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Original Paper

Carvedilol and Cardiac Biomarkers in Dialysis Patients: Secondary Analysis of a Randomized Controlled Trial

Matthew A. Roberts[a] Darsy Darssan[b] Sunil V. Badve[b,c] Robert P. Carroll[d] Magid A. Fahim[b,e] Brian A. Haluska[f] Carmel M. Hawley[b,e] Nicole M. Isbel[e] Mark R. Marshall[g] Elaine M. Pascoe[b] Eugenie Pedagogos[h] Helen L. Pilmore[i] Paul Snelling[j] Tony Stanton[f] Ken-Soon Tan[k] Andrew M. Tonkin[l] Liza A. Vergara[b] Francesco L. Ierino[m,n]

[a]Eastern Health Clinical School, Monash University, Melbourne, [b]Australasian Kidney Trials Network, University of Queensland, Brisbane, [c]St George Hospital, Sydney, [d]Royal Adelaide Hospital, Adelaide, [e]Princess Alexandra Hospital, Brisbane, [f]Cardiovascular Imaging Research Group, University of Queensland, Brisbane, Australia; [g]Middlemore Hospital, Auckland, New Zealand; [h]Epworth HealthCare, Melbourne, Australia; [i]Auckland City Hospital, Auckland, New Zealand; [j]Royal Prince Alfred Hospital, Sydney, [k]Logan Hospital, Brisbane, [l]Cardiovascular Research Unit, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, [m]St Vincent's Health, Melbourne, [n]Department of Medicine, University of Melbourne, Melbourne, Australia

Key Words
Beta-adrenergic receptor blocker • Cardiac biomarkers • Cardiovascular • Dialysis • Echocardiography • Randomized controlled trial

Abstract
Background/Aims: Cardiac biomarkers are associated with cardiac abnormalities and adverse outcomes in dialysis patients. Our aim was to report the effect of the beta-blocker carvedilol on cardiac biomarkers in adult dialysis patients. ***Methods:*** The Beta-Blocker to Lower Cardiovascular Dialysis Events Feasibility Study was a randomized controlled trial comparing carvedilol to placebo. Serum and plasma were collected before the run-in, then 6 and 12 months post-randomization to measure B-type Natriuretic Peptide (BNP), N-terminal BNP (NT-ProBNP), high-sensitivity cardiac troponins I (hs-TnI) and T (hs-TnT), and galectin-3. Left ventricular global longitudinal strain (GLS) was measured by echocardiography at baseline. ***Results:*** Seventy-two participants were recruited of whom 49 completed the run-in and were randomized to carvedilol (n=26) or placebo (n=23). Baseline echocardiography demonstrated median (inter-quartile range) GLS of -14.27% (-16.63 to -11.93). NTproBNP and hs-TnT correlated with GLS (Spearman's rho=0.34 [p=0.018] and rho=0.28 [p=0.049], respectively). Median change scores from baseline to 12 months did not differ significantly between participants with complete biomarker data randomized to carvedilol (n=15) or placebo (n=16)

Matthew Roberts
Eastern Health Clinical School,
5 Arnold Street, Box Hill VIC 3128, Melbourne (Australia)
Tel. +61 3 90952410 Fax +61 3 98996810 E-Mail Matthew.Roberts@easternhealth.org.au

for any biomarkers. **Conclusions:** NT-proBNP and hs-TnT were associated with GLS. However, changes in levels of the biomarkers from baseline to 12 months were not different between groups randomized to carvedilol and placebo.

Introduction

Cardiac structure and function are adversely altered by end-stage kidney disease (ESKD) and these changes contribute to excess morbidity and mortality [1, 2]. Beta-blocking agents (BBA) such as carvedilol reduce sympathetic nervous system activity, blood pressure, heart rate, myocardial oxygen demand and propensity for arrhythmia [3] and thus may reduce the adverse myocardial effects of ESKD. In addition, carvedilol has antioxidant and anti-apoptotic effects that may confer additional cardiac protection [4]. One randomized controlled trial (RCT) in patients receiving hemodialysis with dilated cardiomyopathy demonstrated improved cardiac structure and function by echocardiogram with carvedilol therapy compared to placebo [5], and in a subsequent report, improved clinical outcomes [6]. This trial was the only dialysis study available for a meta-analysis of BBA in patients with chronic kidney disease (CKD) that demonstrated mortality reductions with beta-blocker therapy in patients with CKD and systolic heart failure [7].

