β-blocker dialyzability and the risk of mortality and cardiovascular events in patients undergoing hemodialysis

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ABSTRACT

Background. β-blocker (BB) dialyzability has been proposed to limit their efficacy among hemodialysis (HD) patients. We attempted to confirm this hypothesis by comparing health outcomes associated with the initiation of dialyzable or nondialyzable BBs in a nationwide cohort of HD patients.

Methods. We created a prospective cohort study of 15 699 HD patients who initiated dialyzable BBs (atenolol, acebutolol, metoprolol and bisoprolol) and 20 904 hemodialysis patients who initiated nondialyzable BBs (betaxolol, carvedilol and propranolol) between 2004 and 2011 in Taiwan healthcare. We compared the risk of all-cause mortality and major adverse cardiovascular events (MACEs, a composite of the acute coronary syndrome, ischemic stroke and heart failure) between users of dialyzable versus nondialyzable BBs during a 2-year follow-up.

Results. New users of dialyzable BBs were younger, more often men, with diabetes mellitus, hypertension and hyperlipidemia compared with users of nondialyzable BBs. Compared with nondialyzable BBs, initiation of dialyzable BBs was associated with lower all-cause mortality {hazard ratio [HR] 0.82 [95% confidence interval (CI) 0.75–0.88]} and lower risk of MACEs [HR 0.89 (95% CI 0.84–0.93)]. Results were confirmed in subgroup analyses, censoring at BB discontinuation or switch, after 1:1 propensity score matching, reclassifying bisoprolol or excluding bisoprolol/carvedilol users.

Conclusions. This study does not offer support for the hypothesis that the dialyzability of BBs reduces their efficacy in HD patients.

Keywords: β blocker, cardiovascular event, dialysis, mortality, Taiwan National Health Insurance Research Database

INTRODUCTION

Patients on maintenance hemodialysis (HD) are at high risk of cardiovascular (CV) disease [1, 2] and β-blockers (BBs) are one of the most commonly prescribed CV medications among them [3]. There is, however, scarce interventional evidence to inform clinicians on their use [4].

The BB family contains heterogeneous medications of different pharmacodynamic and pharmacokinetic profiles. Differences in molecular weight, protein binding ability and volume distribution can make some BBs susceptible to filtering by the HD membrane. A single HD session resulted in significant losses in plasma concentration for atenolol and metoprolol [5] but minimally affected carvedilol [6] and propranolol [7] levels. Based on this evidence, a recent retrospective study hypothesized that the dialyzability of some BBs can limit their effectiveness [8]. The authors observed that patients consuming low-dialyzable BBs had fewer deaths than patients consuming high-dialyzable ones [8]. Confirming this hypothesis in other healthcare systems is important given its clinical implications, but we are not aware of any other study in this regard. First, a recent pharmacokinetic study found that, contrary to the initial pharmacopeia classification, bisoprolol is moderately dialyzed [5], which may have resulted in exposure misclassification in the previous study [8]. Second, a comparative effectiveness study from the USA reported that carvedilol (nondialyzable BB) initiation was associated with higher 1-year all-cause and CV mortality compared with metoprolol (dialyzable BB) [9].

Against this conflictive background, we attempted to confirm whether the dialyzability potential of BBs differentially affects outcomes in patients undergoing HD. We did so in a large national healthcare system, with a focus on the outcomes of death and major adverse cardiovascular events (MACEs).

MATERIALS AND METHODS

Source of data

This study is based on the dialysis population of Taiwan, as registered in the Taiwan National Health Insurance Research Database (NHIRD), which covers >99% of the Taiwanese population [10]. The NHIRD records comprehensive registration and claims information, including patient characteristics, disease diagnoses, pharmaceutical claims, examinations, operations, procedures and fees incurred. Furthermore, insured persons with major diseases (including patients receiving dialysis) must apply for a catastrophic illness registration card to protect vulnerable beneficiaries by exempting these patients from copayments. Inclusion in the dialysis register requires the medical examination of two nephrologists that investigate underlying disease, laboratory data, renal ultrasonography and indications for dialysis treatment. Patients' original identification numbers were encrypted to protect their privacy, but the encrypting procedure was consistent so that the linkage of the claims belonging to the same patient was feasible within the NHIRD and can be followed continuously. This study was approved by the research ethics board of Kaohsiung Medical University Hospital [KMUHIRB-EXEMPT(I)-20190010], and because patients' identification was not possible, the need for informed consent for this study was waived.

