



## The $\beta$ -Blocker to Lower Cardiovascular Dialysis Events (BLOCADE) Feasibility Study: A Randomized Controlled Trial

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**Background:**  $\beta$ -Blocking agents reduce cardiovascular mortality in patients with heart disease, but their potential benefit in dialysis patients is unclear. We aimed to determine the feasibility of a randomized controlled trial (RCT).

**Study Design:** Pilot RCT.

**Setting & Participants:** Patients who received dialysis for 3 or more months and were 50 years or older (or  $\geq 18$  years with diabetes or cardiovascular disease) were recruited from 11 sites in Australia and New Zealand. We aimed to recruit 150 participants.

**Intervention:** After a 6-week run-in with the  $\beta$ -blocker carvedilol, we randomly assigned participants to treatment with carvedilol or placebo for 12 months.

**Outcomes & Measurements:** The prespecified primary outcome was the proportion of participants who tolerated carvedilol, 6.25 mg, twice daily during the run-in period. After randomization, we report participant withdrawal and the incidence of intradialytic hypotension (IDH).

**Results:** Of 1,443 patients screened, 354 were eligible, 91 consented, and 72 entered the run-in stage. 49 of 72 run-in participants (68%; 95% CI, 57%-79%) achieved the primary outcome. 5 of the 23 withdrawals from run-in were attributable to bradycardia or hypotension. After randomization, 10 of 26 allocated to carvedilol and 4 of 23 allocated to placebo withdrew. 4 participants randomly assigned to carvedilol withdrew because of bradycardia or hypotension. Overall, there were 4 IDH events per 100 hemodialysis sessions; in participants allocated to carvedilol versus placebo, respectively, there were 7 versus 2 IDH events per 100 hemodialysis sessions ( $P = 0.1$ ) in the 2 weeks immediately following a dose increase and 4 versus 3 IDH events per 100 hemodialysis sessions after no dose increase ( $P = 0.7$ ).

**Limitations:** Unable to recruit planned sample size.

**Conclusions:** Recruiting patients receiving dialysis to an RCT of  $\beta$ -blocker versus placebo will prove challenging. Possible solutions include international collaboration and exploring novel trial designs such as a registry-based RCT.

*Am J Kidney Dis.* 67(6):902-911. © 2016 by the National Kidney Foundation, Inc.

**INDEX WORDS:** Beta-blocker; carvedilol; Dilatrend; adrenergic receptor blockade; dialysis; hemodialysis; cardiovascular disease (CVD); cardiovascular mortality; intradialytic hypotension (IDH); bradycardia; feasibility study; study recruitment; drug tolerability; randomized controlled trial (RCT); end-stage kidney disease (ESKD).

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Received June 10, 2015. Accepted in revised form October 27, 2015. Originally published online December 22, 2015.

Trial registration: [www.anzctr.org.au](http://www.anzctr.org.au); study number: 1260900 0174280.

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0272-6386

<http://dx.doi.org/10.1053/j.ajkd.2015.10.029>

## Editorial, p. 822

The increased prevalence of cardiovascular diseases in patients with end-stage kidney disease requiring dialysis contributes to their high morbidity and mortality.<sup>1,2</sup> Sympathetic nervous system overactivity in this population<sup>3</sup> has deleterious cardiovascular effects.  $\beta$ -Adrenergic receptor antagonists, or  $\beta$ -blockers, reduce sympathetic nervous system activity and reduce morbidity and mortality in randomized controlled trials (RCTs) that recruited people with cardiac disease.<sup>4,5</sup> Therefore, a role for  $\beta$ -blockers as a cardiac “protection” strategy in end-stage kidney disease is highly plausible.<sup>6,7</sup>

Most RCTs of cardiovascular therapies have excluded patients with advanced chronic kidney disease.<sup>8</sup> A meta-analysis of RCTs studying  $\beta$ -blockers in chronic kidney disease demonstrated that participants receiving a  $\beta$ -blocker had a 28% relative risk reduction and a 6% absolute risk reduction in mortality after 1 to 2 years of follow-up.<sup>9</sup> These studies were predominantly trials in heart failure and recruited few patients with chronic kidney disease stages 4 or 5. Only a single trial recruited individuals receiving dialysis. This trial randomly assigned 114 hemodialysis patients with comorbid heart failure to treatment with the  $\beta$ -blocker carvedilol or placebo and detected reduced mortality in patients receiving carvedilol.<sup>10</sup> This result has not been replicated. Agarwal et al<sup>11</sup> randomly assigned 200 maintenance hemodialysis patients with hypertension and left ventricular hypertrophy to the  $\beta$ -blocker atenolol or the angiotensin-converting enzyme inhibitor lisinopril in the Hypertension in Hemodialysis Patients Treated With Atenolol or Lisinopril (HDPAL) Study. This trial was terminated by the data safety monitoring board because of increased serious adverse cardiovascular events in the lisinopril group, suggesting that atenolol may be superior to lisinopril in patients receiving hemodialysis. Despite the potential promise of  $\beta$ -blockers in patients receiving dialysis, the RCT evidence relating to efficacy and safety is limited to these 2 trials.

Carvedilol, an antagonist of  $\beta_1$ -,  $\beta_2$ -, and  $\alpha_1$ -adrenergic receptors, is eliminated wholly by hepatic metabolism, highly protein bound, and not removed with hemodialysis. It has antioxidant properties and a good metabolic profile in comparison to other  $\beta$ -blockers.<sup>12-14</sup> However, blood pressure lowering from  $\alpha_1$ -adrenergic receptor blockade might increase the risk for symptomatic hypotension when fluid is removed during hemodialysis and thus reduce tolerability of this  $\beta$ -blocker.