In clinical practice, echocardiography is the major tool for diagnosing systolic heart failure and assessing cardiac structure and function in centres managing patients with ESKD. Important measurements include left ventricular (LV) dimensions, ejection fraction, LV mass and measures of diastolic function such as the E/A ratio. Although LV ejection fraction is an important prognostic factor, there are limitations to this measurement in hemodialysis patients and measurement of global longitudinal strain has been demonstrated to provide better assessment of LV function [8]. Another form of assessment of cardiovascular disease in ESKD, which is yet to find an established clinical role, is measurement of biochemical markers. This may offer complementary information regarding cardiac pathology to the echocardiogram because often they reflect a range of pathological processes [9].

Numerous biomarkers have demonstrated associations with cardiac structure and function. B-type natriuretic peptide (BNP) is increased by myocardial stretch. Measurement of both the active hormone BNP and its inactive N-terminal end (NT-proBNP) have demonstrated strong associations with LV hypertrophy and reduced LV ejection fraction, as well as adverse outcomes in patients with ESKD [10-12]. Furthermore, one uncontrolled [13] and one randomized controlled trial [14] have demonstrated a reduction in BNP in patients receiving dialysis treated with BBA, raising the possibility that these agents reduce myocardial stretch. Galectin-3 is a marker of cardiac fibrosis, a process that may be reduced by the antioxidant properties of carvedilol [15], and has been associated with adverse outcomes in ESKD [16, 17]. However, galectin-3 may be elevated with fibrosis in other organs. The cardiac troponins I and T are associated with mortality [18] and LV hypertrophy in patients with ESKD [19]. Because levels of these cardiac biomarkers are generally substantially higher in patients receiving dialysis than people with normal kidney function [9], we hypothesized that BBA therapy with carvedilol by reducing myocardial stretch, cardiac fibrosis and myocardial damage would reduce levels of the associated biomarkers.

To test this hypothesis, we report a planned secondary outcome study from the Beta-blocker to LOwer CArdiovascular Dialysis Events (BLOCADE) Feasibility Study [20] that aimed to determine the effect of BBA therapy on these biochemical markers of cardiovascular disease.

Materials and Methods

The BLOCADE Feasibility Study was a randomized, double-blind, placebo-controlled, parallel group study in which patients with ESKD receiving dialysis were randomized 1:1 to receive carvedilol or placebo (up to 25mg twice daily) for 12 months [21]. This trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000174280) and the University of Queensland Medical Research Ethics Committee approved the study (Project Number: 2009000775), as did the Ethics Committees at individual sites. All participants provided written informed consent and study conduct adhered to the Declaration of Helsinki.

Participants

Inclusion and exclusion criteria were described previously [21]. Briefly, ESKD patients receiving either hemodialysis or peritoneal dialysis were approached to participate if they were aged 50 years or more, or aged 18 years or more with co-morbid diabetes and/or cardiovascular disease, and their treating physician agreed to them being randomized to a BBA or placebo.

Intervention and control

The intervention was the BBA carvedilol (Dilatrend®; F. Hoffmann-La Roche Ltd., Basel, Switzerland) and the control was placebo; both drug and placebo were encapsulated to render them identical and they were administered in identical fashion.

Outcomes

The primary outcomes for this planned secondary analysis are changes in BNP, NT-proBNP, high sensitivity cardiac troponinT (hs-TnT) and I (hs-TnI) and galectin-3 from randomization to 12 months. The planned sample size was based on the feasibility outcome for the original study [21] and not these biomarker outcomes.

