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Original Article

The rationale and design of the Beta-blocker to LOwer CArdiovascular Dialysis Events (BLOCADE) Feasibility Study

MATTHEW A ROBERTS,[1] HELEN L PILMORE,[2] FRANCESCO L IERINO,[3,4] SUNIL V BADVE,[5,6] ALAN CASS,[7] AMIT X GARG,[8] CARMEL M HAWLEY,[5,6] NICOLE M ISBEL,[6] HENRY KRUM,[9] ELAINE M PASCOE,[5] ANDREW M TONKIN,[10] LIZA A VERGARA[5] and VLADO PERKOVIC[11] for the BLOCADE Study Collaborative Group

[1]Department of Renal Medicine, Eastern Health Clinical School, [9]Centre of Cardiovascular Research and Education in Therapeutics, Department of Epidemiology and Preventive Medicine, [10]Cardiovascular Research Unit, Department of Epidemiology and Preventive Medicine, Monash University, [3]Department of Nephrology, Austin Health, [4]Department of Medicine, University of Melbourne, Melbourne, Victoria, [5]Australasian Kidney Trials Network, The University of Queensland, [6]Department of Nephrology, Princess Alexandra Hospital, Brisbane, Queensland, [7]Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, [11]The George Institute for Global Health, University of Sydney, Sydney, New South Wales, Australia, [2]Department of Renal Medicine, Auckland City Hospital, Auckland, New Zealand, and [8]Division of Nephrology, Department of Medicine, Western University, London, Ontario, Canada

KEY WORDS:
beta-blocking agent, feasibility study, haemodialysis, peritoneal dialysis, randomized controlled trial.

Correspondence:
Dr Matthew A Roberts, Eastern Health Integrated Renal Service, Level 2, 5 Arnold Street, Box Hill Vic. 3128, Australia. Email: matthew.roberts@monash.edu

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SUMMARY AT A GLANCE

This study aimed to reduce cardiovascular (CV) events among dialysis patients. This is a trial design paper for the feasibility of a randomized controlled trial to evaluate beta-blockade (carvedilol 3.125 mg bid titrated to 6.25 mg bid or heart rate threshold 55 beats per minute *vs* placebo) among patients on dialysis. The feasibility will inform recruitment, logistics and intra-dialytic hypotension. Findings will be used to design full-scale study on CV outcomes.

ABSTRACT:

Aims: **The Beta-blocker to LOwer CArdiovascular Dialysis Events (BLOCADE) Feasibility Study aims to determine the feasibility of a large-scale randomized controlled trial with clinical endpoints comparing the beta-blocking agent carvedilol with placebo in patients receiving dialysis.**

Methods: **The BLOCADE Feasibility Study is a randomized, double-blind, placebo-controlled, parallel group feasibility study comparing the beta-blocking agent carvedilol with placebo. Patients receiving dialysis for ≥3 months and who are aged ≥50 years, or who are ≥18 years and have diabetes or cardiovascular disease, were eligible. The primary outcome was the proportion of participants who complete a 6-week run-in phase in which all participants received carvedilol titrated from 3.125 mg twice daily to 6.25 mg twice daily. Other measures included how many patients are screened, the proportion recruited, the overall recruitment rate, the proportion of participants who remain on study drug for 12 months and the incidence of intra-dialytic hypotension while on randomized treatment.**

Results: **The BLOCADE Feasibility Study commenced recruiting in May 2011 and involves 11 sites in Australia and New Zealand.**

Conclusions: **The BLOCADE Feasibility Study will inform the design of a larger clinical endpoint study to determine whether beta-blocking agents provide benefit to patients receiving dialysis, and define whether such a study is feasible.**

Beta-adrenergic receptor antagonists, or beta-blocking agents, have potential to reduce morbidity and mortality related to cardiovascular disease (CVD) in patients with end-stage kidney disease (ESKD) requiring dialysis. They reduce mortality and morbidity in patients without ESKD who have ischaemic heart disease[1] and heart failure,[2] and in patients with heart failure, reduce the incidence of atrial fibrillation, ventricular arrhythmias[3] and sudden death.[4]

These comorbidities are very prevalent in patients with ESKD,[5,6] who also have sympathetic nervous system overactivity with deleterious cardiovascular effects[7] that may be ameliorated by beta-blocking agents.