Study cohort

For this study we enrolled all adult (>18 years) patients who underwent chronic maintenance HD ($n = 101\ 222$) for >90 days between 1 January 2004 and 31 December 2011. Diagnosis of end-stage renal disease (ESRD) requiring chronic HD was confirmed by International Classification of Diseases, Ninth Revision (ICD-9) code 585, two consecutive HD procedure codes for an outpatient claim and inclusion in the Registry for Catastrophic Illness Patient Database. We selected those that initiated BB therapy after HD initiation (identified as the first prescription postdialysis with the absence of any other BB prescription in the previous 90 days). The date of the BB prescription was set as the index date (Figure 1).

Positive control cohort

Because peritoneal dialysis (PD) minimally affects the concentration of BBs in circulation [11], we assembled a positive control cohort of incident patients on PD who filled a new BB prescription during the same time period as the HD cohort. We then applied the same inclusion/exclusion criteria to our main cohort (Figure 1).

Study exposure

The study exposure was BB initiation, grouped according to their dialyzability properties as follows: dialyzable BBs (atenolol, acebutolol, metoprolol and bisoprolol) and nondialyzable BBs (betaxolol, carvedilol and propranolol; Supplementary data, Table S1). Note that this classification differs from the original publication of Weir *et al.* [8], after the realization of pharmacopeia errors in classifying bisoprolol as a nondialyzable BB [5].
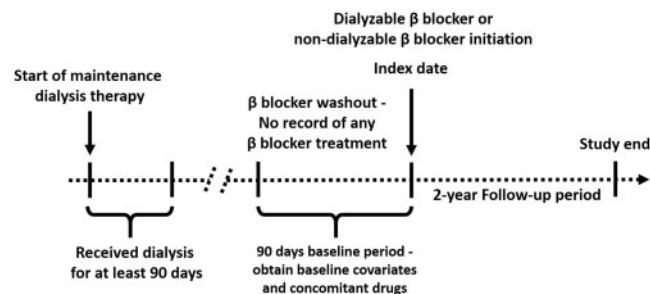

FIGURE 1: Study design. New users of dialyzable and nondialyzable BBs were identified from incident HD patients. The index date was the date of the initiation of BBs. Baseline covariates were identified in the 90-day period before the index date. Study participants were required to have dialysis vintage >90 days.

Study covariates

Comorbidities were defined by the presence of at least one hospital discharge or three consistent diagnoses in medical records during the 90-day period before the index date. Comorbidities included diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease, myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease and tachyarrhythmias (included paroxysmal supraventricular tachycardia, atrial flutter and atrial fibrillation). Definitions are outlined in the Supplementary data, Table S2. We also extracted information on other ongoing medications, including renin–angiotensin–aldosterone system (RAAS) inhibitors, calcium channel blockers, warfarin, statins, digoxin and antiplatelets (aspirin or clopidogrel), as identified by Anatomical Therapeutic Chemical codes (Supplementary data, Table S3).

Study outcomes and follow-up

The study's main outcomes were all-cause mortality and MACEs. A MACE was defined as a hospital admission with a primary diagnosis of acute myocardial infarction, heart failure or ischemic stroke. The diagnostic accuracy of the NHIRD has been validated for our main outcomes of interest [10, 12, 13]. Outcome definitions are detailed in the Supplementary data, Table S2. Patients were followed up until death, deregistration, events, dialysis modality change, kidney transplantation or until 2 years from the index date, whichever occurred first.

Statistical analyses

Data are presented as the mean and standard deviation for normally distributed continuous variables and proportions for categorical variables. To observe differences in clinical characteristics between categories, we used the unpaired two-tailed *t*-test for continuous values analysis and the chi-squared test for categorical variables analysis.

Kaplan–Meier curves were generated showing cumulative probabilities of study outcomes over a 2-year observation time and differences were tested using a log-rank test in the full cohort. After ensuring the fulfillment of proportional hazards assumption by Schoenfeld residuals trend tests, we applied the univariable and multivariable Cox proportional hazards model regarding the risk of death associated with different dialyzable BB groups. Cause-specific hazard models were applied to estimate

the associated risks of MACEs and single components of MACEs accounting for death as a competing risk. Our main analysis followed an intention-to-treat (ITT) design, whereby we assumed that the patient remained on therapy until the event or the end of follow-up. In addition, we also performed as-treated analyses, whereby patients were censored on the day that they switched to a BB of a different dialyzability category or discontinued BBs, both ascertained by subsequent prescriptions recorded.

To assess the robustness of our findings, we performed three additional sensitivity analyses. First, we performed 1:1 propensity score (PS) matching [14, 15] to balance confounders and attempt to minimize confounding by indication bias resulting from nonrandom treatment. We used the Mahalanobis metric method [16, 17] without replacement by the nearest number matching and with an interval of 0.0001. Baseline characteristics were compared before and after PS matching using standardized mean difference. A standardized mean difference <0.1 was considered to indicate an adequate variable balance between groups. Second, we performed similar analyses in a positive control population consisting of incident PD patients initiating BB therapy because of presumed low BB removal with this technique [11]. Third, because purported BB benefits derive from trials of patients with CV disease, we ran subgroup analyses stratifying by baseline coronary artery disease or heart failure comorbidity.