Study procedures

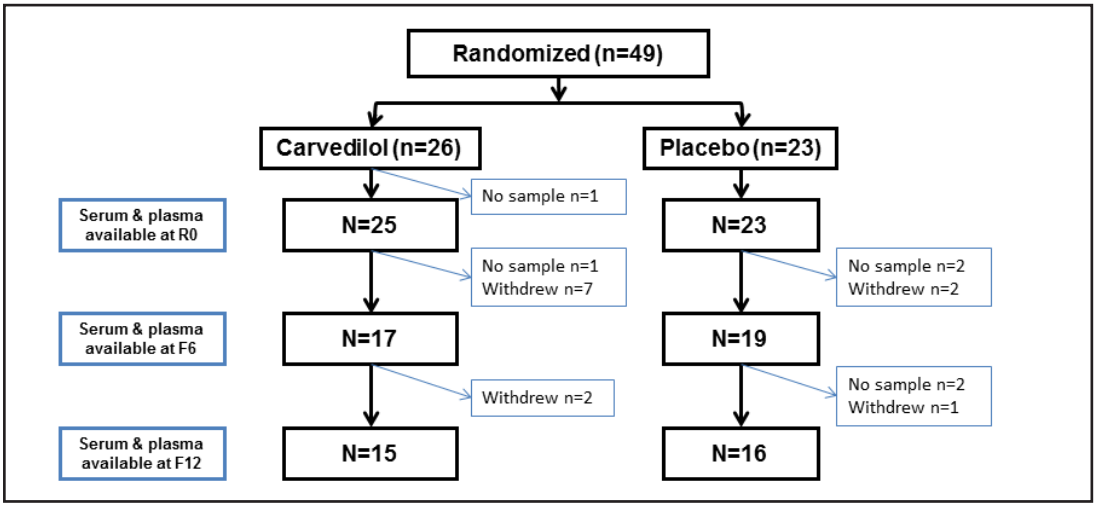
After a 6 week run-in phase in which carvedilol was commenced at 3.125mg twice daily, participants who tolerated carvedilol 6.25mg twice daily were randomized 1:1 to carvedilol or placebo with an adaptive allocation algorithm to minimize treatment imbalances at each study site and across dialysis modality (hemodialysis or peritoneal dialysis). Participants, investigators, coordinating center staff, and assessors of biochemical and echocardiographic measures were blinded to treatment assignment. The study drug was titrated every 2 weeks to the maximum tolerated dose or 25mg twice daily. Participants remained on study drug for 12 months and then underwent a supervised down-titration then cessation of study drug with maintenance of blinding.

Blood samples were collected at the commencement of the run-in, 6 months and 12 months post-randomization and placed in serum separator and EDTA tubes (in hemodialysis patients, this was immediately before the mid-week hemodialysis session). The blood samples were transported on ice to be processed and centrifuged at 3, 200g for 10 minutes before being divided into aliquots of serum and plasma that were stored at -80^{o}C until central laboratory analysis.

Laboratory procedures

Samples were analyzed by Sullivan Nicolaides Pathology (Brisbane, Australia) on automated platforms. BNP (ARCHITECT BNP, Abbott Laboratories, Abbott Park, IL), galectin-3 (ARCHITECT Galectin-3, Abbott Laboratories, Abbott Park, IL) and hs-TnI (ARCHITECT STAT High Sensitive Troponin-I, Abbott Laboratories, Abbott Park, IL) were all analyzed by chemiluminescent immunoassay on the Abbott i4000 Analyzer (Abbott Diagnostics, Abbott Park, IL). NT-ProBNP (proBNP; Roche Diagnostics, Indianapolis, IN) and hs-TnT (Elecsys Troponin T hs, Roche Diagnostics, Indianapolis, IN) were measured by electro-chemiluminescent immunoassay on a Roche Elecsys E170 Analyzer (Roche Diagnostics, Indianapolis, IN). The total coefficients of variation across a wide range of values of BNP, NT-proBNP, hs-cTnI, hs-cTnT and galectin-3 were <7%, <4%, <6%, <9% and <9%, respectively.

Fig. 1. Flow of participants through the study after randomization.



Echocardiography

An echocardiogram was performed once prior to commencing the run-in phase according to the recommendations of the American Society for Echocardiography [22]. Standard apical and parasternal views were obtained with patients in the left lateral decubitus position and Simpson's biplane method was used to calculate left ventricular volumes and ejection fraction (LVEF). Tissue Doppler echocardiography was used to evaluate diastolic function and the early diastolic mitral inflow (E) and late diastolic mitral inflow (A) to derive the E/A ratio. Global longitudinal strain (GLS) was measured using 2D speckle tracking echocardiography. A more negative GLS number indicates better cardiac function.

The echocardiogram was performed as soon after the hemodialysis procedure as was feasible to ensure patients were as close as possible to their dry weight.