A meta-analysis of randomized controlled trials (RCTs) of beta-blocking agents in patients with chronic kidney disease (CKD) demonstrated a 28% relative risk reduction for mortality using beta-blocking agents, with a reduction in the absolute risk of death of approximately 6% after between 1 and 2 years of follow-up.[8] Bradycardia and hypotension were more frequent in patients randomized to beta-blocking agents. Most data came from *post hoc* analyses of RCTs in heart failure patients; few patients had CKD IV or V, and only one trial recruited people undergoing dialysis. When the Beta-blocker to LOwer CArdiovascular Dialysis Events (BLOCADE) Feasibility Study commenced, this RCT of beta-blocking agents in ESKD was the only such study published. It specifically enrolled patients with heart failure and demonstrated reduced mortality in patients receiving carvedilol compared with placebo.[9] Recently, a trial comparing the effects of the beta-blocking agent atenolol with the angiotensin-converting enzyme inhibitor lisinopril on regression of left ventricular (LV) hypertrophy in hypertensive haemodialysis patients was terminated early because of excess cardiovascular adverse events in participants randomized to lisinopril.[10]

Carvedilol is an antagonist of β_1-, β_2- and α_1-adrenergic receptors that has been used extensively in patients with heart failure,[11] including patients with ESKD.[9] Carvedilol is potentially a good beta-blocking agent for patients with ESKD because it is eliminated entirely by hepatic metabolism, is highly protein bound and not removed by haemodialysis, and has anti-oxidant properties and a favourable metabolic profile compared with other beta-blocking agents.[12–14] However, blood pressure lowering due to α_1-adrenergic receptor blockade could potentially increase the risk of symptomatic hypotension during the haemodialysis procedure. For peritoneal dialysis patients, the risk of symptomatic hypotension is theoretically lower because of lesser volume state fluctuations, but there is no randomized data to support this.

The potential benefit of beta-blocking agents in ESKD is best measured by outcomes important to patients such as reduced mortality, cardiovascular events and hospital admissions. Measurement of B-type natriuretic peptide (BNP), a biochemical marker of LV wall stress, may provide a surrogate measure of clinical benefit. If carvedilol reduces plasma concentration of BNP, as one small study demonstrated,[15] LV wall stress may also be reduced. The plasma concentration of BNP in patients with ESKD is markedly elevated,[16] and higher plasma concentration is associated with increased mortality.[17] Quality of life is important to patients and can be measured using a variety of instruments. The EuroQol-5D (EQ-5D) instrument performs well compared with more detailed instruments and has been used in Australia and New Zealand.[18] It can be used to calculate quality-adjusted life years and thus, for health economic analyses that are important to evaluate in a larger study.

Uncertainty about how many patients receiving dialysis would be eligible, consent to participate and continue taking beta-blocking agents for long enough to gain a benefit meant that a feasibility study should be performed before a large-scale RCT. The aims of the BLOCADE Feasibility Study are to determine:

- The tolerability of carvedilol in this population as measured by the proportion of patients who complete the run-in phase
- The feasibility, and inform the design of, a large-scale RCT with clinical endpoints comparing the beta-blocking agent carvedilol with placebo
- The effects of treatment with carvedilol compared with placebo on concentration of plasma of BNP and quality of life

METHODS

Design

The BLOCADE Feasibility Study is a randomized, double-blind, placebo-controlled, parallel group study with stratification for study centre and dialysis modality (Fig. 1). After a 6-week run-in phase in which all participants received carvedilol, participants who tolerated carvedilol 6.25 mg twice daily were randomized 1:1 to receive carvedilol or placebo (up to 25 mg twice daily) for 12 months.

Participants

The BLOCADE Feasibility Study commenced recruiting in May 2011 and involves 11 sites in Australia and New Zealand. For inclusion (Table 1), 3 months must elapse from dialysis initiation to establish volume state. Although ESKD is itself a significant risk factor for CVD, restricting recruitment to patients over 50 years or with significant comorbidities (Table 1) aimed to select a population at higher risk of CVD events in order to minimize the required sample size while maintaining adequate statistical power. Both coronary artery disease and heart failure were thus possible *inclusion criteria* for the BLOCADE Feasibility Study. Although there was strong evidence that beta-blocking agents reduce mortality in patients not requiring dialysis with these conditions, the quality of evidence in dialysis patients was considered insufficient to make these comorbidities *exclusion criteria*. However, patients whose treating physician believed a beta-blocking agent was indicated were excluded. Thus, these criteria tested the willingness of physicians to cease beta-blocking therapy and enter patients into an RCT.

Intervention and control

The experimental intervention was the beta-blocking agent carvedilol taken orally twice daily. The control was identical placebo prescribed in identical fashion. Carvedilol (Dilatrend (R); F. Hoffmann-La Roche Ltd, Basel, Switzerland) was purchased and delivered to Pharmaceutical Packaging Professionals Pty Ltd (Thebarton, South Australia, Australia) where identical encapsulation of active drug and placebo

