hospitals were assessed weekly for 5 weeks and then monthly for 4 months between October 2010 and April 2012. Assessments were conducted at the same time in the dialysis cycle and entailed NT-proBNP testing, clinical review, electrocardiography, and bioimpedance spectroscopy. Patients were excluded if they became unstable.

Results This study analyzed 136 weekly and 113 monthly NT-proBNP measurements from 40 and 41 stable patients, respectively. Results showed that 22% had ischemic heart disease; 9% and 87% had left ventricular systolic and diastolic dysfunction, respectively. Respective between- and within-person coefficients of variation were 153% and 27% for weekly measurements, and 148% and 35% for monthly measurements. Within-person variation was unaffected by dialysis modality, hydration status, inflammation, or cardiac comorbidity. NT-proBNP concentrations measured at weekly intervals needed to increase by at least 46% or decrease by 84% to exclude change due to biologic and analytic variation alone with 90% certainty, whereas monthly measurements needed to increase by at least 119% or decrease by 54%.

Conclusions The between-person variation of NT-proBNP was large and markedly greater than within-person variation, indicating that NT-proBNP testing might better be applied in the dialysis population using a relative-change strategy. Serial NT-proBNP concentrations need to double or halve to confidently exclude change due to analytic and biologic variation alone.

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Introduction

The N-terminal fragment of the pro–B-type natriuretic peptide (NT-proBNP) is an inactive peptide secreted from the myocardium in response to stretch, strain, ischemia, inflammation, and sympathetic overactivity (1). Cohort studies in the dialysis population have demonstrated a direct association between NT-proBNP concentrations and the risk of cardiovascular and all-cause mortality (2–5), prompting calls to incorporate NT-proBNP testing into dialysis practice as a means of monitoring individual patients' cardiovascular risk (6–8).

However, before these findings can be translated into clinical practice, the biologic variation of NT-proBNP in dialysis patients needs to be determined in order to avoid misinterpreting serial measurements. Biologic or within-person variation is the random fluctuation of a biomarker around a homeostatic set point in healthy individuals or those with stable disease (9), resulting in potentially large numerical changes in serial biomarker concentrations that are of no clinical significance. Failure to account for biologic variation can result in false reassurance or alarm, as well as unnecessary changes to therapy with their associated morbidity and costs (10).

This study aimed to estimate the within- and between-person variation of NT-proBNP measured at weekly and monthly intervals in stable dialysis patients and to use these estimates to calculate the percentage change between serial NT-proBNP measurements needed to exclude change due to biologic and analytic variation alone. We also sought to determine whether the within-person variation of NT-proBNP differed according to cardiac comorbidity, hydration, or inflammatory status or between dialysis modalities.

Materials and Methods

Study Design and Patient Recruitment

A prospective cohort study was conducted between October 2010 and April 2012 according to methods

described by Fraser and Harris (11). The study complied with the Declaration of Helsinki and received ethics approval from the Metro-South Human Research Ethics Committee (HREC/10/QPAH/131).

Participants were recruited from the in-center hemodialysis and peritoneal dialysis units of a tertiary-care teaching hospital in Brisbane, and a secondary-care hospital in Logan, Australia. Eligible participants identified from an electronic database of all patients receiving dialysis therapy were adults (aged ≥18 years) on maintenance dialysis for ≥90 days who had a stable dialysis prescription for ≥30 days and a transthoracic echocardiogram ≤12 months before screening.

Eligibility criteria were chosen to ensure that the study cohort was physiologically and clinically stable at enrollment, and was likely to remain stable for the duration of the study while still being representative of the dialysis population. Patients were excluded if they met any of the following criteria: if they had undergone coronary and/or valvular intervention or suffered a myocardial infarction or pulmonary embolism in the 6 months before screening; had echocardiographic evidence of severe pulmonary hypertension, severe functional aortic and/or mitral valvular disease, or a left ventricular ejection fraction <30%; had been hospitalized for any indication or undergone an unscheduled dialysis for the treatment of hypertension, heart failure, or dyspnea in the 30 days before screening; had been commenced on or undergone a dose change of a diuretic, β-blocker, aldosterone receptor antagonist, angiotensin-converting enzyme inhibitor or angiotensin receptor type 1 blocker in the 30 days before screening; had experienced worsening angina, a new cardiac arrhythmia, or undergone change in associated therapies in the 30 days before screening; had a contraindication to bioimpedance measurement including a pacemaker, joint replacements, or mechanical heart valve; were pregnant; had advanced malignancy; or were unable to provide informed consent.