Statistical considerations

Biomarker data were heavily skewed and are summarized as median (interquartile range, IQR). We analyzed biomarker change scores in order to account for baseline differences. Differences between intervention groups on median biomarker change

Table 1. Baseline characteristics of randomized participants with complete biomarker data. ESKD=End-stage kidney disease; PD=peritoneal dialysis

	Carvedilol (n=15)	Placebo (n=16)
Age	57.8±11.6	62.2±13.5
Male sex	6 (40%)	14 (88%)
Ethnicity		
Caucasoid	7 (47%)	6 (38%)
New Zealand Maori	3 (20%)	5 (31%)
Pacific Islander	4 (27%)	4 (25%)
Other	1 (7%)	1 (6%)
Cardiac risk factors		
Diabetes	10 (67%)	12 (75%)
Hypertension	13 (87%)	15 (94%)
Known coronary disease	0	3 (19%)
Known heart failure	0	0
Ever smoked	12 (80%)	9 (56%)
Cause of ESKD		
Diabetes	8 (53%)	11 (69%)
Hypertension or vascular	3 (20%)	1 (6%)
Glomerulonephritis	2 (13%)	3 (19%)
Other	2 (13%)	1 (6%)
Hemodialysis (v PD)	11 (73%)	13 (81%)
Months on dialysis	14 (5-24)	31 (20-50)
Daily urine volume<500mL	9 (69%)	11 (73%)
Clinical measurements		
Body mass index (kg/m^2)	30.8±4.5	30.8±6.0
Heart rate (beats per minute)	74±9	79±9
Systolic blood pressure (mmHg)	133±19	140±17
Diastolic blood pressure (mmHg)	71±17	76±9
Laboratory measures		
Hemoglobin (g/L)	110 (103-123)	111 (104-117)
Albumin (g/L)	37 (35-40)	36 (34-40)
C-reactive protein (mg/L)	3.2 (2.9-5.0)	6.0 (4.0-8.4)
Echocardiography		
Ejection fraction (%)	63 (58-65)	63 (57-65)
Global longitudinal strain	-14.4 (-16.7 to -12.9)	-13.7 (-18.1 to -11.9)
E:A Ratio	0.8 (0.6-0.9)	0.8 (0.7-1.1)

scores at six and twelve months were analyzed using Wilcoxon rank-sum tests. These analyses were performed on data from participants who had complete data (i.e. measurements at baseline, six and twelve months) because our primary interest was whether the intervention resulted in any change in biomarker. Additional analyses were performed on data from all patients to determine whether including data from participants who withdrew from the study for any reason altered the findings. Associations of baseline global longitudinal strain, LV ejection fraction and E/A ratio with biomarker measures were assessed by Spearman's rank correlation coefficient. Data for these analyses were restricted to participants who had a baseline global longitudinal strain measurement.

Results

Recruitment of participants to the BLOCADE Feasibility Study and baseline characteristics of all participants were described in the main report [21]. Seventy-two participants entered the run-in phase of whom 23 failed to complete this, leaving 49 participants randomized to carvedilol (n=26) or placebo (n=23). Participants who had serum and plasma available at baseline, 6 months and 12 months were included in the analyses: 15 participants were allocated carvedilol and 16 were allocated placebo (Fig. 1). The baseline characteristics