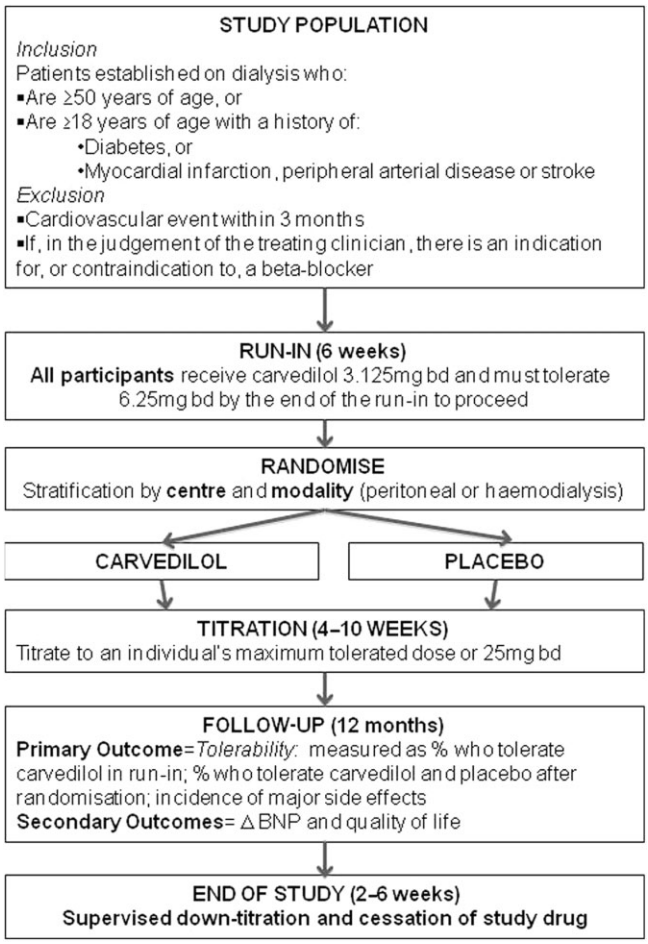

Fig. 1 Study schema. BNP, B-type natriuretic peptide.

was performed. Encapsulation was performed because the different colouring of different strengths of carvedilol made identical placebo manufacture difficult, complex and costly. Because we did not undertake formal pharmacokinetic testing, we cannot exclude the possibility that encapsulated carvedilol has a different absorption profile to non-encapsulated carvedilol. We believe the risk to be low.

Regular omission of the dose of study drug immediately before a haemodialysis session was permitted if the site investigator believed study therapy was contributing to hypotension during the procedure provided all other doses were taken. Although not encouraged, this was allowed as it is common practice with blood pressure-lowering agents in haemodialysis. The site investigators' clinical judgement was used rather than specific blood pressure criteria.

Study procedures

Patients receiving dialysis at participating centres who met eligibility criteria and provided written informed consent underwent the baseline visit. A site screening log recorded the number of patients screened who were potentially eligible to participate and the reasons for ineligibility and for non-participation if eligible. Potentially eligible patients already receiving a beta-blocking agent at screening whose treating physician considered it safe to cease the beta-blocking agent underwent supervised down-titration of their beta-blocking agent and a 2-week washout period before attending the baseline visit.

Table 1 Inclusion and exclusion criteria of the BLOCADE Feasibility Study

Inclusion criteria
1. Willing to participate and has provided written informed consent
2. End-stage kidney disease and receiving either haemodialysis or peritoneal dialysis
3. At the time of signing the consent form, has received dialysis for more than 3 months†
4. At the time of signing the consent form, age ≥50 years or age ≥18 years with diabetes or age ≥18 years with cardiovascular disease as determined by the site investigator
5. The treating physician agrees to participation
Exclusion criteria
1. Scheduled for live donor transplant within 6 months
2. Experienced a cardiovascular event in the previous 3 months. Cardiovascular events include: myocardial infarction, admission for unstable angina, coronary revascularization procedure, peripheral arterial revascularization procedure or stroke
3. Definite contraindication to beta-blockers, such as second- or third-degree atrioventricular block or sick sinus syndrome (unless treated with a permanent pacemaker), clinically significant reversible bronchospasm or previous intolerance to beta-blockers
4. Currently taking a beta-blocker, verapamil, diltiazem or moxonidine, and the treating physician does not wish to stop these medications in order to enter the trial
5. Considered by the treating physician to be clinically or haemodynamically unstable for the study
6. Unstable target weight (defined by a change of ≥2.0 kg in target base weight over the preceding month)
7. Severe hepatic dysfunction (transaminases ≥3× higher than the upper normal limit) on the most recent liver function tests (if performed within 3 months)
8. Already involved in a clinical trial where the intervention being trialled is likely to confound the outcome of this trial
9. Considered by the treating physician to have a life expectancy of less than 12 months†
10. Inability to provide consent or follow study instructions due to psychological illness or other condition
11. Pregnant or planning to be pregnant during the trial period

†After preliminary review of screening logs, the protocol was amended such that from 8 March 2012, two criteria – to be within 36 months of starting dialysis and to be under 75 years of age – were removed. BLOCADE, Beta-blocker to LOwer CArdiovascular Dialysis Events.