A large-scale placebo-controlled RCT to determine whether treatment with a  $\beta$ -blocker reduces morbidity and mortality in patients receiving dialysis would

require many thousands of patients and considerable resources. Restricting recruitment to patients considered to have higher cardiac risk may increase the event rate and reduce the sample size required. We therefore performed the  $\beta$ -Blocker to Lower Cardiovascular Dialysis Events (BLOCADE) Feasibility Study with the prespecified primary aim to determine the proportion of patients who could tolerate carvedilol at a dose of 6.25 mg twice daily.

## METHODS

## Study Overview

The BLOCADE Feasibility Study was a randomized, double-blind, placebo-controlled, parallel-group study.<sup>15</sup> All participants received carvedilol in a 6-week run-in phase, and those who tolerated carvedilol, 6.25 mg, twice daily were randomly assigned 1:1 to receive carvedilol or placebo (up to 25 mg twice daily) for 12 months. The University of Queensland Medical Research Ethics Committee approved the study (project number: 2009000775), as did ethics committees of the individual sites. All participants provided written informed consent, and study conduct adhered to the Declaration of Helsinki.

## Participants

We initially included patients who: (1) consented; (2) were receiving either hemodialysis or peritoneal dialysis for more than 3 months and less than 36 months; (3) were 50 years or older or 18 years or older with comorbid diabetes and/or cardiovascular disease, but younger than 75 years; and (4) whose treating physician agreed to their participation. We excluded patients who: (1) had living donor kidney transplantation scheduled within 6 months, (2) had a cardiovascular disease event in the preceding 3 months, (3) had a definite contraindication to  $\beta$ -blockers, (4) were currently receiving a  $\beta$ -blocker or other disallowed agent, (5) were considered clinically too unstable by the treating physician, (6) had an unstable target weight, (7) had severely decreased hepatic function, (8) were enrolled in another trial, (9) were 75 years or older, (10) were unable to provide consent or follow study instructions, or (11) were pregnant or planning pregnancy. Disallowed medications included other  $\beta$ -blockers, verapamil, diltiazem, and moxonidine (a drug that acts by  $I_1$ -imidazoline receptors in the central nervous system to reduce sympathetic nervous system activity). Patients already receiving a  $\beta$ -blocker could undergo supervised downtitration and cessation of their  $\beta$ -blocker treatment and become eligible after a 2-week washout period. After review of the first 12 months of recruitment, the inclusion criteria were amended in March 2012 to allow for inclusion of patients older than 75 years or who had received dialysis for more than 36 months and instead exclude patients who were thought unlikely to be alive in 12 months.

## Intervention and Control

The experimental intervention was the  $\beta$ -blocker carvedilol (Dilatrend; F. Hoffmann-La Roche Ltd) taken orally twice daily. The control was placebo, and both drug and placebo were encapsulated to render them identical.

## Study Procedures

Participants commenced treatment with carvedilol, 3.125 mg, twice daily in the run-in phase. After 2 weeks, carvedilol dosage was increased to 6.25 mg twice daily. Only participants receiving this dose by 6 weeks progressed from run-in to randomization. Participants were randomly assigned using an interactive voice response system (National Health and Medical Research Council

Clinical Trials Centre, Sydney, Australia) with an adaptive allocation algorithm to minimize treatment imbalances at each study site and across dialysis modality (hemodialysis or peritoneal dialysis). Participants, investigators, Australasian Kidney Trials Network coordinating center staff, and outcome assessors remained blinded to treatment assignment.

After randomization, the allocated study drug was continued at 6.25 mg twice daily for 2 weeks, and the dose was doubled every 2 weeks until 25 mg twice daily or the maximum tolerated dose was achieved. Criteria for safe dose increase included heart rate > 55 beats/min, systolic blood pressure > 95 mm Hg, and no heart failure admission in the previous 2 weeks. This achieved dose was continued for 12 months before supervised downtitration and cessation of the study drug at the end of the study. Adjustments of volume state and concomitant medications were allowed provided participants remained on treatment with at least 6.25 mg twice daily.

### Outcomes

The primary outcome was the proportion of participants entering the run-in phase who tolerated carvedilol, 6.25 mg, twice daily and progressed to randomization. Other outcomes included the proportion of randomly assigned participants who discontinued study drug and the incidence of symptomatic bradycardia or hypotension and other adverse events. Outcomes related to logistics of a larger study included the proportion of screened patients considered eligible, the proportion of eligible patients who entered the run-in phase, the distribution of study drug dosages post-randomization, and the overall recruitment rate. The overall recruitment rate was defined as the rate of recruitment of participants to the run-in phase over the course of the entire study (patients per month). A secondary outcome measure reported is quality of life measured using the EQ-5D (EuroQol Research Foundation) instrument that performs well compared with more detailed instruments.<sup>16</sup>

An exploratory outcome in patients receiving hemodialysis was the occurrence of intradialytic hypotension (IDH), defined as the occurrence of all 3 of: (1) decrease in systolic blood pressure  $\geq$  20 mm Hg, (2) symptoms of hypotension, and (3) requirement for treatment. We measured IDH at specific times by obtaining a completed IDH Case Report Form for every hemodialysis session (6 sessions) during the 2 weeks following these visits.