Patient Assessment

Patients were assessed on 10 consecutive occasions—weekly for 5 weeks and then monthly for another 4 months. All assessments were conducted between 6 and 8 a.m., before the mid-week dialysis session for hemodialysis patients, and between 8 and 10 a.m. on the same weekday for peritoneal dialysis patients. Patients avoided strenuous exercise before assessment.

Several factors affect NT-proBNP concentrations, including extracellular volume (12), cardiac rhythm (13), myocardial ischemia (14,15), the dialysis prescription (16), and cardiac pharmacotherapy (17–19). These influences were assessed at every visit using a structured clinical interview, physical examination, and medical records review to ascertain interim hospitalization and changes to medication and/or the dialysis prescription. The Canadian Cardiovascular Society Angina Grading Scale (20) was used to assess change in cardiac ischemic symptoms and the Truncated Framingham Heart Failure Score (21) was used to assess for pulmonary edema. Patients underwent a standard 12-lead electrocardiogram and whole-body, multifrequency bioimpedance analysis using the Body Composition Monitor BCM (Fresenius Medical Care Asia-Pacific) at each visit to measure extracellular volume. This instrument has a detection limit for change in extracellular volume of 0.87±0.64 L (22,23).

Specimen Collection, Storage, and Analyses

NT-proBNP concentrations were measured at eight of 10 visits (baseline then at weeks 1–4 and months 2–4), providing data for 4 weekly and 4 monthly intervals. To ensure that changes in NT-proBNP concentrations during the final measurement interval did not reflect changes in subclinical risk, patients were assessed for stability at week 5 and month 5 without measurement of NT-proBNP.

Blood collected in lithium-heparin tubes was centrifuged and plasma separated within 1 hour of collection. Plasma was stored at −80°C until assayed (24).

Samples were batched and analyzed together in a single analytic run in random duplicate by a single expert operator using a single instrument and a single batch of reagent, control, and calibrators. Plasma NT-proBNP concentration (in picograms per milliliter) was measured using a twin-antibody electrochemiluminescence assay on the Elecsys 2010 instrument (Roche Diagnostics, Australia), which has a reported analytical detection range of 5–35,000 pg/ml (25). NT-proBNP was chosen in preference to brain natriuretic peptide due to its superior stability, which minimizes preanalytic variation (26), and due to the greater agreement between NT-proBNP assays from different manufacturers (27), allowing the study's findings to be more widely generalizable.

C-reactive protein (in milligrams per liter) was measured predialysis at the baseline visit and analyzed using a turbidimetric method on the Beckman DxC800 analyzer (Beckman Coulter, CA). This method has a lower limit of detection of 2.0 mg/L, and analytic coefficients of variation of 6.3% and 3.1% at concentrations of 6.0 and 85.0 mg/L, respectively.

Statistical Analyses

Based on a ratio of analytic to within-person variation of <0.5 for NT-proBNP, we estimated that a study sample of 40 patients undergoing NT-proBNP testing on eight occasions over 4 weekly and monthly intervals would have power >0.99 to estimate the within-person coefficient of variation with a 95% confidence interval of ±3.6% (28). A sample size of 55 patients was chosen to allow for dropouts as a result of instability.

The principal assumption of biologic variation studies is that the cohort is stable with respect to physiologic, pathologic, and extrinsic factors that influence the concentration of the biomarker of interest. In this study, patients were deemed to be unstable if they experienced a change in dose of diuretic, β-blocker, aldosterone receptor antagonist, angiotensin-converting enzyme inhibitor, or angiotensin receptor blocker; a change in severity of cardiac ischemic symptoms, dose of antianginal agents, or cardiac intervention; a change in antiarrhythmic agents or new cardiac arrhythmia; a change in extracellular volume >1 L on bioimpedance analysis; a change in dialysis modality or prescription; hospitalization for any reason; or exhibited pulmonary edema defined as a score ≥2 on the Truncated Framingham Heart Failure Score. If a study participant was deemed to be unstable, the NT-proBNP concentrations from the intervals before and after the event were excluded from the statistical analysis.