After the baseline visit and review of the electrocardiograph, all participants commenced carvedilol 3.125 mg twice daily then increased to 6.25 mg twice daily in the 6-week run-in period (Table 2). Participants must tolerate carvedilol 6.25 mg twice daily to be randomized. Randomization was conducted using an interactive voice response system provided by the National Health and Medical Research Council Clinical Trials Centre in Sydney, Australia, with an adaptive allocation algorithm designed to minimize imbalances at each study site and across dialysis modality (haemodialysis or peritoneal dialysis) within the two treatment groups.

After randomization, participants continued study drug (carvedilol *or* placebo) 6.25 mg twice daily for 2 weeks, then doubled

Table 2 Schedule of visits for the BLOCADE Feasibility Study

Study phase	BA	Run-in†			RA	Titration†					Follow-up†				End of study†		
		R0	R2	R4		T2	T4	T6	T8‡	T10‡	F3	F6	F9	F12	E2	E4	E6§
Assessment																	
History	X																
Examination	X																
Height	X																
Heart rate	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ABPM (optional)	X											X					
IDH			X			X	X				X	X					
Home BP (optional)	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Dry weight	X	X			X						X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug dispensed		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X										X			X			
ECHO		X															
BNP		X										X		X			
Laboratory studies		X			X							X		X			
Quality of life (EQ5D)	X											X		X			
Serious adverse events and adverse drug reactions			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Study phases are: baseline assessment (BA), a run-in phase (R0 to R4 in weeks), randomization (RA), a titration phase (T2 to T10 in weeks), follow-up phase (F3 to F12 in months) and end of study (E2 to E6 in weeks). †Visit windows: run-in = ±4 days; titration = ±4 days; follow-up = ±1 week; end of study = ± 4days; ‡only if required; §study coordinator would contact participant by telephone 1 month after complete cessation of study drug to ascertain vital status and determine if adverse events occurred during this period. ABPM, 24 h ambulatory blood pressure monitoring; BLOCADE, Beta-blocker to LOwer CArdiovascular Dialysis Events; BNP, measurement of plasma B-type natriuretic peptide; ECG, electrocardiograph; ECHO, echocardiograph; EQ-5D, EuroQol-5D; home BP, blood pressure measurement by the participant at home; IDH, intra-dialytic hypotension.

the dose every 2 weeks in the titration phase until they reached the maximum tolerated dose or 25 mg twice daily. Participants must have a heart rate above 55 beats per minute, a systolic blood pressure above 95 mmHg and no heart failure admission in the previous 2 weeks for the site investigator to increase the dose. The titration phase lasted up to 10 weeks (Table 2) to allow extra time to achieve the maximum tolerated dose if clinical circumstances require deferring a dose increase, temporary dose reduction, reducing other blood pressure-lowering agents or adjusting volume state.

Participants continued a stable dose of study drug during the follow-up phase. Dose changes were discouraged but allowed provided the dose was not less than 6.25 mg twice daily, unless the site investigator anticipates this to be temporary. A hypotension algorithm (Fig. 2) was provided to highlight common causes of hypotension in patients undergoing dialysis and assist investigators to keep participants in the study. Additional antihypertensive therapy was allowed but beta-blocking agents verapamil, diltiazem or moxonidine were not allowed to avoid exacerbating the negative chronotropic effects of carvedilol, and to avoid rebound hypertension if beta-blocking agents and moxonidine are combined (with moxonidine ceased first).

After 12 months, supervised down-titration of the study drug was followed by a telephone visit 1 month later to ascertain vital status. Supervised down-titration is important because 11.5% of patients in the Carvedilol or Metoprolol European Trial of heart failure who switched from blinded beta-blocking agent to another beta-blocking agent experienced an adverse event.[19] Participants underwent end of study down-titration even if the treating physician wanted them to continue carvedilol after the study was completed to maintain blinding.

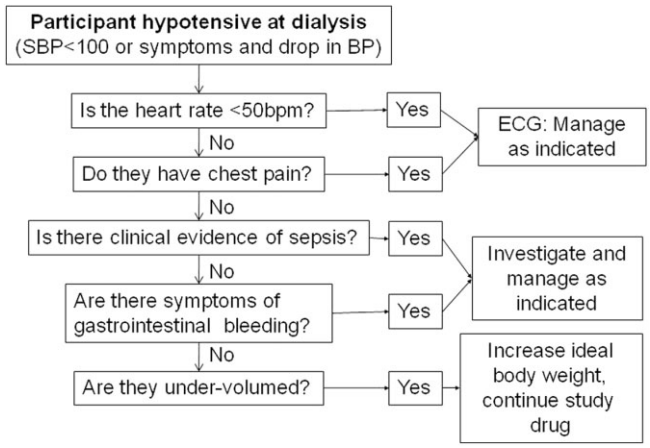

Fig. 2 Study algorithm for suggested investigation and management of hypotension. SBP, systolic blood pressure; bpm, beats per minute; ECG, electrocardiograph.