### Statistical Considerations

The planned sample size of 150 patients to enter the run-in phase was based on a confidence interval (CI) approach for the primary outcome. Assuming 70% of patients who enter the run-in tolerate carvedilol, 150 patients would give sufficiently narrow 95% confidence limits of 62.5% and 77.5%.

The primary outcome was estimated using an intercept-only generalized linear model from the binomial family with identity link function to determine the binomial proportions and 95% CIs for the proportion of participants who completed the run-in phase. This model was used to separately determine the proportion of participants within each group who discontinued study drug after randomization. The incidence rate of IDH during run-in was estimated using an intercept-only Poisson regression model, and incidence rates for IDH between randomly assigned treatment groups were compared using a Poisson regression model with treatment group as a covariate.

Outcome data from all randomly assigned participants were analyzed according to the intention-to-treat principle. Baseline characteristics were compared between groups using *t* test or appropriate nonparametric tests for continuous variables and  $\chi^2$  tests for categorical variables. We analyzed EQ-5D separately at 2 follow-up times using analysis of covariance to adjust the effect of the intervention group for baseline EQ-5D measurements.

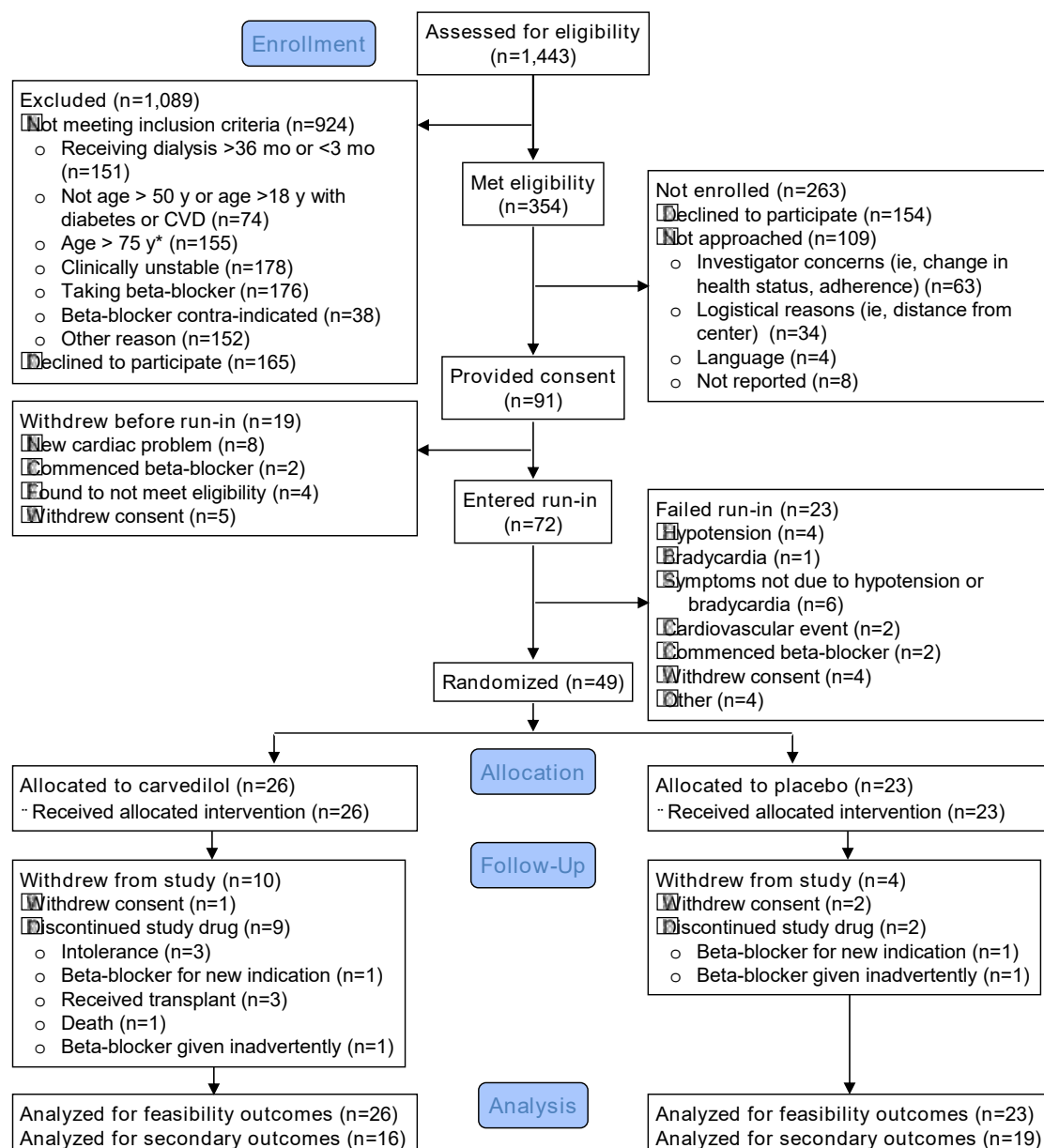
## RESULTS

The BLOCADE Feasibility Study commenced recruiting in May 2011; a total of 11 sites in Australia and New Zealand participated. Slow recruitment led to a protocol amendment in March 2012. Prior to this, entry criteria excluded patients who had commenced dialysis therapy more than 36 months prior and those older than 75 years. These criteria were removed because combined, they were the reason for exclusion of 42% of screened patients. Recruiting ceased in February 2013 because the planned sample size could not be achieved in an acceptable time frame.