Normally distributed variables are presented as the mean±SD, and non-normally distributed variables are presented as the median and interquartile range. NT-proBNP

concentrations were logarithmically transformed for the variation analyses. We fitted mixed-effects models with random intercepts to calculate the between-person coefficient of variation across the cohort (CV_G), the within-person coefficient of variation at weekly and monthly intervals (CV_I), and the within-run analytic coefficient of variation (CV_A). Outlying variances were excluded using the Reed and Cochran tests. Linear regression was used to identify and exclude participants who demonstrated a consistent increase or decrease in log NT-proBNP concentrations throughout the study, because such a trend may represent a change in future risk that may not have manifest clinically during the study.

The cohort was also divided into eight subgroups according to dialysis modality, hydration status, ischemic heart disease status, severity of left ventricular diastolic dysfunction, presence or absence of left ventricular systolic dysfunction and left ventricular hypertrophy, tertiles of C-reactive protein concentrations, and quartiles of NT-proBNP concentrations at enrollment. CV_I was estimated for each subgroup and compared using Bartlett's test. Overhydration was assessed using the ratio of absolute overhydration volume to total extracellular volume measured using bioimpedance and categorized as absent (<6.8%), moderate (6.8%–15%), or severe (>15%) (29). Ischemic heart disease was defined as any of inducible ischemia on noninvasive cardiac stress testing and/or ≥50% stenosis in ≥1 epicardial coronary artery on coronary angiography and/or a history of myocardial infarction. Left ventricular diastolic dysfunction (30) and left ventricular hypertrophy (31) were graded as absent, mild, moderate, or severe according to established algorithms using echocardiographic measurements. Left ventricular systolic

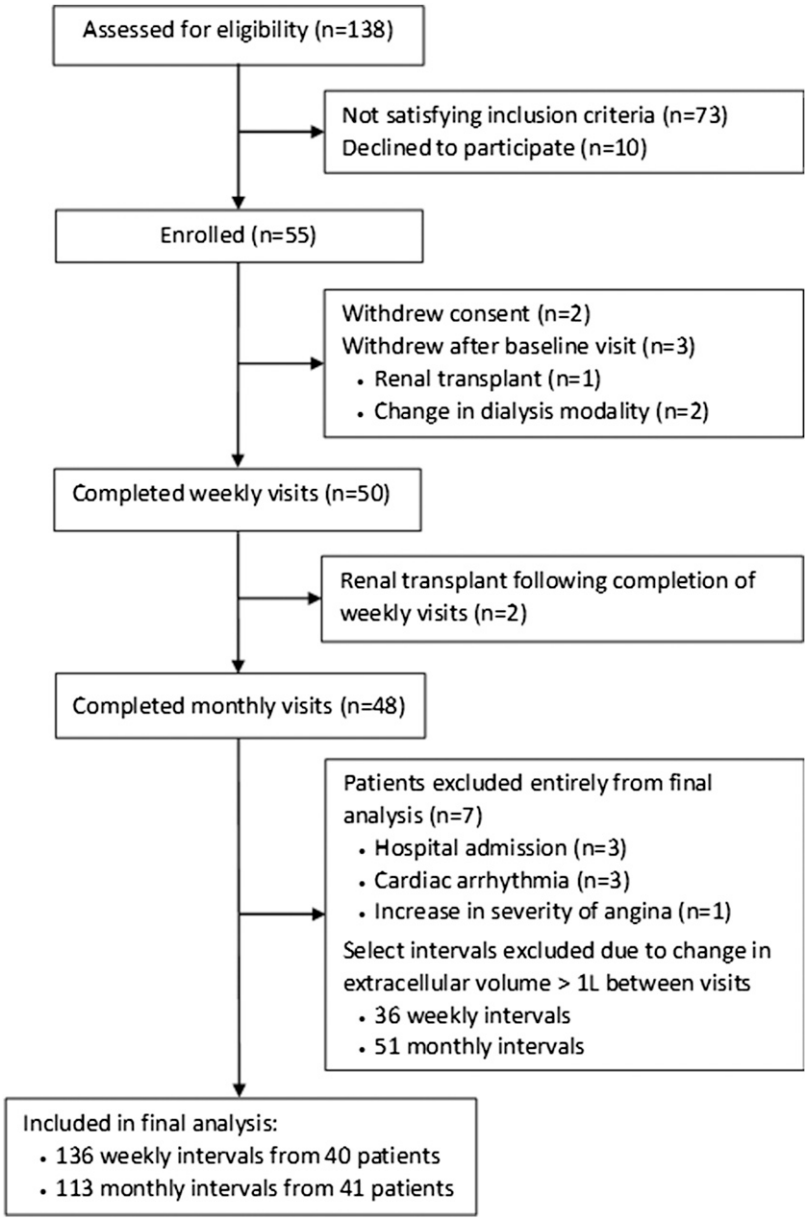

Figure 1. | **Flow diagram of patients assessed for eligibility, enrolled, and analyzed in the study.**

