Nephrol Dial Transplant (2011) 0: 1–8
doi: 10.1093/ndt/gfr460

NDT
Nephrology Dialysis Transplantation

Original Article

Beta-blockers and cardiovascular outcomes in dialysis patients: a cohort study in Ontario, Canada

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Abstract

Background. Beta-blockers may be cardioprotective in patients receiving chronic dialysis. We examined cardiovascular outcomes among incident dialysis patients receiving beta-blocker therapy.

Methods. We conducted a retrospective cohort study employing linked healthcare databases in Ontario, Canada. We studied all consecutive chronic dialysis patients aged ≥66 years who initiated dialysis between 1 July 1991 and 31 July 2007. Patients were divided into three groups according to new medication use after the initiation of chronic dialysis. The three groups were patients initiated on beta-blockers, calcium channel blockers and statins only. Patients in the beta-blocker and calcium channel blocker groups could also be concurrently receiving a statin. The primary outcome was time to a composite endpoint of death, myocardial infarction, stroke or coronary revascularization.

Results. There were a total of 1836 patients (504 beta-blocker, 570 calcium channel blocker and 762 statin-only users). Compared to statin-only use, beta-blocker use was not associated with improved cardiovascular outcomes [adjusted hazard ratio (aHR) 1.07, 95% confidence interval (CI) 0.92–1.23]. As expected, calcium channel blocker use was also not associated with improved cardiovascular outcomes (aHR 0.91, 95% CI 0.79–1.06). Among all subgroup analyses by beta-blocker attributes, only high-dose beta-blocker therapy was associated with better cardiovascular outcomes as compared to low-dose beta-blockers (aHR 0.50, 95% CI 0.29–0.88).

Conclusions. We observed no beneficial effect of beta-blocker use among patients receiving chronic dialysis relative to our comparator groups. Given current uncertainty around the cardioprotective benefits of beta-blockers in patients receiving dialysis, a large randomized clinical trial is warranted.

Keywords: adrenergic beta-antagonists; cardiovascular disease; renal dialysis

Introduction

Cardiovascular disease accounts for 50% of mortality in patients receiving chronic dialysis [1]. Beta-blockers may be suitable cardioprotective agents in the setting of chronic dialysis, as patients with chronic kidney disease have overactivation of the sympathetic nervous system [2, 3]. Although the efficacy of beta-blockers has been established for certain indications among patients with adequate renal function [4, 5], the utility of beta-blockers remains poorly understood in dialysis patients who have been excluded from most randomized controlled trials [6, 7]. The best data to determine the efficacy of beta-blockers in the dialysis population will come from large multicentre randomized controlled trials. Such trials will require substantial funding and large sample sizes to provide adequate statistical power. To inform future randomized clinical trials and guide clinical practice until such trials are done, we conducted a population-based retrospective cohort study designed to measure the effectiveness of beta-blocker treatment in chronic dialysis patients. We examined new medication use after the initiation of chronic dialysis. We hypothesized that beta-blocker treatment would be associated with fewer cardiovascular events in follow-up

compared to treatment with calcium channel blockers or statins alone. Rather than beta-blocker non-use, we chose the latter two as comparator groups to reduce confounding by indication, as all three drug classes are used for presumed cardioprotective benefit.

Materials and methods

Design and setting

We conducted a retrospective cohort study employing linked healthcare databases in Ontario, Canada. Ontario's population is ~13 million, of which 14% are >65 years of age, 51% are female and 77% are Caucasian [8]. Emigration from the province is <1% annually [9]. Ontario residents have universal access to physician services and hospital care and those older than 65 years have universal prescription drug coverage. We conducted this study according to a prespecified protocol approved by the Research Ethics Board of Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada). We report this study as per guidelines in the Strengthening the Reporting of Observational Studies in Epidemiology statement (as detailed in supplementary Appendix A1) [10].