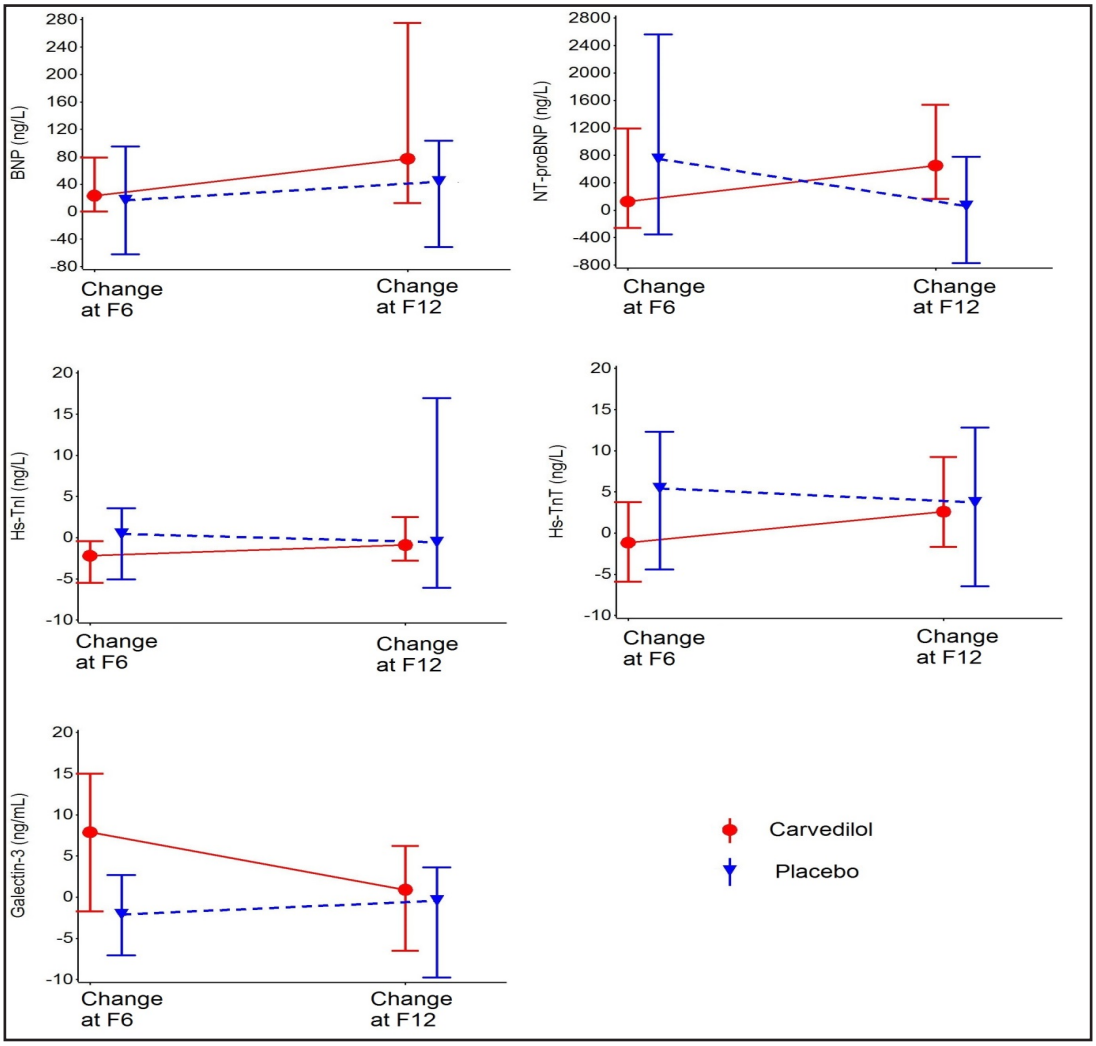


Fig. 2. Median (IQR) change scores at 6 and 12 months for each of the 5 biochemical markers according to assigned treatment.

of participants with complete biomarker data by randomized group were reasonably balanced apart from a smaller proportion of males and a shorter median dialysis vintage in participants receiving carvedilol, and LVEF was well preserved (Table 1).

In these 31 participants combined, median BNP increased from 70.6ng/L (30.7 - 155.5) at baseline to 159.3ng/L (85.5-274.7) at 12 months (p=0.003) and NT-proBNP increased from 1, 219ng/L (718-2680) to 1, 883ng/L (1, 073-3, 496) at 12 months (p=0.07). For the other biomarkers, corresponding values were 13.0ng/L (7.8-20.3) and 12.2ng/L (6.6-26.2) respectively for hs-TnI (p=0.58), 54.8ng/L (39.8 - 83.8) and 59.5ng/L (43.0 - 89.3) for hs-TnT (p=0.07), and 71.2ng/mL (46.7 – 92.9) and 68.5ng/mL (47.8 - 87.9) for galectin-3 (p=0.99). The change in BNP and NT-BNP was greater in the carvedilol group as compared to the placebo group, but the difference between groups was not statistically significant. There was no statistically significant difference between the randomized groups in the change from baseline to 12 months in hs-TnI, hs-TnT or galectin-3 (Table 2 and Fig. 2). Analyses that included participants who did not have complete biomarker data at each time point did not alter this finding.