Table 1. Baseline characteristics of the study cohort

Characteristic	Value (*n*=55)
Men (%)	45
Age	
Mean±SD (yr)	59±15
Age distribution (%)	
18–49	33
50–69	40
70–79	22
80–90	5
Hemodialysis (%)	51
Dialysis sessions per week (*n*)	3
Duration of dialysis session (h)	5.1±0.7
Single pool Kt/V	1.73±0.38
Interdialytic weight gain (kg)	1.7 (1.5–2.3)
Interdialytic weight gain relative to estimated dry weight (%)	2.3±1
Peritoneal dialysis (%)	49
Volume of peritoneal dialysis solution exchanged per 24 h (L)	8 (8–10)
4-h D/P creatinine	0.72±0.52
Weekly Kt/V	2.21 (1.95–2.49)
Time on dialysis (mo)	35 (16–58)
Body mass index (kg/m^2)	30.2 (28.5–34.6)
Systolic BP (mmHg)	130±15
Diastolic BP (mmHg)	74±12
Diabetes mellitus (%)	40
Current or former smoker (%)	51
Ischemic heart disease (%)	22
Peripheral vascular disease and/or cerebrovascular disease (%)	9
Hydration status	
Ratio of extracellular to total body water	0.48±0.04
Overhydration volume relative to extracellular volume (%)	3±9
Normohydrated (%)	69
Moderately overhydrated (%)	21
Severely overhydrated (%)	10
Left ventricular structure and function	
Left ventricular hypertrophy (%)	
Nil	56
Mild	33
Moderate	11
Ejection fraction (%)	60±7
Left ventricular systolic dysfunction (%)	9
Diastolic dysfunction (%)	
Nil	13
Mild	24
Moderate	45
Severe	18
Antihypertensive agents	
Median number of antihypertensive agents	1 (1–2)
Proportion taking β-blockers (%)	42
Proportion taking ACEIs or ARBs (%)	38
C-reactive protein (mg/L)	5.0 (2.1–12)
NT-proBNP (pg/ml)	
Median (interquartile range)	1698 (718–3742)
Distribution (%)	
<300	7
300–899	20
900–4999	51
5000–19,999	11
≥20,000	11

D/P creatinine, ratio of creatinine concentration in dialysate to plasma; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin type 1 receptor blocker; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

dysfunction was defined as a left ventricular ejection fraction ≤50% using Simpson's rule (30).

The index of individuality (IOI) was calculated as CV_I/CV_G. This ratio gives an indication of whether a biomarker is best used within a relative-change monitoring strategy (IOI <0.6) or a reference interval strategy (IOI>0.6). The bidirectional reference change value (RCV) was calculated according to the method described by Fokkema *et al.* (32) for logarithmically transformed data as = $\exp(-Z\times\sqrt{2}\times\sigma)$ to $\exp(+Z\times\sqrt{2}\times\sigma)$, where $\sigma=\sqrt{\ln(CV_i^2+1)}$ and Z is the Z score of a standard normal distribution corresponding to a given probability.

Results

Patient Characteristics

Details of the number of patients assessed, enrolled, and included in the final analysis are shown in Figure 1. Fifty-five patients were recruited from the hemodialysis (*n*=28) and peritoneal dialysis (*n*=27) units of the participating institutions and their baseline characteristics are summarized in Table 1. Cardiovascular risk factors, including hypertension (100%), diabetes mellitus (40%), and current or former smoking (51%) were highly prevalent. A substantial proportion of the cohort also had evidence of established cardiovascular disease including ischemic heart disease (22%), left ventricular hypertrophy (44%), diastolic (87%) and/or systolic (9%) dysfunction, and peripheral vascular disease and/or cerebrovascular disease (9%). Baseline NT-proBNP concentrations demonstrated a right-skewed frequency distribution with a median of 1698 pg/ml (interquartile range, 718–3742). Ninety-three percent of the study cohort had a NT-proBNP concentration >300 pg/ml, the threshold used to exclude acute decompensated heart failure in the general population (33).