Participants, investigators, Australasian Kidney Trials Network (AKTN) coordinating centre staff and outcome assessors were all blinded to treatment assignment in the BLOCADE Feasibility Study.

Measurement issues

Blood pressure

Blood pressure measurement in haemodialysis patients is prone to substantial variation at the haemodialysis unit.[20] Two measures that

Table 3 Outcome measures used in the BLOCADE Feasibility Study

Outcome	Reported as (unit)
Primary feasibility outcome	
Proportion of participants who complete the run-in phase on carvedilol 6.25 mg twice daily	% (95% CI)
Other tolerability outcome measures	
Proportion of participants randomized to carvedilol (or placebo) that discontinue carvedilol (or placebo) due to any adverse event attributable to carvedilol	% (95% CI)
Incidence of symptomatic hypotension or bradycardia in participants randomized to carvedilol (or placebo)	Events per unit time
All adverse events and serious adverse events in participants randomized to carvedilol (or placebo)	Events per unit time
Measures relevant to sample size estimation	
Proportion of participants randomized to carvedilol (or placebo) that discontinue carvedilol (or placebo) for any reason	% (95% CI)
The overall post-randomization rate of the proposed composite primary outcome for a larger study	Events per unit time
Measurements relevant to logistics of a larger study	
Overall recruitment rate	Number per month
Proportion of screened patients eligible for run-in	% (95% CI)
Proportion of eligible patients who actually enter run-in	% (95% CI)
The distribution of the three study drug strengths (6.25 mg, 12.5 mg and 25 mg) among participants randomized to carvedilol *versus* placebo	Number (%)
Secondary outcomes	
Change in plasma B-type natriuretic peptide over time (at 6 and 12 months separately) in participants randomized to carvedilol compared with placebo	Mean change
Change in EuroQol-5D quality of life score over time (at 6 and 12 months separately) in participants randomized to carvedilol compared with placebo	Mean change
Tertiary (exploratory) outcomes	
Incidence of intra-dialytic hypotension in the run-in phase	Events per unit time
Incidence of intra-dialytic hypotension post-randomization in participants randomized to carvedilol *versus* placebo	Events per unit time

BLOCADE, Beta-blocker to LOwer CArdiovascular Dialysis Events; CI, confidence interval.

perform well compared with 44 h ambulatory inter-dialytic blood pressure measurement are the post-dialysis blood pressure and the median dialysis unit blood pressure.[21] Thus, blood pressure was measured, using manual or automated sphygmomanometer according to local practice, as follows:

- The post-dialysis blood pressure was recorded and used for dose titration decisions. The average of three readings measured 15 min after the haemodialysis procedure with the participant seated upright was recorded.
- The median of at least four blood pressure measurements from the haemodialysis procedure was calculated using an Excel-based calculator and recorded.
- For peritoneal dialysis patients and non-haemodialysis unit study visits, the average of three measurements 5 min apart with the participant seated upright was recorded.

Echocardiography

Echocardiography was used to measure LV volumes, LV ejection fraction, left atrial volume, ratio of mitral peak velocity of early filling to early diastolic mitral annular velocity (E : E′), ratio of mitral peak velocity of early filling to mitral peak velocity of late filling (E : A), diastolic filling time (EA duration) and global strain. These characteristics may be associated with whether a participant was able to remain on carvedilol. Because the ability to obtain timely echocardiograms varied from site to site, a 4-week window from starting carvedilol in the run-in phase was allowed (Table 2). For haemodialysis patients, echocardiography was performed as soon after dialysis as possible with participants as close as possible to their dry weight. The cardiac imaging departments at all sites performed echocardiography on local machines according to a pre-defined protocol and electronic copies were stored at the Core Laboratory (Princess Alexandra Hospital, Brisbane). Assessment of myocardial parameters of stored images using Velocity Vector Imaging software (Siemens Medical Solutions, Mountain View, CA, USA) was performed at the Core Laboratory blinded to treatment allocation.

Laboratory tests

Standard biochemical measurements such as serum potassium, liver function tests and full-blood examination were performed in hospital laboratories with appropriate regulatory accreditation to monitor for adverse reactions. Cardiac troponin was measured by the local laboratory at baseline to assist adjudication of future events and abnormal levels were expected.[22] The baseline cardiac troponin result was recorded and given the clinical complexity, action was taken if the cardiac troponin was abnormal at the discretion of the site investigator. Participants had blood collected immediately before the haemodialysis procedure, transported to the laboratory on ice, centrifuged at 3200g and aliquots of serum and plasma stored at −70°C. These were used for measurement of BNP and other biochemical markers.

Outcomes

The BLOCADE Feasibility Study had primary, secondary and tertiary objectives that determine the important outcomes assessed (Table 3). The primary feasibility outcome was the proportion of participants who entered the run-in phase and completed it by tolerating carvedilol 6.25 mg twice daily and progressing to randomization.