Data sources

Prescription medication use was ascertained using the Ontario Drug Benefit Program (ODB) database, which accurately records all outpatient drug prescriptions for residents aged ≥65 years. Chronic dialysis use was determined using the Ontario Health Insurance Plan (OHIP) claims database, which records all inpatient and outpatient physician service claims. Baseline characteristics and outcomes were ascertained using the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), which records detailed admission, diagnostic and procedural information and the Ontario Registered Persons Database which records demographic and vital statistics information on all Ontarians who have been issued a health insurance card. These four databases are effectively complete for all variables examined and have been routinely used to study clinical outcomes [11–17].

Patients

We studied consecutive chronic dialysis patients, aged ≥66 years, who initiated dialysis between 1 July 1991 and 31 July 2007. Incident chronic dialysis was defined by first evidence of dialysis treatments that persisted for 90 days. We followed patients with chronic dialysis forward in time and separated them into three exposure groups when two prescriptions were filled for a drug in one of the following classes: beta-adrenergic blockers; calcium channel blockers or statins, respectively. For the patient to be considered in these analyses, the medication specified by the two prescriptions had to be dispensed within 60–120 days of each other. Chronic dialysis patients who did not meet these criteria were excluded. Our cohort consisted of chronic dialysis patients at the time of their first use of these drugs following dialysis initiation. Patients with previous evidence of any prescriptions for beta-blockers or calcium channel blockers in the 180 days prior to the first of the two identifying prescriptions were not entered into the study cohort. The index date was defined as the date of the second prescription for an exposure drug and represented the first day of follow-up. Supplementary Appendix A2 illustrates the timelines for patient accrual as well as the initiation and termination of follow-up.

Patients could receive different types of beta-blockers and calcium channel blockers during follow-up. Patients within the beta-blocker and calcium channel blocker groups could also be concurrently taking a statin. Once patients were accrued into a group, they remained within that group regardless of initiation or discontinuation of the study exposure drugs. Our reason for categorizing patients according to these three drug classes (beta-blockers, calcium channel blockers and statin-only) is that they are all taken chronically for presumed cardioprotective benefit and this would minimize confounding by indication. We used two comparator groups to more convincingly show a hypothesized benefit of beta-blockers. Prior to November 2010 (release of SHARP trial), there was no evidence to support statin efficacy for our outcomes of interest in patients receiving dialysis. Similarly, with the exception of a single study by Tepel *et al.* [18], there were no randomized trials demonstrating improved outcomes associated with calcium channel blocker use in this population.

We included patients both with and without known cardiovascular disease in all three groups. We excluded the following patients from the analysis: patients on both beta-blockers and calcium channel blockers and patients with evidence of myocardial infarction in the 3 months prior to the index date. We excluded this latter group, as clinical practice guidelines recommend that patients be prescribed a beta-blocker after a myocardial infarction [19]. As these patients are at high risk of death in the subsequent 90 days, we wanted to avoid accruing such patients preferentially into the beta-blocker group.

Baseline characteristics

We examined demographic characteristics, comorbidities and measures of healthcare access and screening in the 3 years prior to the index date. Diagnostic and procedural codes with established validity were used where possible [20–25] (see supplementary Appendices A3 and A4). We also assessed concomitant medication exposure in the year prior to the index date as another measure of comorbidity.

Outcomes

The primary outcome was a composite of death, hospitalization for myocardial infarction, stroke or coronary revascularization. These outcomes are accurately coded in our data sources with sensitivity and specificity of 81–96% and 69–100%, respectively (detailed in supplementary Appendix A5). Secondary outcomes included the individual components of the primary outcome. Patients were censored after emigration from the province (evidenced by 1 year without healthcare contact in the absence of death), 5 years after the index date or the end of the follow-up period, 31 March, 2009.