Weekly and Monthly Variation of NT-proBNP

Seven patients and their corresponding NT-proBNP measurements were excluded due to hospital admission (*n*=3), paroxysmal atrial fibrillation (*n*=3), and escalating anginal symptoms (*n*=1). In addition, 36 weekly and 51 monthly NT-proBNP sample pairs were excluded due to a change in extracellular volume of >1 L between consecutive visits. None of the participants were excluded on the basis of outlying variances or the linear regression

analysis. NT-proBNP measurements made over 136 weekly intervals from 40 patients and 113 monthly intervals from 41 patients were included in the final analysis. These data are shown in Figure 2 with excluded measurements represented by gaps.

The respective analytic, within-person, and between-person coefficients of variation of NT-proBNP were 1.9%, 27%, and 153% for weekly intervals, and 1.6%, 35%, and 148% for monthly intervals (Table 2). Between-person variation was much greater than within-person variation (Figure 3), yielding low indices of individuality of 0.18 and 0.24 for the weekly and monthly intervals, respectively (Table 2).

Weekly and monthly RCVs for the 70%, 80%, and 90% degrees of statistical confidence are shown in Table 2. Thus, NT-proBNP concentrations measured at weekly intervals needed to increase by 84% or decrease by 46% to ensure with 90% confidence that the observed change exceeded