Echocardiograms with complete data for global longitudinal strain were available for 49 of the 72 participants who entered the run-in (not necessarily the same participants who were randomized). At baseline in these participants, median LV global longitudinal strain was -14.27 (IQR -16.63 to -11.93), median E/A ratio was 0.83 (IQR 0.69-1.00) and median LV ejection fraction was 61% (IQR 56 to 65). Only NT-proBNP and hs-TnT were significantly positively

Table 2. Median (IQR) levels of the 5 biomarkers at baseline and 12 months, and the median difference, by randomized treatment group

	Carvedilol (n=15)	Placebo (n=16)	P-value
BNP (ng/L)			
Baseline	71.9 (43.8 - 124.2)	68.6 (25.8 – 186.4)	
12 months	198.2 (88.5 - 407.6)	151.9 (76.2 – 267.5)	
Difference	+77.2 (+12.4 to +275.0)	+43.7 (-51.5 to +103.5)	0.15
NT-proBNP (ng/L)			
Baseline	1,219 (843.3 - 1,668)	1,885 (618 - 4,286)	
12 months	1,883 (1,290 - 2,559)	2,216 (822 - 4,388)	
Difference	+651 (+165 to +1,538)	+60 (-769 to +781)	0.14
hs-TnI (ng/L)			
Baseline	10.5 (7.4 - 16.3)	18.2 (9.5 – 22.0)	
12 months	10.0 (5.9 - 12.7)	17.6 (10.0 - 39.3)	
Difference	-0.9 (-2.8 to +2.5)	-0.6 (-6.1 to +17.0)	0.89
hs-TnT (ng/L)			
Baseline	51.4 (33.6 - 80.1)	58.8 (51.5 – 104.8)	
12 months	51.0 (33.6 – 77.5)	80.4 (53.9 – 109.4)	
Difference	+2.6 (-1.7 to +9.2)	+3.7 (-6.5 to +12.8)	0.99
Galectin-3 (ng/mL)			
Baseline	69.5 (46.7 - 84.0)	75.4 (47.8 - 94.5)	
12 months	66.8 (47.8 - 87.6)	68.7 (47.8 – 90.7)	
Difference	+0.9 (-6.5 to +6.2)	-0.4 (-9.8 to +3.6)	0.51

Table 3. Spearman rank correlation (rho) of the 5 biomarkers with echocardiographic measurements at baseline in the 49 participants with data for global longitudinal strain and biomarker levels

	Global longitudinal		LV Ejection		E/A ratio	
	Rho	P-value	Rho	P-value	Rho	P-value
BNP	+0.26	0.067	-0.12	0.40	+0.19	0.19
NT-proBNP	+0.34	0.018	-0.16	0.28	-0.01	0.95
hs-cTnI	+0.17	0.24	-0.13	0.38	-0.21	0.16
hs-cTnT	+0.28	0.049	-0.13	0.37	-0.12	0.43
Galectin-3	+0.02	0.88	-0.06	0.69	-0.11	0.46