Statistical analyses

We compared baseline characteristics in the three groups using standardized differences. This metric compares differences between group means relative to pooled standard deviations and unlike conventional significance testing. It is unconfounded by sample size [26]. Standardized differences were deemed significant if >10%. We used a Cox proportional hazards model to estimate hazard ratios and 95% confidence intervals (CIs), using the statin group as the referent. We performed a multivariable analysis forcing the following variables into the model: age (66–70, 71–75, 76–80, 81–85, ≥86), gender, diabetes, hypertension, coronary artery disease (including previous myocardial infarction, angina and percutaneous coronary intervention), heart failure, duration of dialysis until the time of index date and the Deyo Revised Charlson Comorbidity score [27–29]. We assessed the following additional covariates for inclusion in the model by performing univariate regression with a P-value <0.2 resulting in model inclusion: socioeconomic status (by quintile), year of cohort entry (before or after 2000), cerebrovascular disease, peripheral arterial disease, atrial fibrillation/flutter and the number of distinct drugs prescribed in the year preceding the index date, as an additional measure of comorbidity [28]. We conducted all statistical analyses with SAS software Version 9.2 (SAS Institute Inc., Cary, NC).

Additional analyses

We examined the primary outcome within six predefined patient subgroups: male and female, age greater than or less than the median, year of cohort entry before or after year 2000, previous history of coronary artery disease, heart failure and dialysis modality (hemodialysis, peritoneal dialysis or unspecified). We also studied the association between various beta-blocker characteristics and outcome: high and low (or unknown) removal with dialysis (classification described in supplementary Appendix A6), high and low dose (threshold doses for each drug were selected using dose ranges established in randomized controlled trials of beta-blockers in patients with adequate kidney function [30–35] as described in supplementary Appendix A7), cardioselective/beta-1 selective drugs and non-selective drugs and lipophilic and hydrophilic drugs (classifications described in supplementary Appendices A8 and A9, respectively) [4, 36–39]. Carvedilol, which is the only beta-blocker shown to have efficacy in a randomized trial of dialysis patients was also compared against all other beta-blockers [40].

Results

Baseline characteristics

We identified a total of 1836 consecutive chronic dialysis patients who were treated with one of the study exposure drugs (504 beta-blocker, 570 calcium channel blocker and

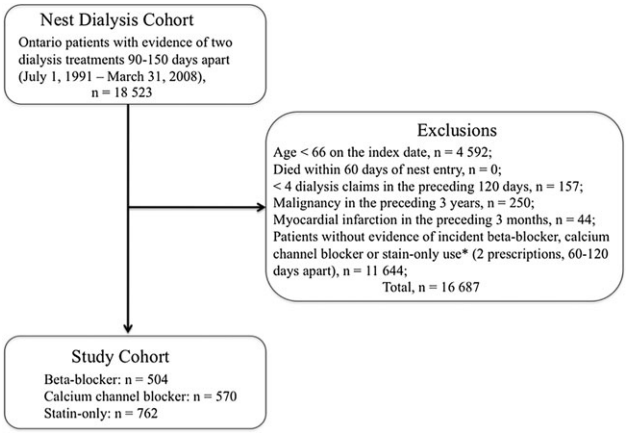

Fig. 1. Study flow diagram. *Patients considered to not have evidence of incident medication use include those without evidence of two prescriptions for the study medications and those patients with evidence of prescriptions in the 180 days prior to the first of the two identifying prescriptions (i.e. prevalent medication users).