Of 1,443 patients screened: 354 (25%; 95% CI, 22%-27%) were eligible, 91 of these (26%; 95% CI, 21%-30%) gave informed consent, and 72 (20%; 95% CI, 16%-25%) entered the run-in phase. Thus, we screened approximately 20 patients to enter 1 participant (Fig 1). The other major reasons for nonparticipation included patients being considered too clinically unstable and patients already receiving a  $\beta$ -blocker. Only 6 patients receiving a  $\beta$ -blocker at the time of screening ceased treatment with the  $\beta$ -blocker to become eligible for the run-in. Of these, 3 participated and completed the run-in phase. One other patient had a resuscitated cardiac arrest soon after completing supervised downtitration of  $\beta$ -blocker therapy to enter the study. This person survived but did not enter the study.

The primary outcome was that 49 of these 72, or 68% (95% CI, 57%-79%), tolerated carvedilol 6.25 mg twice daily and progressed from run-in to randomization. Participants who completed the run-in phase had lower hemoglobin levels but otherwise did not differ substantially on baseline demographic and clinical characteristics from those who did not complete the run-in phase (Table S1, available as online supplementary material). Of the 23 participants not completing the run-in phase, 5 had bradycardia or hypotension potentially attributable to carvedilol; the rest withdrew for other reasons. No participant receiving peritoneal dialysis withdrew because of hypotension or bradycardia, but there was no difference in the proportion of participants receiving peritoneal dialysis between those who completed and did not complete the run-in. Sixteen participants had at least 1 serious adverse event (SAE) in the run-in phase: 7 (30%) of the 23 participants not completing the run-in and 9 of the 49 (18%) participants who did ( $P = 0.3$ ). All SAEs were associated with hospitalizations (Table S2).

Participants randomly assigned to carvedilol tended to be younger and were more likely to be women and have a shorter median dialysis vintage than those randomly assigned to placebo (Table 1). After randomization, 10 of 26 (38%; 95% CI, 20%-57%)



**Figure 1.** Flow diagram of participants from screening to end of study. Abbreviation: CVD, cardiovascular disease.

participants allocated to carvedilol withdrew during follow-up compared with 4 of 23 (17%; 95% CI, 2%-33%) receiving placebo. Four (15%; 95% CI, 2%-29%) participants receiving carvedilol, compared to none receiving placebo, withdrew because of events attributable to carvedilol, such as bradycardia, hypotension, or dizziness (Table 2). Three participants in the carvedilol group, but none in the placebo group, received a kidney transplant. One participant in each group withdrew in order to initiate open-label  $\beta$ -blocker therapy. Fourteen participants in each group had a total of 57 SAEs. These were hospitalization events predominantly for dialysis complications (Table 3). There was 1 death and 1 adjudicated

myocardial infarction in a participant randomly assigned to carvedilol; no such events occurred in the placebo group.

Throughout titration and follow-up, the majority of randomly assigned participants received study drug at the maximum dose of 25 mg twice daily (Fig 2). At 12 months, 11 of 16 (69%) remaining participants allocated to carvedilol and 16 of 19 (84%) allocated to placebo were receiving this dose. At the 3-month visit, after reaching a stable dose of study drug, participants receiving carvedilol had a mean heart rate of  $69 \pm 8$  (standard deviation) beats/min compared to  $80 \pm 12$  beats/min in the placebo group ( $P = 0.5$ ). Mean blood pressures at



**Table 1.** Baseline Characteristics of Participants in the Feasibility Study by Randomization Status

	Carvedilol (n = 26)	Placebo (n = 23)	P
Male sex	13 (50%)	18 (78%)	0.04
Age, y	56.1 ± 10.3	61.4 ± 13.0	0.1
Ethnicity			0.6
White	16 (62%)	11 (48%)	
New Zealand Maori	3 (12%)	5 (22%)	
Pacific Islander	5 (19%)	6 (26%)	
Other	2 (8%)	1 (4%)	
Cause of ESKD			0.9
Diabetes	14 (54%)	14 (61%)	
Hypertension or vascular	3 (12%)	2 (9%)	
Glomerulonephritis	5 (19%)	5 (22%)	
Other	4 (15%)	2 (9%)	
Diabetes	16 (62%)	15 (65%)	0.8
Hypertension	23 (89%)	21 (91%)	0.7
Coronary disease	2 (8%)	4 (17%)	0.3
Heart failure	0 (0%) <sup>a</sup>	0 (0%)	—
Cerebrovascular disease	4 (15%)	2 (9%)	0.5
Chronic lung disease	3 (12%)	3 (14%)	0.8
Ever smoked	21 (81%)	13 (56%)	0.07
Hemodialysis <sup>b</sup>	19 (73%)	19 (83%)	0.4
Dialysis vintage, mo	13 [9-24]	29 [14-37]	0.03
Daily urine volume			0.3
≤500 mL	15 (65%)	17 (81%)	
501-1,000 mL	6 (26%)	4 (19%)	
>1,000 mL	2 (9%)	0 (0%)	
Weight, kg	89.4 ± 14.2	88.3 ± 19.6	0.6
Body mass index, kg/m <sup>2</sup>	30.9 ± 5.8	29.9 ± 5.4	0.3
Heart rate, beats/min	75 ± 9	79 ± 10	0.3
Systolic blood pressure, mm Hg	135 ± 18	138 ± 17	0.8
Diastolic blood pressure, mm Hg	72 ± 14	76 ± 10	0.9
Cardiac medications			
RAAS antagonist	11 (42%)	7 (30%)	0.4
Lipid-lowering agent	17 (65%)	14 (61%)	0.7
β-Blocker agent	1 (4%)	3 (13%)	0.2
Antiplatelet agent	9 (35%)	7 (30%)	0.8
Calcium channel antagonist	11 (42%)	6 (26%)	0.2
Anticoagulant	1 (4%)	1 (4%)	0.9
Diuretic	10 (39%)	7 (30%)	0.6
Other antihypertensive	1 (4%)	1 (4%)	0.9
Hemoglobin, g/L	106.5 [102-122]	110 [106-116]	0.1
Albumin, g/L	36 [34-39]	36 [34-40]	0.1
Potassium, mmol/L	5.0 [4.6-5.6]	4.6 [4.2-4.9]	0.5