Safety monitoring included collecting data on potential drug-related and other adverse events. To assist sample size estimation, data relating to the proposed primary outcome and proportion of participants who cease study drug post-randomization for reasons such as kidney transplant, patient choice or need for open-label beta-blocking agent were collected. Cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and resuscitated cardiac arrest were the proposed composite primary outcome and were adjudicated by an independent Endpoint Adjudication Committee (Appendix) blinded to treatment allocation. Although the process for measuring these outcomes will be tested, this feasibility study is not powered to provide an event rate estimate sufficiently reliable for sample size estimation for a larger study.

Screening log data provided important logistical information regarding the number of patients screened, those screened and eligible that agree to participate and the overall recruitment rate (Table 3). These data allow estimation of the potential participant pool size required for a study testing effects on hard clinical outcomes. Reporting the distribution of the three different strengths of carvedilol and placebo in randomized participants will help plan the most efficient way to provide study drug in a larger trial.

Secondary objectives were to assess the effect of carvedilol on biochemical markers such as BNP, and on quality of life. A tertiary objective for patients receiving haemodialysis was to determine whether the blood pressure-lowering effects of carvedilol contribute to intra-dialytic hypotension (IDH). This is defined as the occurrence of all three of: (i) fall in systolic blood pressure ≥20 mmHg; (ii) symptoms of hypotension; and (iii) requirement for treatment with Trendelenburg manoeuvre, saline infusion or modifying the ultrafiltration rate. We measured IDH at specific time periods, including three times after a dose increase (Table 2), by obtaining a completed IDH Case Report Form for every haemodialysis session over the 2 weeks following these visits. Targeting specific time periods ensured an accurate and consistent denominator to use in calculating the number of episodes of IDH in each treatment group.

Statistical considerations

It is critical in planning a large clinical endpoint study to know the proportion of participants that progress from screening to randomization, in order to calculate the number of patients and dialysis centres required. The planned sample size of 150 patients to enter the run-in phase was based on a confidence interval approach for estimating the proportion of patients who tolerate carvedilol during this phase. Assuming a tolerability of 70%, 150 patients give 95% confidence limits of 62.5% and 77.5%. Of note, 14% discontinued carvedilol in the run-in phase of a previous RCT.[9] In RCTs of blood pressure-lowering agents in dialysis patients, between 0 and 34% of participants discontinued therapy after randomization.[23]

The primary outcome will be estimated using an intercept-only generalized linear model from the binomial family with identity link function to determine the binomial proportions and 95% confidence intervals for the proportion of participants who completed the run-in phase. This model will be used to estimate the proportion of participants who discontinued study drug after randomization and compare groups. The incidence rate of IDH will be estimated using an intercept-only Poisson regression model with randomized treatment group as a covariate to compare incidence rates for IDH between groups.

Outcome data from all randomized participants will be analysed according to the intention-to-treat principle. We will separately analys BNP and EQ5D using a linear mixed model with treatment group and baseline measurements as fixed effects and participant identifier and study visit as random effects. The effect of intervention group on outcome will be adjusted for baseline measurements. In addition, a logistic regression model will be used to predict successful completion of the run-in phase from baseline BNP measurements.

Sub-studies

Two sub-studies evaluated different methods of blood pressure measurement and described the effect of carvedilol on blood pressure. Participants in the Home Blood Pressure sub-study received an Omron HEM7211 Premium Blood Pressure Device and blood pressure diary to record the average of three blood pressure measurements 5 min apart at three specific time points during the middle 15 h period between haemodialysis sessions.[24] The 24 h Ambulatory Blood Pressure (ABPM) sub-study was performed at sites able to undertake it using local facilities and protocols. Participants had an ABPM device fitted immediately after the mid-week haemodialysis session to measure their 24 h ABPM at baseline and 6 months after therapy.

Regulatory issues

The BLOCADE Feasibility Study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12609000174280) on 16 April 2009 and with first ethics approval from the University of Queensland Medical Research Ethics Committee on 12 May 2009 (Project number 2009000775).

The BLOCADE Feasibility Study was overseen by a Trial Management Committee and centrally coordinated by the AKTN (University of Queensland, Princess Alexandra Hospital, Brisbane). The safety of participants in the BLOCADE Feasibility Study was overseen by a Data Safety Monitoring Board (Appendix).