762 statin-only users, as shown in Figure 1). The largest group of patients excluded from the analysis (11 644 patients), consisted of those not meeting criteria for incident medication use following the initiation of dialysis (this included patients without evidence of two prescriptions for the study medications or those with evidence of use of the study medications prior to the initiation of dialysis—i.e. prevalent medication users). Beta-blocker users were similar to calcium channel blocker and statin-only users on most baseline characteristics (Table 1), with the exception of higher rates of diabetes, hypertension, cerebrovascular and peripheral vascular disease in beta-blocker users than statin-only users. Beta-blocker users also had higher rates of cardiac comorbidities including coronary artery disease, heart failure and atrial fibrillation/flutter. Beta-blocker users and calcium channel blocker users were more likely to receive hemodialysis compared to peritoneal dialysis. With respect to Charlson comorbidity index, calcium channel blocker users were noted to have slightly lower values than the other two groups; however, the groups were similar in terms of number of distinct drugs used in the previous year. The beta-blocker subclasses demonstrated that 89% of patients (449 patients) were receiving low-dose regimens and 6% (29 patients) high-dose therapy. The majority of patients, 83% (417 patients) were found to be receiving highly dialyzable beta-blockers. Similarly, the majority of patients, 89% (447 patients), were using cardioselective beta-blockers. Most, 78% (394 patients), were using a hydrophilic beta-blocker and 7% (37 patients) were prescribed carvedilol. Concurrent statin use was evident in 54% of beta-blocker users (271 patients) and 32% of calcium channel blocker users (183 patients).

We used the period between 365 and 720 days following the index date to assess durability of medication use and crossover. Most patients remained on the study medications, with 74–87% demonstrating a repeat prescription for the index medication. Crossover measures demonstrated that 17% of calcium channel blocker users and 10% of statin-only users initiated a beta-blocker during this period. Among beta-blocker and statin-only users, 14 and 11%, respectively, had evidence of calcium channel blocker use. Lastly, statin use was seen in 49% of beta-blocker users and 31% of calcium channel blocker users during this period.

Outcomes

The mean follow-up time was 2.1 years for beta-blocker users (1034 total person-years), 2.5 years for calcium channel blocker users (1417 total person-years) and 2.2 years for statin users (1658 total person-years). There was a total of 1233 primary outcome events in all three groups, with 360, 473 and 400 events, respectively, in the beta-blocker, calcium channel blocker and statin-only groups, respectively. Compared to statin-only and calcium channel blocker use, beta-blocker use was not associated with a decrease in the primary outcome in unadjusted or adjusted analyses [adjusted hazard ratio (aHR) 1.07 compared to the statin-only group, 95% CI 0.92–1.23, Table 2]. Similarly, there was no association between beta-blocker use and any of the components of the primary outcome (Table 2).

Additional analyses

The results were consistent across all patient characteristic subgroups (Figure 2). With respect to the beta-blocker characteristics, the only attribute associated with reductions in the primary outcome was beta-blocker dose, with a higher dose associated with better outcomes (aHR 0.50 compared to low dose, 95% CI 0.29–0.88, Table 3).

Discussion

Main finding

In our population-based cohort study of incident dialysis patients, beta-blocker use relative to our comparator groups was not independently associated with a reduction in mortality and cardiovascular events.

Interpretation

In patients with adequate renal function, large meta-analyses have shown significant reductions in cardiovascular events with beta-blocker use when compared to placebo or no treatment [4, 5, 41]. Conversely, guidelines for patients with kidney disease explicitly acknowledge the paucity of high quality evidence for beta-blocker use in the dialysis population [42].

A randomized controlled trial in this population by Cice *et al.* examined dialysis patients with cardiomyopathy randomized to carvedilol (a low dialyzability, non-selective beta-blocker) or placebo and demonstrated a 30% relative risk reduction of cardiovascular death in those receiving carvedilol [40, 43]. Our analysis differs from this trial in that we employed statins and calcium antagonists as comparators, while Cice *et al.* used a placebo control with standard therapy (consisting of digitalis, angiotensin-converting enzyme (ACE) inhibitors and nitrates). As such, if there is any beneficial effect of either statins or calcium antagonists, this may have influenced our results but would

Table 1. Baseline characteristics[a]

