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Original Investigation

The β-Blocker to Lower Cardiovascular Dialysis Events (BLOCADE) Feasibility Study: A Randomized Controlled Trial

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Background: β-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 ≥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 β-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 β-blocker versus placebo will prove challenging. Possible solutions include international collaboration and exploring novel trial designs such as a registry-based RCT.

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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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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.[1,2] Sympathetic nervous system overactivity in this population[3] has deleterious cardiovascular effects. β-Adrenergic receptor antagonists, or β-blockers, reduce sympathetic nervous system activity and reduce morbidity and mortality in randomized controlled trials (RCTs) that recruited people with cardiac disease.[4,5] Therefore, a role for β-blockers as a cardiac "protection" strategy in end-stage kidney disease is highly plausible.[6,7]

Most RCTs of cardiovascular therapies have excluded patients with advanced chronic kidney disease.[8] A meta-analysis of RCTs studying β-blockers in chronic kidney disease demonstrated that participants receiving a β-blocker had a 28% relative risk reduction and a 6% absolute risk reduction in mortality after 1 to 2 years of follow-up.[9] 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 β-blocker carvedilol or placebo and detected reduced mortality in patients receiving carvedilol.[10] This result has not been replicated. Agarwal et al[11] randomly assigned 200 maintenance hemodialysis patients with hypertension and left ventricular hypertrophy to the β-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 β-blockers in patients receiving dialysis, the RCT evidence relating to efficacy and safety is limited to these 2 trials.

Carvedilol, an antagonist of β_1-, β_2-, and α_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 β-blockers.[12-14] However, blood pressure lowering from α_1-adrenergic receptor blockade might increase the risk for symptomatic hypotension when fluid is removed during hemodialysis and thus reduce tolerability of this β-blocker.

A large-scale placebo-controlled RCT to determine whether treatment with a β-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 β-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.[15] 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 β-blockers, (4) were currently receiving a β-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 β-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 β-blocker could undergo supervised downtitration and cessation of their β-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 β-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