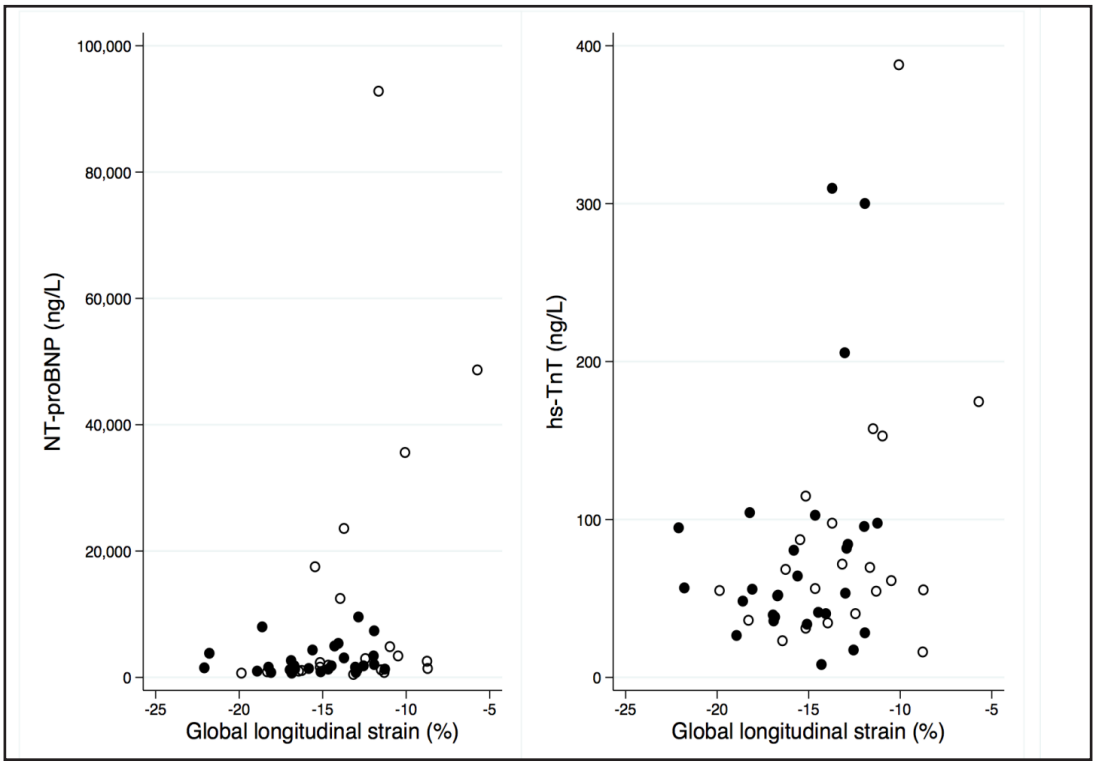


Fig. 3. Scatter plots of NT-proBNP (left) and Hs-TnT (right) versus global longitudinal strain. Open circles are participants with LVEF<61% and closed circles are participants with LVEF≥61%.

correlated with global longitudinal strain; no marker was significantly correlated with LV ejection fraction or E/A ratio (Table 3). Values of global longitudinal strain were higher for participants with LV ejection fraction below the median; fewer participants with LV ejection fraction above the median had markedly elevated NT-proBNP whereas some participants with LV ejection fraction below the median had markedly elevated hs-TnT (Fig. 3).

Discussion

This secondary analysis of the BLOCADE Feasibility Study demonstrates that in ESKD patients receiving dialysis, both NT-proBNP and hs-TnT were associated with global longitudinal strain, a sensitive measure of LV systolic function. Treatment with carvedilol did not significantly modify the change of any of the measured cardiac biomarkers over 12 months compared to placebo. In fact, the increase in both BNP and NT-proBNP at 12 months was greater in the carvedilol group. Thus we could not confirm our hypothesis that carvedilol reduces myocardial stretch, fibrosis and damage as determined by changes in levels of the relevant biomarkers.

In contrast to our results, two previous studies have demonstrated that treatment with a BBA reduces BNP in patients with ESKD receiving dialysis [13, 14]. No study examining the effect of BBA therapy in dialysis patients on either troponin or galectin-3 could be found by Medline search (searched 3 November 2016). There are reports of the effect of BBA therapy on these biomarkers in other clinical situations. Most reports relate to BNP, including a sub-study of the Carvedilol Prospective Randomized Cumulative Survival Study (COPERNICUS) that demonstrated a reduction in NT-proBNP with carvedilol therapy in patients with chronic heart failure [23]. In another heart failure trial, no significant effect of medications, including BBA therapy, on serial measurement of galectin-3 was evident [24]. The effects of

BBA therapy on cardiac troponin levels have been studied following vascular surgery [25] and cardiac percutaneous intervention [26] with variable results.

Global longitudinal strain may be a better measure of LV systolic function in patients receiving dialysis [8] and an association of global longitudinal strain with cardiac troponin T has been reported in patients receiving dialysis [27, 28]. However, associations of global longitudinal strain with BNP or galectin-3 have not been previously reported in dialysis patients. In other populations, such as patients following acute myocardial infarction, global longitudinal strain correlates strongly with NT-proBNP [29]. No studies examining an association of global longitudinal strain with galectin-3 could be found.