Finally, because of the observed associations versus the original report by Weir et al. [8], we explored whether differences in results were attributed to bisoprolol misclassification or to a different pattern of BB use in Canada versus Taiwan. We thus repeated analyses excluding bisoprolol users (thus comparing strictly nondialyzable versus highly dialyzable BBs) and repeated analyses after reallocating bisoprolol to the nondialyzable BB group and removing carvedilol users, the latter of which is only approved for persons with documented heart failure in Ontario, where the Canadian study was performed.

All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and Stata 14 (StataCorp, College Station, TX, USA). A two-tailed P-value <0.05 was considered significant.

RESULTS

Patient characteristics

During 2004–11, a total of 101 222 patients initiated dialysis in Taiwan. Among these, 58 476 received BBs. After excluding prevalent BB users ($n = 18\,240$), we selected 15 699 patients initiating dialyzable BBs and 20 904 patients initiating nondialyzable BBs (see flow chart selection in Figure 2).

The characteristics of the included patients are listed in Table 1. Patients receiving dialyzable BBs were younger; more often men; had a higher proportion of diabetes, hypertension and hyperlipidemia and more commonly used RAAS inhibitors, statins and antiplatelets than patients receiving nondialyzable BBs. Conversely, dialyzable BB users had a lower proportion of coronary artery disease, heart failure, peripheral vascular disease and tachyarrhythmia and lower use of digoxin compared with nondialyzable BB users.

Primary analysis

The mean follow-up time was 1.65 years in the dialyzable BB group and 1.49 years in the nondialyzable BB group. During this period, 2456 deaths and 7930 MACEs were recorded (Supplementary data, Table S4). Kaplan–Meier curves graphically showed a lower incidence of all-cause mortality and MACEs among patients taking dialyzable BBs compared with nondialyzable BB users (Figure 3).

In multivariable-adjusted Cox regression analysis, patients taking dialyzable BBs present a lower all-cause mortality risk {adjusted hazard ratio [HR] 0.82 [95% confidence interval (CI) 0.75–0.88]} compared with patients taking nondialyzable BBs (Table 2). Using cause-specific hazard models, dialyzable BB initiators were associated with a lower risk of MACEs [HR 0.89 (95% CI 0.84–0.93)] (Table 2), mainly attributed to a lower heart failure risk [HR 0.85 (95% CI 0.80–0.91); Supplementary data, Table S5]. As-treated (per protocol) approaches (Supplementary data, Table S6) showed results in line with our primary analyses.

Secondary analyses

Associations similar to those observed in our main results were found in subgroup analysis stratifying by coronary artery disease or heart failure comorbidity (Supplementary data, Table S7). PS matching resulted in 8583 matched pairs with well-balanced baseline characteristics (all standardized differences <0.1) (Supplementary data, Table S8). Outcome analyses in this PS-matched cohort yielded similar results to our main analysis (Supplementary data, Table S9). Characteristics of PD patients confirming the positive control cohort are presented in the Supplementary data, Table S10. No statistically significant differences were found with regards to study outcomes between dialyzable and nondialyzable BBs among PD patients (Supplementary data, Table S11). However, the magnitude of the relative risks consistently favored the initiation of dialyzable BBs.

Supporting analyses

After excluding bisoprolol users, highly dialyzable BBs (this time composed of atenolol, acebutolol and metoprolol) did not present a mortality risk difference compared with nondialyzable BBs (this time betaxolol, carvedilol and propranolol) but still showed a lower risk of MACEs (Table 3). Reclassifying bisoprolol as nondialyzable BB and excluding carvedilol users reversed the direction of the association between BB groups and death, showing an increased mortality risk associated with dialyzable BB use [HR 1.16 (95% CI 1.04–1.30 ITT approach)] but still a lower MACE risk [HR 0.91 (95% CI 0.85–0.98)] (Table 3).