Variable	Beta-blocker	Calcium channel blocker	Statin-only
Total number	$n = 504$	$n = 570$	$n = 762$
Demographics			
Age			
Mean (SD)	76.57 ± 5.66[b]	75.96 ± 5.70	76.07 ± 5.65
66–70	75 (14.9%)	101 (17.7%)	138 (18.1%)
71–75	159 (31.5%)	193 (33.9%)	235 (30.8%)
76–80	142 (28.2%)	158 (27.7%)	223 (29.3%)
81–85	94 (18.7%)[b]	81 (14.2%)	117 (15.4%)
≥86	34 (6.7%)	37 (6.5%)	49 (6.4%)
Female	201 (39.9%)[b]	265 (46.5%)	322 (42.3%)
Lowest income quintile	113 (22.4%)	144 (25.3%)	159 (20.9%)
Charlson comorbidity index			
≤2	162 (32.2%)[b,c]	246 (43.2%)	299 (39.3%)
3	93 (18.5%)[c]	105 (18.4%)[d]	109 (14.3%)
4	103 (20.4%)	115 (20.2%)	161 (21.1%)
5	76 (15.1%)	68 (11.9%)	104 (13.6%)
>5	81 (16.1%)	54 (9.5%)[d]	111 (14.6%)
Major comorbidities			
Diabetes	185 (36.7%)[c]	213 (37.4%)[d]	332 (43.6%)
Hypertension	406 (80.6%)	452 (79.3%)	583 (76.5%)
Cerebrovascular disease	133 (26.4%)[c]	128 (22.5%)	165 (21.7%)
Peripheral vascular disease	219 (43.5%)[b,c]	188 (33.0%)	253 (33.2%)
Chronic lung disease	172 (34.1%)	182 (31.9%)[d]	288 (37.8%)
Previous kidney transplant	11 (2.2%)	16 (2.8%)	18 (2.4%)
Coronary artery disease (including angina)	395 (78.4%)[b,c]	294 (51.6%)	428 (56.2%)
Heart failure and cardiomyopathy	270 (53.6%)[b,c]	216 (37.9%)[d]	337 (44.2%)
Atrial fibrillation/flutter	128 (25.4%)[b,c]	74 (13.0%)	124 (16.3%)
Dialysis modality[e]			
Hemodialysis	422 (83.7%)[c]	463 (81.2%)[d]	520 (68.2%)
Peritoneal dialysis	70 (13.9%)[b,c]	50 (8.8%)[d]	219 (28.7%)
Unspecified	12 (2.4%)[b]	57 (10.0%)[d]	23 (3.0%)
Number of hospitalizations per year	1.7 (1.0–2.3)[c]	1.3 (0.7–2.3)[d]	1.3 (0.7–2.0)
Procedures in 3 years prior to index date			
Echocardiogram	349 (69.2%)[b,c]	310 (54.4%)[d]	488 (64.0%)
Stress test	187 (37.1%)[b]	143 (25.1%)[d]	273 (35.8%)
Medications			
No. of distinct drugs in previous year	15.0 (11.0–19.0)[b]	14.0 (10.0–18.0)	14.0 (10.0–19.0)
No. of distinct drugs in previous year, by category			
≤5	9 (1.8%)[b,c]	33 (5.8%)	31 (4.1%)
6–10	104 (20.6%)	122 (21.4%)	183 (24.0%)
11–15	172 (34.1%)	192 (33.7%)	250 (32.8%)
16–20	122 (24.2%)	126 (22.1%)	162 (21.3%)
21–26	63 (12.5%)	63 (11.1%)	85 (11.2%)
≥26	34 (6.7%)	34 (6.0%)	51 (6.7%)
Medications in year prior to index date			
Statins	271 (53.8%)[b,c]	183 (32.1%)[d]	762 (100.0%)
Oral anticoagulants	197 (39.1%)[b,c]	165 (28.9%)	238 (31.2%)
Anti-platelets[f]	155 (30.8%)[b,c]	137 (24.0%)	171 (22.4%)
Digoxin	82 (16.3%)[b,c]	66 (11.6%)	75 (9.8%)
ACE inhibitors or angiotensin receptor blockers	312 (61.9%)	334 (58.6%)	458 (60.1%)
Insulins	112 (22.2%)[c]	108 (18.9%)[d]	205 (26.9%)
Oral hypoglycemic	56 (11.1%)	64 (11.2%)	109 (14.3%)