this time were 131 ± 18/68 ± 10 and 139 ± 15/78 ± 12 mm Hg, respectively (*P* = 0.4; [Table S3](#)). Of participants who completed all 3 measures, there was no difference in change in quality of life by either the 3-level descriptive system or visual analogue scale between groups ([Table S4](#)).

**Table 1 (Cont'd).** Baseline Characteristics of Participants in the Feasibility Study by Randomization Status

	Carvedilol (n = 26)	Placebo (n = 23)	P
C-Reactive protein, mg/L	3.3 [1.7-9.0]	4.7 [3.0-8.4]	0.3
Total cholesterol, mmol/L	3.8 [3.1-4.7]	4.1 [3.4-4.7]	0.8
Parathyroid hormone, pmol/L	17.9 [12.9-39.3]	22.1 [12.5-49.7]	0.6

*Note:* Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range].  
Abbreviations: ESKD, end-stage kidney disease; RAAS, renin-angiotensin-aldosterone system.  
<sup>a</sup>One missing observation.  
<sup>b</sup>Remaining patients were receiving peritoneal dialysis.

The overall incidence of IDH following randomization was 4 events per 100 sessions. In the 2 weeks following an increase in dose, participants receiving carvedilol had 7 events per 100 sessions compared to 2 events per 100 sessions with placebo. The incidence rate ratio for IDH events with carvedilol versus placebo was 2.94 (95% CI, 0.70-12.28; *P* = 0.1). In the 2 weeks following no change in dose, there were 4 events per 100 sessions versus 3 events per 100 sessions, respectively. The incidence rate ratio was 1.25 (95% CI, 0.44-3.52; *P* = 0.7). However, neither incidence rate ratio was statistically significant or significantly different from the other.

DISCUSSION

In this feasibility study, the major findings were that 20 patients were required to be screened to enter 1 participant in the run-in phase of an RCT, 68% of participants tolerated what was accepted as the lowest effective dose of carvedilol, and 62% and 83% of participants randomly assigned to carvedilol and placebo, respectively, completed 12 months on study drug. These findings indicate that large numbers of patients requiring dialysis, a modified recruiting strategy, and strategies to prevent participant attrition are required to perform a larger study with important clinical outcomes.

Recruitment to the BLOCADE Feasibility Study was challenging because of both trial design and patient factors that resulted in a small proportion of screened patients being eligible for inclusion. The criteria we chose to enrich the recruited population with cardiovascular risk factors, or that assumed longer dialysis vintage might attenuate response to β-blockers, excluded substantial numbers of patients ([Fig 1](#)). The latter criterion was modified during the study. We also started recruiting with an upper age limit criterion that was modified because a large

Table 2. Feasibility and Tolerability Outcomes After Randomization			
Outcome	Carvedilol	Placebo	P
Tolerability; proportion who dropped out due to			
Adverse events attributable to carvedilol	4/26 (15)	0 (0)	0.1
Symptomatic hypotension or bradycardia	2/26 (8)	0 (0)	0.5
Sample size			
Proportion who dropped out for any reason	10/26 (38)	4/23 (17)	0.1
Proportion who required β-blocker therapy	1/26 (4)	1/23 (4)	0.9
Proportion who withdrew consent	0 (0)	2/23 (9)	0.2
Logistics: proportion receiving study drug, 25 mg, twice daily			
When dose titration complete	14/26 (54)	18/23 (78)	0.1
3-mo follow-up	13/20 (65)	18/22 (82)	0.3
6-mo follow-up	12/18 (67)	17/22 (77)	0.5
9-mo follow-up	10/15 (67)	16/19 (84)	0.4
12-mo follow-up	11/16 (69)	16/19 (84)	0.4

Note: Values given as number/number at risk (percentage).

number of patients were being excluded and thus generalizability was being limited. With a mean age of 57.2 ± 12.9 years, participants in BLOCADE were younger than prevalent patients receiving dialysis in Australia and New Zealand at the time, who had an mean age of 62.4 ± 15.4 years (Kylie Hurst, ANZDATA [The Australia and New Zealand Dialysis and Transplant Registry], personal communication, August 9, 2015). The initial exclusion of patients 75 years or older may have caused this difference, but younger patients may have had more favorable “patient-related” factors.