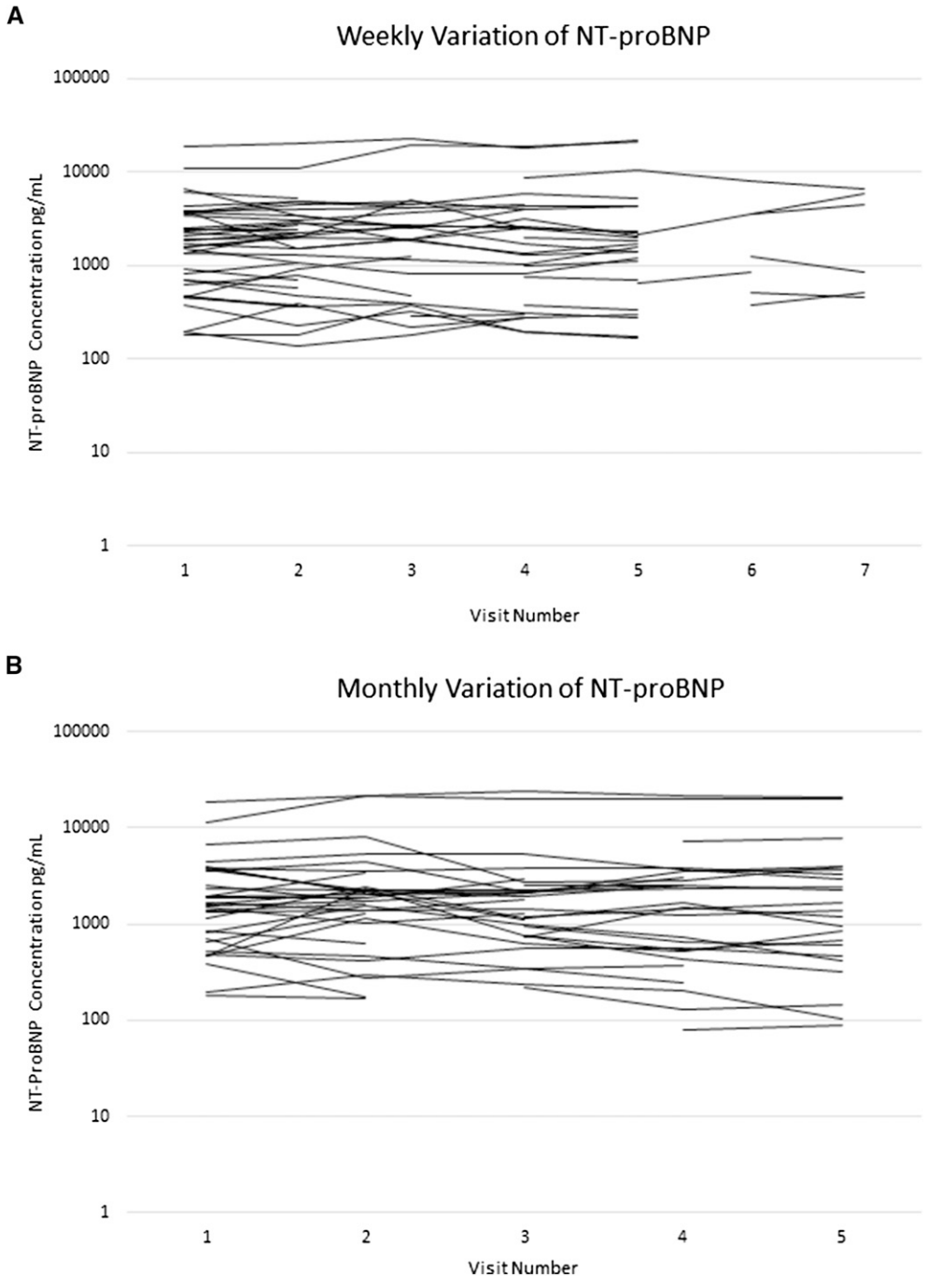

Figure 2. | Variation of N-terminal pro–B-type natriuretic peptide (NT-proBNP) concentrations measured from each of the stable participants over the course of the study. (A) Weekly and (B) monthly follow-up phases. Gaps represent measurements excluded due to a change in extracellular volume >1L between consecutive visits.

analytic and biologic variation alone. Monthly RCVs were slightly larger than weekly values for a given degree of statistical confidence.

The within-person coefficient of variation did not differ significantly between dialysis modalities; by ischemic heart disease, hydration, or inflammatory status; by severity of diastolic dysfunction; by presence or absence of left ventricular hypertrophy; or across quartiles of NT-proBNP concentration (Table 3). The effect of left ventricular systolic dysfunction on within-person variation was unable to be meaningfully analyzed because only one such patient was retained in the final analysis after the exclusion of unstable patients.

Discussion

This study demonstrated that NT-proBNP concentrations vary considerably across the dialysis population with a between-person coefficient of variation of 158%, markedly greater than that reported for healthy individuals (36%–70%) (34,35). This marked variability likely reflects the broad range of hydration status, residual renal function, dialysis regimens, pharmacotherapies, and the numerous types and severities of cardiac pathologies present in the dialysis population. By contrast, the within-person coefficient of variation of NT-proBNP among stable dialysis patients in this study was markedly smaller, equating to 27% and 35% for the weekly and monthly measurement intervals, respectively.

The large discrepancy between the within- and between-person coefficients of variation has important implications for how NT-proBNP is interpreted in the dialysis population. The ratio of within- to between-person variation is termed the IOI, and in this study equated to 0.18 and 0.24 for the weekly and monthly measurement intervals, respectively. Ratios <0.6 indicate a high degree of individuality and imply that NT-proBNP testing is better applied in the dialysis population using a relative-change strategy wherein serial measurements from the same patient are compared with each other rather than comparing single values to a reference interval or a threshold value (36). This finding represents an important departure from the majority of contemporary studies in this area that have sought to derive an absolute NT-proBNP concentration, below which cardiac dysfunction and/or overhydration can be confidently excluded in a manner analogous to which a NT-proBNP concentration <300 pg/ml is used to exclude acute decompensated heart failure in the non-dialysis population (33,37–41). Our findings suggest that such a strategy would be inaccurate for predicting cardiovascular risk in the dialysis population, resulting in unacceptably high false negative or false positive rates depending on the threshold value chosen, while also missing the majority of important changes in serial NT-proBNP concentrations measured from an individual dialysis patient (36). Instead, we suggest that a relative-change strategy would be of greater clinical value by accurately detecting significant changes in serial NT-proBNP concentrations irrespective of the absolute values. Significant changes in NT-proBNP concentrations would likely reflect important changes in composite cardiovascular risk caused by one or more pathophysiologic processes including volume overload, ventricular dysfunction, and/or cardiac ischemia.

Table 2. Estimates of variance components of NT-proBNP, bidirectional reference change values for stated degrees of statistical confidence, and index of individuality over weekly and monthly intervals for stable study participants

Interval	Coefficient of Variation (%)			Reference Change Value			Index of Individuality
	Analytic (CV_A)	Between-Person (CV_G)	Within-Person (CV_I)	90%	80%	70%	CV_I:CV_G
Weekly	1.9	153	27	−46% and +84%	−38% and +61%	−32% and +47%	0.18
Monthly	1.6	148	35	−54% and +119%	−46% and +84%	−39% and +64%	0.24

CV_A, analytic coefficient of vatiation; CV_G, between-person coefficient of variation; CV_I, within-person coefficient of variation.