[a]Patients receiving a beta-blocker or calcium channel blocker could also be receiving a statin.
[b]Significant standardized difference between beta-blocker and calcium channel blocker groups.
[c]Significant standardized difference between beta-blocker and statin groups.
[d]Significant standardized difference between calcium channel blocker and statin groups.
[e]Dialysis modality on index date.
[f]Excludes over-the-counter acetylsalicylic acid.

not have been a factor in the analysis of Cice *et al.* Also, all patients in the study of Cice *et al.* had evidence of a decreased left ventricular ejection fraction and it is possible that the benefits of the beta-blocker are limited to this subpopulation, which we could not identify using our datasets.

Two major cohort studies employing the United States Renal Data System (USRDS) have also shown benefits associated with beta-blocker therapy. Abbot *et al.* studied 2550 dialysis patients stratified by previous heart failure status. In patients without prior evidence of heart failure, beta-blocker use compared to non-use was associated with a lower risk of hospitalization for heart failure (aHR 0.69; 95% CI 0.52–0.91) with a similar reduction in risk of cardiac and all-cause death. No significant difference was

Table 2. Outcomes in three groups of dialysis patients[a]

	No. of patients	No. of Events	Event Rate per 1000 person-years	Unadjusted hazard ratio	Adjusted hazard ratio
Primary outcome: composite of death, hospitalization for MI, stroke, coronary revascularization					
Statin-only	762	473	285	1 (referent)	1
Calcium channel blocker	570	400	282	0.98 (0.85–1.12)	0.91 (0.79–1.06)
Beta-blocker	504	360	348	1.23 (1.07–1.41)	1.07 (0.92–1.23)
Secondary outcomes					
Death					
Statin-only	762	452	261	1 (referent)	1
Calcium channel blocker	570	379	253	0.95 (0.83–1.09)	0.88 (0.76–1.02)
Beta-blocker	504	339	296	1.13 (0.98–1.30)	0.96 (0.83–1.11)
MI[b]					
Statin-only	762	73	43	1 (referent)	1
Calcium channel blocker	570	64	44	1.01 (0.72–1.42)	0.99 (0.68–1.43)
Beta-blocker	504	64	59	1.36 (0.97–1.90)	1.12 (0.79–1.58)
Stroke[b]					
Statin-only	762	28	16	1 (referent)	1
Calcium channel blocker	570	41	28	1.68 (1.04–2.72)	1.39 (0.82–2.36)
Beta-blocker	504	32	29	1.78 (1.07–2.95)	1.59 (0.93–2.71)
Coronary revascularization[b]					
Statin-only	762	21	12	1 (referent)	1
Calcium channel blocker	570	14	10	0.78 (0.39–1.53)	0.90 (0.42–1.93)
Beta-blocker	504	14	13	1.03 (0.52–2.03)	1.06 (0.52–2.16)
Hospitalization for heart failure[b]					
Statin-only	762	130	80	1 (referent)	1
Calcium channel blocker	570	112	80	1.03 (0.80–1.32)	0.89 (0.66–1.16)
Beta-blocker	504	97	92	1.15 (0.89–1.50)	0.89 (0.68–1.17)

[a]Patients receiving a beta-blocker or calcium channel blocker could also be receiving a statin. MI, myocardial infarction.
[b]Outcome censored for all-cause death.