Important patient-related factors included fitness for participation in an RCT, ability to tolerate

Table 3. Serious Adverse Events by Body System and Number of Participants in the Randomly Assigned Groups Affected

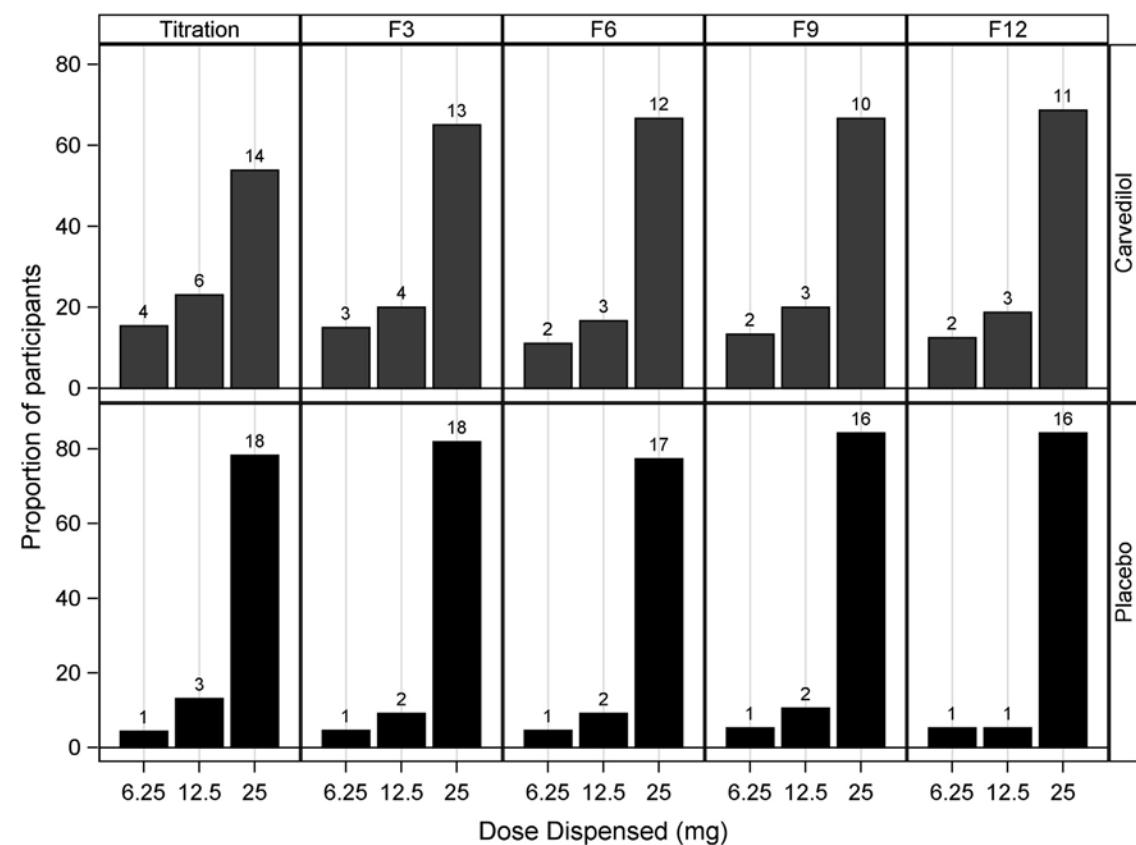
	Total No. of Events	Carvedilol (n = 26)	Placebo (n = 23)	P
Any serious adverse event	57	14 (54)	14 (61)	0.6
Cardiovascular	4	1 (4)	3 (13)	0.2
Gastrointestinal	5	3 (12)	2 (9)	0.7
Dialysis complication	21	6 (23)	6 (26)	0.8
Respiratory	8	2 (8)	4 (17)	0.3
Endocrine disorder	1	1 (4)	0 (0)	0.3
Hematology	1	0 (0)	1 (4)	0.3
Skin	2	1 (4)	1 (4)	0.9
Other	15	6 (23)	6 (26)	0.8

Note: Unless otherwise indicated, values given as number (percentage).

carvedilol, and motivation to participate. Patients receiving dialysis are a particularly unwell group, as evidenced by frequent SAEs (Table 3), and many patients were not considered for enrollment because they were “clinically unstable” (Fig 1). To address concerns about carvedilol lowering blood pressure in hemodialysis patients, we measured IDH episodes at specific time points. At most, IDH events occurred in 7% of hemodialysis treatments, which compares favorably with 17% of all treatments in a study of 13 US hemodialysis centers,<sup>17</sup> indicating that carvedilol was reasonably well tolerated in our study. Alternatively, this may reflect selection bias, with patients prone to IDH not being asked or not agreeing to participate. Finally, the primary reason for nonparticipation for >20% of all screened patients was simply choosing not to participate. Motivating patients to participate in an RCT of a blood pressure–lowering medication with no immediately perceivable benefit proved challenging.

Another major challenge recruiting dialysis patients to an RCT of a β-blocker versus placebo is how to handle prevalent β-blocker use. In contrast to the study of Cice et al,<sup>10,18</sup> we intended to randomly assigned patients with and without heart failure or coronary artery disease because we considered there was sufficient clinical equipoise because of the difficulties applying results of RCTs in patients not requiring dialysis. However, the prevalence of coronary artery disease at baseline in BLOCADE participants who entered the run-in was 13%, and no participant had heart failure. It is likely, although not known, that the prevalence of coronary artery disease and heart failure was much higher in the excluded individuals because they were receiving a β-blocker and were not prepared to cease treatment with it. These were 16% of excluded patients (Fig 1), and although the trial protocol did not specifically exclude them, this figure indicates that treating physicians were reluctant to cease β-blocker therapy to enroll patients. The impact of prevalent β-blocker prescription on an RCT would differ across jurisdictions because β-blocker use varies from 10% in Japan to >40% in the United States,<sup>19</sup> and even within the United States, varies substantially between the highest and lowest prescribing states.<sup>20</sup> Furthermore, there are important differences between β-blockers. Atenolol, used in the HDPAL RCT,<sup>11</sup> is eliminated by renal excretion and removed by dialysis, whereas carvedilol is eliminated by hepatic metabolism and not removed by dialysis. The influence of dialysis may result in different β-blockers having different effects on mortality.<sup>21</sup>