DISCUSSION

The high morbidity and mortality from CVD in patients with ESKD have not improved commensurate with event reductions in the general population.[25] The rationale for an RCT of beta-blocking agent in patients receiving dialysis is that these patients have sympathetic nervous system overactivity[7] and that beta-blocking agents demonstrate strong benefit in CVDs prevalent in ESKD, including heart failure patients with CKD.[8] The clinical equipoise is the possibility of increased harm through symptomatic hypotension and is highlighted by the large variation in practice that exists both between countries[26] and between states within a country.[27]

A feasibility study is an important prerequisite to a large-scale clinical endpoint trial[28] when critical factors important to the design of such a study are unknown. Unknown factors relevant to BLOCADE include the proportion of patients who meet eligibility criteria, the proportion of patients already receiving beta-blocking agents, the preparedness of patients and clinicians to stop beta-blocking agents to enter the study, the ability of sites to recruit patients and the proportion of patients unable to stay on study drug due to

tolerability, comorbid illnesses, kidney transplant or choosing to discontinue. A feasibility study should have clear aims[29] and for the BLOCADE Feasibility Study, this is to determine the proportion of eligible patients with ESKD, who are prone to marked variations in blood pressure, that can tolerate the lowest acceptable dose.

In conclusion, the BLOCADE Feasibility Study will provide randomized data on the tolerability of carvedilol in patients receiving dialysis that will inform the design of a large clinical endpoint study, and data relevant to sample size estimation and logistical issues of such a study. Ultimately, it will help determine whether conducting such an important RCT is feasible.

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APPENDIX

Trial Management Committee

Matthew A Roberts (Chair), Department of Renal Medicine, Eastern Health Clinical School, Monash University, Melbourne, Australia; Alan Cass, Menzies School of Health Research, Charles Darwin University, Darwin, Northern Territory, Australia; Amit X Garg, Division of Nephrology, Department of Medicine, Western University, London, Canada; Carmel M Hawley, Australasian Kidney Trials Network, The University of Queensland, Brisbane; Francesco L Ierino, Department of Nephrology, Austin Health, Melbourne, Australia; Nicole M Isbel, Department of Nephrology, Princess Alexandra Hospital, Brisbane, Australia; Henry Krum, Centre of Cardiovascular Research and Education in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; Elaine M Pascoe, Australasian Kidney Trials Network, The University of Queensland, Brisbane, Australia; Vlado Perkovic, The George Institute for Global Health, Sydney, Australia; Helen L Pilmore, Department of Renal Medicine, Auckland City Hospital, Auckland, New Zealand; Andrew M Tonkin, Cardiovascular Research Unit, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia; and Liza A Vergara, Australasian Kidney Trials Network, The University of Queensland, Brisbane, Australia.

Data Safety Monitoring Board

Adeera Levin (Chair), Department of Medicine, University of British Columbia, Vancouver, Canada; David Hare, Cardiology Department, Austin Health, Melbourne, Australia; Andrew Martin, University of Sydney, Sydney, Australia; and David C Wheeler, Centre for Nephrology, Royal Free and University College Medical School, London, the United Kingdom.

Endpoint Adjudication Committee

Greg Fulcher (Chair), Royal North Shore Hospital, Sydney, Australia; Helen Brown, Princess Alexandra Hospital, Brisbane, Australia; David Colquhoun, Wesley Medical Centre, Brisbane, Australia; Dariusz Korczyk, Princess Alexandra Hospital, Brisbane, Australia; Amanda Mather, Royal North Shore Hospital, Sydney, Australia; and Andrew Wong, Royal Brisbane and Women's Hospital, Brisbane, Australia.

Project Management Team

Australasian Kidney Trials Network, Brisbane, Queensland, Australia: Carmel Hawley (Chair, AKTN Operations Secretariat), Sunil Badve, Alan Cass, Alicia Morrish, Elaine Pascoe, Peta-Anne Paul-Brent, Donna Reidlinger, Anish Scaria and Liza Vergara.

REFERENCES

1. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta-blockade after myocardial infarction: Systematic review and meta regression analysis. *BMJ* 1999; **318**: 1730–7.
2. Shibata MC, Flather MD, Wang D. Systematic review of the impact of beta-blockers on mortality and hospital admissions in heart failure. *Eur. J. Heart Fail.* 2001; **3**: 351–7.
3. McMurray J, Køber L, Robertson M *et al*. Antiarrhythmic effect of carvedilol after acute myocardial infarction: Results of the Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction (CAPRICORN) trial. *J. Am. Coll. Cardiol.* 2005; **45**: 525–30.
4. Adamson PB, Gilbert EM. Reducing the risk of sudden death in heart failure with beta-blockers. *J. Card. Fail.* 2006; **12**: 734–46.
5. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am. J. Kidney Dis.* 1998; **32**: S112–19.
6. Whalley GA, Marwick TH, Doughty RN *et al*. Effect of early initiation of dialysis on cardiac structure and function: Results from the echo substudy of the IDEAL trial. *Am. J. Kidney Dis.* 2013; **61**: 262–70.
7. Converse RL, Jr, Jacobsen TN, Toto RD *et al*. Sympathetic overactivity in patients with chronic renal failure. *N. Engl. J. Med.* 1992; **327**: 1912–18.
8. Badve SV, Roberts MA, Hawley CM *et al*. Effects of beta-adrenergic antagonists in patients with chronic kidney disease: A systematic review and meta-analysis. *J. Am. Coll. Cardiol.* 2011; **58**: 1152–61.
9. Cice G, Ferrara L, D'Andrea A *et al*. Carvedilol increases two-year survival in dialysis patients with dilated cardiomyopathy: A