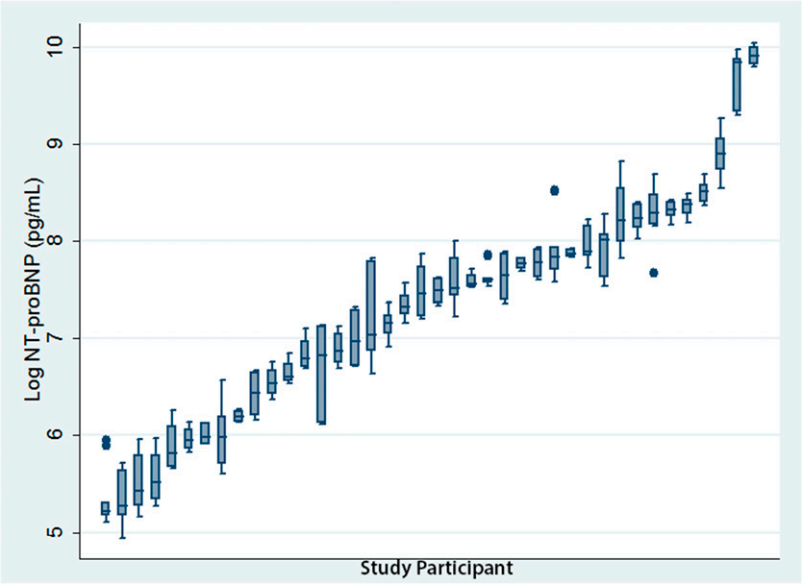

Figure 3. | Box plot of NT-proBNP concentrations for stable participants during the weekly follow-up phase plotted in ascending order of median NT-proBNP concentrations. Each box plot depicts five logarithmically transformed NT-proBNP concentrations taken from a single stable participant over the first 5 weeks of the study. The whiskers delimit the range and the middle, lower, and upper lines of the box represent the median, upper, and lower quartiles respectively. Between-person variation is reflected in the variation between median NT-proBNP concentrations across the entire cohort and was large. By comparison, within-person variation depicted by the box plots was much smaller and largely uniform between patients.

This hypothesis is supported by longitudinal studies that have demonstrated a direct correlation between change in NT-proBNP concentrations and the risk of fatal cardiovascular events (2–5), change in left ventricular mass (42), and change in surrogate measures of volume status (4,7).

However, not all changes in serial NT-proBNP concentrations are of clinical significance and may instead be attributed to analytic and/or biologic variation. The within-person coefficients of variation estimated in this study will play a crucial role in making this distinction in both the clinical and research settings (10,43,44). Using these estimates, we calculated a bidirectional magnitude of change between serial NT-proBNP measurements that excludes change due to biologic and analytic variation alone for a prespecified degree of statistical confidence—the RCV (32,43). The 90% RCV for NT-proBNP measured at weekly intervals was −46% and +84%, implying that serial NT-proBNP concentrations must increase by at least 84% or decrease by at least 46% to exclude change due to biologic and analytic variation alone with 90% certainty. Reducing the degree of statistical confidence reduces the magnitude of change required in either direction and increases the sensitivity but reduces the specificity for detecting a clinically important change. The degree of statistical confidence used is dictated by whether a change in biomarker levels is intended to rule in a given medical condition (high specificity required) or rule it out (high sensitivity required). Although the precise role of NT-proBNP monitoring in the dialysis population has yet to be absolutely defined, we hypothesize that it will primarily be used to identify patients at risk of major adverse cardiac events who require further evaluation to determine which pathophysiologic process is responsible. A lower degree of statistical confidence would be suitable for such a strategy because neither diagnosis nor therapy would be solely predicated on changing NT-proBNP concentrations alone. Finally, we found that the within-person coefficient of variation of NT-proBNP was not significantly different between dialysis modalities; by ischemic heart disease, inflammatory, or hydration status; by severity of diastolic dysfunction; by presence or absence of left ventricular hypertrophy; or across quartiles of baseline NT-proBNP concentrations, implying that a single decision limit can be applied across the entire dialysis population.