In addition to recruiting a population that is generalizable to the patients to whom the intervention is to



**Figure 2.** Proportion of participants randomly assigned to (top panel) carvedilol or (bottom panel) placebo receiving either 6.25, 12.5, or 25 mg twice daily. “Titration” is the final titration visit, and F3, F6, F9, and F12 represent follow-up visits at 3, 6, 9, and 12 months. Numbers above columns are the numbers of patients receiving each dose.

be applied, the BLOCADE Feasibility Study sought to measure how well participants could be retained. We aimed to have narrower 95% confidence limits around the proportion of patients who tolerated the lowest dose of carvedilol. Because we did not recruit the planned 150 participants, this result of 68% could reasonably lie between 57% and 79%. The previous RCT of carvedilol in patients receiving dialysis with heart failure lost fewer participants (14%) during the run-in phase.<sup>10</sup> Of the participants who tolerated carvedilol in the run-in, 38% randomly assigned to carvedilol and 17% allocated to placebo did not remain on study drug by 12 months. Not all reasons for withdrawal were directly related to the effects of carvedilol (Fig 1). In the HDPAL RCT, 23% of participants randomly assigned to atenolol and 34% randomly assigned to lisinopril dropped out by 12 months for reasons predominantly unrelated to drug tolerability.<sup>11</sup> Thus, retaining participants will require more than preventing adverse effects of the drug.

This high drop out of patients in RCTs in the dialysis population may have been a significant factor in the inability to demonstrate benefits for calcimimetics,<sup>22</sup> phosphate binders,<sup>23</sup> and

statins.<sup>24-26</sup> Novel clinical trial methodologies must be considered if an RCT of a  $\beta$ -blocker versus placebo is to be performed in dialysis patients. One novel RCT methodology is the “randomized clinical registry trial,” which uses an existing registry as a platform for case records, randomization, and follow-up.<sup>27</sup> This design was used successfully in the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE trial).<sup>28</sup> The balance of data quality versus trial efficiency<sup>29</sup> must be addressed to apply this design to our research question.

In conclusion, the BLOCADE Feasibility Study has informed the design of a larger clinical outcome study (Table 4). It has done this by demonstrating that a very large pool of patients from which to recruit, and thus greater international collaboration, is required, as are broad inclusion criteria and a sample size that allows for substantial withdrawal of participants. The high prevalence of  $\beta$ -blocker prescription in this population substantially reduces the patients available for participation and must be specifically addressed. Earlier and more effective consumer and site staff engagement and education, including use of

**Table 4.** Key Limitations of the BLOCADE Feasibility Study and How They Would Inform a Large-Scale RCT With Important Patient-Centered Outcomes

Limitation of BLOCADE Feasibility Study	How It Informs Design of a Larger Study
Generalizability	
Narrow inclusion criteria	Keep inclusion/exclusion criteria broad by removing age, dialysis vintage, and cardiovascular risk factor criteria
Prevalent β-blocker prescription	Difficult to resolve satisfactorily: <ul style="list-style-type: none"><li>• Could maximize generalizability by encouraging physicians to randomly assigned patients receiving β-blocker for whom they believe there is clinical equipoise; however, in BLOCADE, physicians were reluctant to do this</li><li>• Could maximize practicality by only including participants not receiving β-blocker, but this would reduce generalizability</li></ul>
Target sample size not achieved	
Standard RCT screening methodology inefficient	Optimize number of participants recruited in Australia and New Zealand by developing registry-based methodology for recruitment
Many patients declined to participate	Systematic education of people with CKD and receiving dialysis about clinical trials and their benefit prior to a direct approach could result in higher participation; novel methods of providing participant information (videos [eg, by YouTube], smart phone apps); consumer/participant engagement in design stages of trial to ensure it is more practical and appealing to participants
11 dialysis units not sufficient	Increase number of patients to be screened by multinational site involvement
Large numbers of participants dropped out at all stages	Closer monitoring of included participants; improve training packages (including novel training methods) for site investigators and research teams in relation to appropriate and informed consent and importance of adherence and follow-up may lead to decreased drop outs; improve consumer/participant engagement to improve adherence and follow-up; ultimately, factor high drop-out rates into sample size estimation

Abbreviations: BLOCADE, β-Blocker to Lower Cardiovascular Dialysis Events; CKD, chronic kidney disease; RCT, randomized controlled trial.

innovative educational and training tools, also needs to be considered. Moreover, novel trial designs, including registry-based RCTs, may be more appropriate than the conventional RCT design to determine the efficacy and safety of β-blockers in the end-stage kidney disease population.

ACKNOWLEDGEMENTS

Members of the BLOCADE Study Collaborative Group are as follows: Trial Steering 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, Australia; 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; Liza A. Vergara,

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Jean Helyar, Alicia Morrish, Elaine M. Pascoe, Peta-Anne Paul-Brent, Donna Reidlinger, Anish Scaria, Liza A. Vergara, and Lei Zhang.

Professor Henry Krum, who was an Investigator on the initial major funding application for the BLOCADE Feasibility Study, died on November 28, 2015, after the acceptance of this manuscript. His coauthors are grateful for his contribution to BLOCADE and wish to acknowledge more broadly his extraordinary contribution to cardiovascular research.

These data were presented at the American Society of Nephrology Kidney Week, November 11-16, 2014, Philadelphia, PA (*J Am Soc Nephrol*. 2014;25:B4).