prospective, placebo-controlled trial. *J. Am. Coll. Cardiol.* 2003; **41**: 1438–44.
10. Agarwal R, Sinha AD, Pappas MK, Abraham TN, Tegegne GG. Hypertension in hemodialysis patients treated with atenolol or lisinopril: A randomized controlled trial. *Nephrol. Dial. Transplant.* 2014; **29**: 672–81.
11. Wali RK, Iyengar M, Beck GJ *et al*. Efficacy and safety of carvedilol in treatment of heart failure with chronic kidney disease: A meta-analysis of randomized trials. Circ. *Heart Fail.* 2011; **4**: 18–26.
12. Bakris GL, Fonseca V, Katholi RE *et al*. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: A randomized controlled trial. *JAMA* 2004; **292**: 2227–36.
13. Bakris GL, Hart P, Ritz E. Beta-blockers in the management of chronic kidney disease. *Kidney Int.* 2006; **70**: 1905–13.
14. Dulin B, Abraham WT. Pharmacology of carvedilol. *Am. J. Cardiol.* 2004; **93**: 3–6.
15. Kojima M, Sato K, Kimura G, Ueda R, Dohi Y. Carvedilol reduces elevated B-type natriuretic peptide in dialyzed patients without heart failure: Cardioprotective effect of the beta-blocker. *J. Cardiovasc. Pharmacol.* 2007; **49**: 191–6.
16. Roberts MA, Srivastava PM, Macmillan N *et al*. B-type natriuretic peptides strongly predict mortality in patients who are treated with long-term dialysis. Clin. *J. Am. Soc. Nephrol.* 2008; **3**: 1057–65.
17. Gutierrez OM, Tamez H, Bhan I *et al*. N-terminal Pro-B-Type natriuretic peptide concentrations in hemodialysis patients: Prognostic value of baseline and follow-up measurements. *Clin. Chem.* 2008; **54**: 1339–48.
18. Glasziou P, Alexander J, Beller E, Clarke P. Which health-related quality of life score? A comparison of alternative utility measures in patients with Type 2 diabetes in the ADVANCE trial. *Health Qual. Life Outcomes* 2007; **5**: 21–31.
19. Di Lenarda A, Remme WJ, Charlesworth A *et al*. Exchange of beta-blockers in heart failure patients. Experiences from the poststudy phase of COMET (the Carvedilol or Metoprolol European Trial). *Eur. J. Heart Fail.* 2005; **7**: 640–9.
20. Roberts MA, Pilmore HL, Tonkin AM *et al*. Challenges in blood pressure measurement in patients treated with maintenance hemodialysis. *Am. J. Kidney Dis.* 2012; **60**: 463–72.
21. Agarwal R, Light RP. Median intradialytic blood pressure can track changes evoked by probing dry-weight. *Clin. J. Am. Soc. Nephrol.* 2010; **5**: 897–904.
22. Hickman PE, Koerbin G, Southcott E *et al*. Newer cardiac troponin I assays have similar performance to troponin T in patients with end-stage renal disease. *Ann. Clin. Biochem.* 2007; **44**: 285–9.
23. Heerspink HJ, Ninomiya T, Zoungas S *et al*. Effect of lowering blood pressure on cardiovascular events and mortality in patients on dialysis: A systematic review and meta-analysis of randomised controlled trials. *Lancet* 2009; **373**: 1009–15.
24. Agarwal R, Light RP. Chronobiology of arterial hypertension in hemodialysis patients: Implications for home blood pressure monitoring. *Am. J. Kidney Dis.* 2009; **54**: 693–701.
25. Roberts MA, Polkinghorne KR, McDonald SP, Ierino FL. Secular trends in cardiovascular mortality rates of patients receiving dialysis compared with the general population. *Am. J. Kidney Dis.* 2011; **58**: 64–72.
26. Tentori F. Trends in medication use and clinical outcomes in twelve countries: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Contrib. Nephrol.* 2008; **161**: 48–54.
27. Wetmore JB, Mahnken JD, Mukhopadhyay P *et al*. Geographic variation in cardioprotective antihypertensive medication usage in dialysis patients. *Am. J. Kidney Dis.* 2011; **58**: 73–83.
28. Thabane L, Ma J, Chu R *et al*. A tutorial on pilot studies: The what, why and how. *BMC Med. Res. Methodol.* 2010; **10**: 1.
29. Lancaster GA, Dodd S, Williamson PR. Design and analysis of pilot studies: Recommendations for good practice. *J. Eval. Clin. Prac.* 2004; **10**: 307–12.