Our estimates of within-person variation are supported by the findings of Aakre *et al*. (35), who recently reported a within-person coefficient of variation of 26% for NT-proBNP measured at weekly intervals from a cohort of 17 hemodialysis patients. This study was limited by its small sample size, the exclusion of peritoneal dialysis patients, and a lack of rigor in ensuring patient stability, wherein the investigators relied either on patient report or a history of hospitalization alone to determine stability and did not measure volume status. As previously described, NT-proBNP concentrations may be affected by volume status, cardiac arrhythmias, the dialysis prescription, and changes in angina class that may not necessarily warrant admission. Ensuring stability of all of these parameters is essential to deriving accurate estimates of within-person variation.

Our study has a number of strengths that address these limitations, including the use of a rigorous approach to ensure the stability of all factors that influence NT-proBNP concentrations, the enrollment of both peritoneal dialysis and hemodialysis patients, measurement of NT-proBNP over both weekly and monthly intervals, and a larger sample size. Nevertheless, our study has several potential

Table 3. Within-person coefficients of variation of NT-proBNP by subgroups of dialysis modality, ischemic heart disease status, left ventricular hypertrophy, cardiac diastolic function, hydration status, tertiles of C-reactive protein concentration, and quartiles of NT-proBNP concentration

Subgroup	Weekly Within-Person Coefficient of Variation, CV_I (%)	*P* Value
Dialysis modality		
Peritoneal dialysis	24.5 (20.5 to 29.2)	0.45
Hemodialysis	29.3 (24.5 to 35.2)	
Coronary artery disease		
Absent	29.3 (25.3 to 34.0)	0.15
Present	18.8 (14.7 to 24.1)	
Left ventricular hypertrophy		
Absent	28.6 (24.3 to 33.7)	0.52
Present	24.3 (19,9 to 29.7)	
Diastolic dysfunction		
Nil/mild	27.3 (22.8 to 32.8)	0.98
Moderate/severe	27.1 (22.7 to 32.5)	
Hydration status		
Normohydration	28.4 (24.7 to 32.7)	0.28
Moderate/severe overhydration	22.3 (15.9 to 31.3)	
C-reactive protein concentration (mg/L)		
First tertile (2–4)	29.6 (23.9 to 36.7)	0.43
Second tertile (5–13)	28.8 (23.3 to 35.7)	
Third tertile (14–59)	20.6 (16.3 to 26.0)	
NT-proBNP concentration (pg/ml)		
First quartile (180–718)	29.4 (22.6 to 38.5)	0.89
Second quartile (719–1698)	29.7 (22.6 to 39.0)	
Third quartile (1699–3742)	25.1 (19.6 to 32.1)	
Fourth quartile (3743–44,091)	23.9 (19.0 to 30.2)	

Data are presented as mean (95% confidence interval).

limitations. First, patients with the most severe cardiovascular comorbidities were excluded to maximize the likelihood that patients would remain stable for the duration of follow-up. Although this potentially limits the generalizability of the study's findings, the baseline characteristics of our study cohort were similar to those reported for prevalent Australasian dialysis patients in the Australian and New Zealand Dialysis and Transplant Registry (45). Second, mean hemodialysis session duration in this study was considerably longer than that reported by most North American centers (46). Whether hemodialysis session length affects the within-person variation of NT-proBNP could not be investigated in this study due to the homogeneity of dialysis prescriptions and should be investigated by future studies before these results are applied to populations receiving shorter hemodialysis sessions. Third, we were unable to determine whether the within-person coefficient of variation of NT-proBNP was affected by left ventricular systolic impairment as only one such patient remained stable during the study. Finally, RCVs only exclude biologic and analytic variation, and changes in biomarker concentrations exceeding the RCV are not automatically of clinical significance.

NT-proBNP holds much promise as a biomarker of cardiovascular risk in the dialysis population; however, much remains to be established before it can be adopted into clinical practice. This study represents an important step in that direction. On the basis of these findings, we suggest that NT-proBNP testing may be better applied in the dialysis population using a relative-change strategy rather than by comparing absolute values to a reference interval or threshold value, and that large changes in NT-proBNP concentrations are needed to confidently exclude change due to biologic variation alone. Moving forward, longitudinal cohort studies are needed to determine the accuracy of serial NT-proBNP testing for predicting adverse cardiovascular events in the dialysis population and potential targets for therapeutic intervention.

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Disclosures

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