**Support:** The BLOCADE Feasibility Study acknowledges the following funding sources: Don & Lorraine Jacquot Collaborative Research Initiative Grant (2008), the New Zealand Health Research Council Feasibility Study Grant (10-163), the NHMRC Project Grant (1006171), and Pfizer CVL (2008). Roche Products, Pty Limited, provided Dilatrend at a discounted price. Dr Roberts was supported by an NHMRC Training Fellowship (628902). The funding sources had no role in the study design; collection, analysis, and interpretation of data; writing the re-port; and the decision to submit the report for publication.

**Financial Disclosure:** The authors declare that they have no other relevant financial interests.

**Contributions:** Research idea and study design: MAR, HLP, FLI, SVB, AC, AXG, NMI, HK, VP, AMT, CMH; data acquisition: MAR, HLP, NMI, CMH, LAV; data analysis/interpretation: MAR, HLP, FLI, SVB, AC, AXG, NMI, HK, VP, AMT, CMH, EMP, AS; statistical analysis: EMP, AS; supervision or mentorship: FLI, CMH. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. MAR takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned and registered have been explained.

**Peer Review:** Evaluated by 2 external peer reviewers, a Statistical Editor, a Co-Editor, and the Editor-in-Chief.

## SUPPLEMENTARY MATERIAL

Table S1: Baseline characteristics of all participants in feasibility study and by run-in completion status.

Table S2: Serious adverse events during run-in phase of feasibility study.

Table S3: Heart rate and blood pressure measurements by randomized group and study visit.

Table S4: Mean scores and change scores in EQ-5D quality of life, by randomized group.

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2015.10.029>) is available at [www.ajkd.org](http://www.ajkd.org)

## REFERENCES

1. 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(1):64-72.
2. 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(2):262-270.
3. Converse RL Jr, Jacobsen TN, Toto RD, et al. Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med*. 1992;327(27):1912-1918.

4. Freemantle N, Cleland J, Young P, Mason J, Harrison J. Beta-blockade after myocardial infarction: systematic review and meta regression analysis. *BMJ*. 1999;318(7200):1730-1737.
5. 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(3):351-357.
6. Furgeson SB, Chonchol M. Beta-blockade in chronic dialysis patients. *Semin Dial*. 2008;21(1):43-48.
7. Kalaitzidis R, Bakris G. Should nephrologists use beta-blockers? A perspective. *Nephrol Dial Transplant*. 2009;24(3):701-702.
8. Coca SG, Krumholz HM, Garg AX, Parikh CR. Underrepresentation of renal disease in randomized controlled trials of cardiovascular disease. *JAMA*. 2006;296(11):1377-1384.
9. 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(11):1152-1161.
10. 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(9):1438-1444.
11. 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(3):672-681.
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(18):2227-2236.
13. Bakris GL, Hart P, Ritz E. Beta blockers in the management of chronic kidney disease. *Kidney Int*. 2006;70(11):1905-1913.
14. Dulin B, Abraham WT. Pharmacology of carvedilol. *Am J Cardiol*. 2004;93(9)(suppl 1):3-6.
15. Roberts MA, Pilmore HL, Ierino FL, et al. The rationale and design of the Beta-blocker to LOwer Cardiovascular Dialysis Events (BLOCADE) Feasibility Study. *Nephrology (Carlton)*. 2015;20(3):140-147.
16. 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.
17. Sands JJ, Usvyat LA, Sullivan T, et al. Intradialytic hypotension: frequency, sources of variation and correlation with clinical outcome. *Hemodial Int*. 2014;18(2):415-422.
18. Cice G, Ferrara L, Di Benedetto A, et al. Dilated cardiomyopathy in dialysis patients - beneficial effects of carvedilol: a double-blind, placebo-controlled trial. *J Am Coll Cardiol*. 2001;37(2):407-411.
19. 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.
20. Wetmore JB, Mahnken JD, Mukhopadhyay P, et al. Geographic variation in cardioprotective antihypertensive medication usage in dialysis patients. *Am J Kidney Dis*. 2011;58(1):73-83.
21. Weir MA, Dixon SN, Fleet JL, et al.  $\beta$ -Blocker dialyzability and mortality in older patients receiving hemodialysis. *J Am Soc Nephrol*. 2015;26(4):987-996.

22. Chertow GM, Block GA, Correa-Rotter R, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. *N Engl J Med*. 2012;367(26):2482-2494.
23. Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int*. 2007;72(9):1130-1137.
24. Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. *Lancet*. 2011;377(9784):2181-2192.
25. Fellstrom BC, Jardine AG, Schmieder RE, et al. Rosuvastatin and cardiovascular events in patients undergoing hemodialysis. *N Engl J Med*. 2009;360(14):1395-1407.
26. Wanner C, Krane V, Marz W, et al. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. *N Engl J Med*. 2005;353(3):238-248.
27. Frobert O, Lagerqvist B, Gudnason T, et al. Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE trial). A multicenter, prospective, randomized, controlled clinical registry trial based on the Swedish angiography and angioplasty registry (SCAAR) platform. Study design and rationale. *Am Heart J*. 2010;160(6):1042-1048.
28. Frobert O, Lagerqvist B, Olivecrona GK, et al. Thrombus aspiration during ST-segment elevation myocardial infarction. *N Engl J Med*. 2013;369(17):1587-1597.
29. Lauer MS, D'Agostino RB Sr. The randomized registry trial—the next disruptive technology in clinical research? *N Engl J Med*. 2013;369(17):1579-1581.