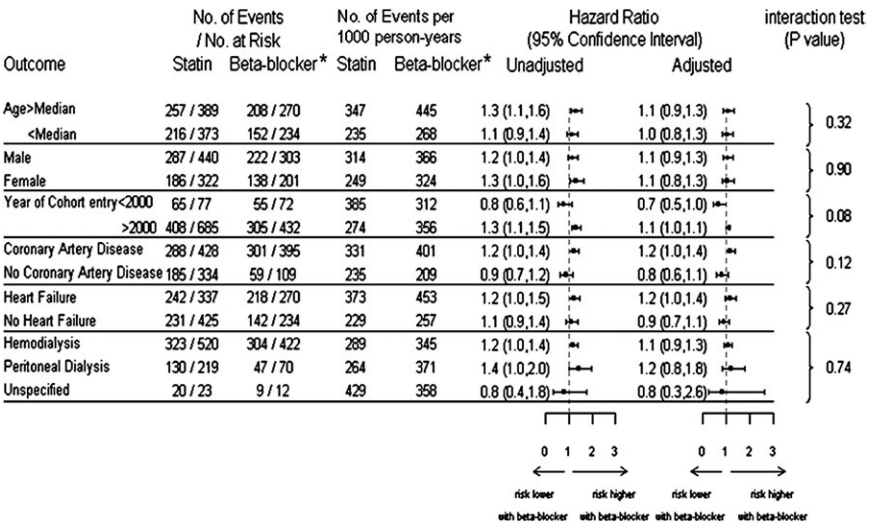

Fig. 2. Effect modification by age, year of cohort entry, coronary artery disease, heart failure and dialysis modality. (Beta-blocker users could also be receiving a statin).

demonstrated in patients with prior evidence of heart failure [44]. In our study, we failed to demonstrate differential effects of beta-blockers in patients with and without heart failure, recognizing our smaller sample provided less precise estimates than the cohort of Abbott *et al.*

Similarly, Foley *et al.* [45] assessed multiple antihypertensive classes among 11 142 hemodialysis patients of whom 8.5% received beta-blockers. Beta-blocker therapy was associated with reduced mortality (hazard ratio 0.84, 95% CI 0.75–0.93). In this study, the control group consisted of patients who were not receiving beta-blockers, calcium antagonists or ACE inhibitors. Therefore, as with Cice *et al.*, the control group would not have received any potential therapeutic benefit from these agents. In contrast, in our study, we selected two active comparators that are prescribed for presumed cardiovascular benefit in order to obtain groups with similar cardiovascular risk to that of beta-blocker users. As this was not the case in the study

Table 3. Beta-blocker type and dosing subgroup analyses

	No. of patients	No. of Events	No. of events per 1000 person-years	Unadjusted hazard ratio	aHR
Dose					
Low dose	449	325	362	1 (referent)	1
High dose	29	14	183	0.51 (0.30–0.87)	0.50 (0.29–0.88)
Missing dose	26	21	347	0.95 (0.61–1.48)	1.22 (0.69–2.16)
Dialyzability					
Low/unknown removal	87	60	359	1 (referent)	1
High removal	417	300	346	0.96 (0.73–1.27)	1.05 (0.78–1.41)
Cardioselectivity					
Cardioselective	447	315	343	1 (referent)	1
Non-selective	57	45	387	1.13 (0.83–1.55)	1.17 (0.83–1.65)
Lipophilicity/hydrophilicity					
Lipophilic	110	76	284	1 (referent)	1
Hydrophilic	394	284	371	1.30 (1.01–1.68)	1.03 (0.78–1.36)
Carvedilol versus other beta-blockers					
Carvedilol	37	29	379	1 (referent)	1
Other beta-blocker	467	331	346	0.91 (0.63–1.34)	1.1 (0.72–1.67)

of Foley *et al.*, the results may have been subject to confounding by indication.

Strengths and limitations

There are several strengths to our study. We included only incident dialysis patients and defined our study groups by incident drug use after the initiation of dialysis. Medication use was accurately coded in the datasets employed. The primary outcome was clinically important and well coded. The follow-up was complete with $<1\%$ of patients lost to emigration.

Limitations to our study include the fact that beta-blocker use was not randomly assigned, and as such, a causal assertion cannot be made between beta-blocker therapy and the outcome. Despite the use of multivariable analysis, residual confounding may have obscured any advantages conferred by beta-blocker use. Beta-blocker users were more likely to have cardiovascular comorbidities that would predispose them to worse outcomes. However, subgroup analyses by baseline cardiovascular disease status did not meaningfully change the results seen in the overall cohort.