Potential reasons why this study demonstrated no significant difference in change in any biomarker level over time with BBA therapy compared to placebo include Type II error, biological variation, the well-preserved LV ejection fraction of our patients and the possibility that the intervention does not work in this population. We did not recruit the planned sample size for the feasibility outcome study and combined with the attrition of patients over 12 months, the number of participants with biomarker data was lower than planned. However, our sample size was slightly larger than the uncontrolled study that used metoprolol to demonstrate a reduction in BNP (n=14) [13], and the randomized controlled trial that demonstrated lower BNP with carvedilol therapy than placebo (n=20) [14]. Although not statistically significant, our findings with BNP (and NT-proBNP) were dissimilar to these studies as the levels of these biomarkers increased over time in both groups, but to a greater degree if receiving carvedilol. This increase in BNP (and NT-proBNP) over time has been demonstrated in observational studies of dialysis patients [30, 31]. The major difference between these two intervention studies and our RCT was the much shorter duration of therapy in these studies (3 months in the carvedilol RCT and 4 months in the metoprolol study). Variation in biomarker levels between patients and within the same patients over time has a significant impact in studies assessing the effect of an intervention on a biomarker. The reference change value (RCV) can be calculated to determine the degree of increase that would be considered a clinically meaningful change (over and above analytic and biological variation) [32]. In dialysis patients undergoing monthly measurements, a clinically meaningful change in NT-proBNP required a decrease of 54% or an increase of 119% [33] and for hs-TnT required a decrease of 25% or increase of 34% [34]. Furthermore, the between person variability for both biomarkers in these studies was very high. Although patients with reduced LV function were eligible for recruitment into BLOCADE, no patient with heart failure was recruited which likely reflects the reluctance of investigators to randomize such patients to carvedilol or placebo. It is possible that patients with reduced LV function would have higher levels of BNP at baseline that may fall after intervention (or through regression to the mean). Against this theory, the randomized controlled trial that demonstrated a lowering of BNP with carvedilol recruited patients with well-preserved LV ejection fraction [14]. Finally, multiple processes contribute to the "uraemic cardiomyopathy" [35] and a particular biomarker may not be sensitive to the effect of a particular intervention or indeed the intervention itself may not have the anticipated effect.

The strengths of the present study relate to the double blind randomized nature of its design and the fact that the study measured five cardiac biomarkers that reflect three different cardiac disease processes: myocardial stretch as measured by B-type natriuretic peptide, myocardial damage as measured by high-sensitivity cardiac troponin and myocardial fibrosis as measured by galectin-3. Our study did however have a number of limitations. The sample size was small and despite randomization, some baseline differences in gender and duration of dialysis occurred. Echocardiogram was performed at baseline only, so we are unable to report if carvedilol therapy affected global longitudinal strain measures. Future studies to address this issue would need to consider follow up imaging with adequate sample size.

Conclusion

This study demonstrated that NT-proBNP and hs-TnT correlated significantly with global longitudinal strain. Treatment of patients receiving dialysis with the BBA carvedilol did not favourably alter levels of the five cardiovascular biochemical markers of three different pathophysiological processes that were measured. However, a larger sample size may be required to detect any differences if they exist. A major challenge in defining a role for biomarker measurement in this population remains the variability of the biomarkers themselves and of the cardiac functional measurement which they may reflect.

Disclosure Statement

The authors report no conflicts of interest.

Acknowledgements

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Shore Hospital (Bruce Cooper, Jacqueline Pearse), Royal Prince Alfred Hospital (Paul Snelling, Jenny Burman, Samantha Hand), Royal Melbourne Hospital (Eugenie Pedagogos, Connie Karschimkus); *New Zealand sites*: Auckland City Hospital (Helen Pilmore, Andrew Pilmore); Dunedin Hospital (Robert Walker, Gaye Ellis), Middlemore Hospital (Mark R Marshall, Cecilia Paul) *Project Management Team:* Australasian Kidney Trials Network, Brisbane, Queensland, Australia: Carmel M Hawley (Chair, AKTN Operations Secretariat), David Johnson (Deputy Chair, AKTN Operations Secretariat), Sunil Badve, Alan Cass, Darsy Darssan, Jean Helyar, Alicia Morrish, Elaine M Pascoe, Peta-Anne Paul-Brent, Donna Reidlinger, Anish Scaria, Liza A Vergara and Lei Zhang.

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