In a clinical trial setting, strong efforts are made to maintain adherence to the intervention to which the participants are assigned. In an observational study, the patients may initiate and discontinue medications in follow-up, minimizing differences between the actual therapy delivered to patients and biasing the results toward the null. However, in our study, adherence to the study drugs was reasonable when we looked at the durability of medication use and crossovers according to prescriptions dispensed in follow-up.

We selected our control groups to be non-active comparators, as at the time of study design there was minimal evidence to suggest cardiovascular benefit from either statins or calcium channel blockers in patients receiving dialysis. Trials such as the Deutsche Diabetes Dialyse Studie (4D) and AURORA demonstrated no significant difference associated with statin use on cardiovascular outcomes in patients receiving dialysis [46, 47]. However, the recently presented findings of the Study of Heart and Renal Protection (SHARP trial) demonstrated that combination therapy with ezetimibe and simvastatin was associated with a reduction in major atherosclerotic events [48]. Given these findings, the statin-only group in our study may have experienced similar benefits and this may have concealed any cardioprotective effect conferred by beta-blocker therapy. However, it is important to recognize that the 54% of beta-blocker users were also receiving a statin at baseline. Therefore the above concern would be reduced, given that we compared beta-blocker users, who may have also been on a statin, to statin-only users.

With regards to the second comparator in our study, there is minimal evidence demonstrating improved cardiovascular outcomes from calcium channel blocker use among patients undergoing dialysis. A single randomized trial by Tepel *et al.* [18] has demonstrated a benefit for amlodipine on a composite secondary endpoint comprised of all-cause mortality and cardiovascular events, but notably, there was no significant effect found in the primary endpoint of all-cause mortality taken alone [18]. Moreover, this study was relatively small (limited to 251 patients) and is yet to be replicated. Meta-analyses examining multiple agents by Heerspink *et al.* and Agarwal *et al.* have suggested a beneficial effect for antihypertensives in general for patients receiving dialysis [49, 50]. However, these authors do acknowledge the need for additional randomized trials to be done for each class before more definitive conclusions can be drawn.

We considered a host of beta-blocker regimens as prescribed in routine practice. If only certain types of beta-blockers or regimens are beneficial, we might have failed to detect this in our primary analysis. However, when we examined beta-blocker characteristics, only higher dose demonstrated a cardiovascular benefit among chronic dialysis patients.

In conclusion, whether beta-blockers improve cardiovascular outcomes and reduce mortality in patients receiving dialysis remains unclear. Our study results demonstrating no associated cardiovascular benefit contrast with other available data. The current uncertainty around the benefits of beta-blockers in patients receiving dialysis will only be reconciled by a large randomized controlled trial. Given the tremendous cardiovascular disease burden in the growing dialysis population, such a definitive trial appears warranted.

Supplementary data

Supplementary data are available online at http://ndt.oxfordjournals.org

Acknowledgements. We thank Lihua Li for her assistance with figure design and Drs Matthew Weir and Michael Paterson for their support and assistance.

Financial Disclosures: Dr Wald has participated in advisory boards for Amgen and Gilead and received an unrestricted educational grant from Amgen. Dr Garg received investigator-initiated grants from Astellas and Roche to support the conduct of a living kidney donor study sponsored by the Canadian Institutes of Health Research.

Funding. This project was conducted at the Institute for Clinical Evaluative Sciences (ICES) and was supported by a grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC) Drug Innovation Fund. ICES is funded by an annual grant from the MOHLTC. Dr Wald was supported by the Randomized Controlled Trial Mentoring Program of CIHR. Dr Garg was supported by a CIHR Clinician-Scientist Award. Abhijat Kitchlu was supported by a Schulich Research Opportunities Program Award. The authors acknowledge Brogan Inc. for providing access to the drug identification numbers used to identify eligible drugs.

Conflict of interest statement. None declared.

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Received for publication: 18.1.11; Accepted in revised form: 5.7.11