DISCUSSION

We cannot confirm the hypothesis that the dialyzability of BBs affects their effectiveness in patients undergoing HD. We observed, instead, that compared with the use of nondialyzable BBs, patients who used dialyzable BBs were at lower mortality and MACE risk. Although we cannot exclude the possibility that BBs are *de facto* lost into the dialysate, this observational
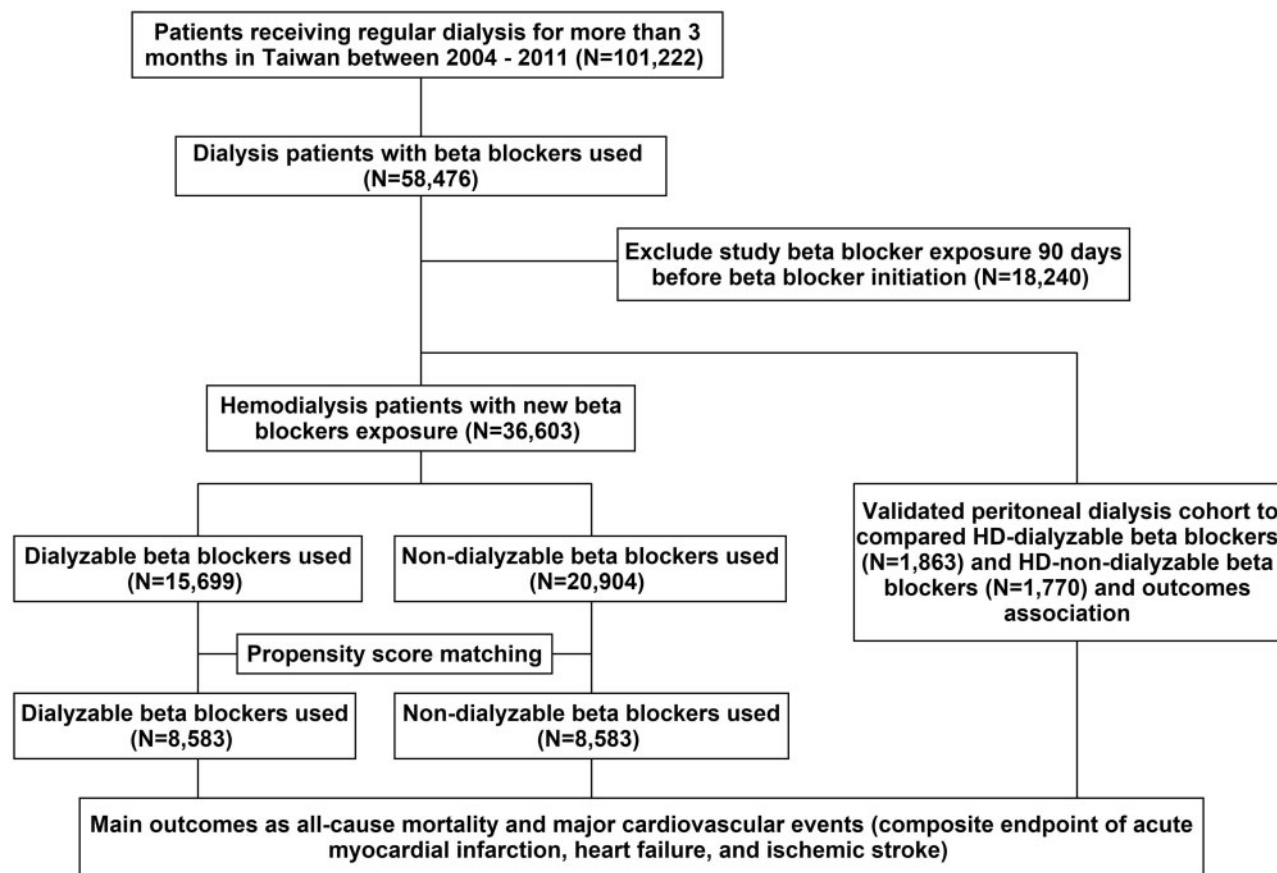
FIGURE 2: Patient selection flow chart.

Table 1. Baseline characteristics of patients on HD starting dialyzable or nondialyzable BBs

Baseline characteristics	Dialyzable BB ($n = 15\,699$)	Nondialyzable BB ($n = 20\,904$)	P-value
Age (years), mean(SD)	55.9 (13.1)	57.2 (13.0)	<0.001
Men, n (%)	8066 (51.4)	9840 (47.1)	<0.001
Comorbidities, n (%)			
Diabetes mellitus	7041 (44.8)	8512 (40.7)	<0.001
Hypertension	12 102 (77.1)	13 532 (64.7)	<0.001
Hyperlipidemia	3240 (20.6)	3713 (17.8)	<0.001
Coronary artery disease[a]	4720 (30.1)	7254 (34.7)	<0.001
Myocardial infarction	1036 (6.6)	1428 (6.8)	0.380
Heart failure	3216 (20.5)	4725 (22.6)	<0.001
Peripheral vascular disease	866(5.5)	1273 (6.1)	0.021
Cerebrovascular disease	1655 (10.5)	2148 (10.3)	0.408
Tachyarrhythmias[b]	520 (3.3)	897 (4.3)	<0.001
Concomitant drugs, n (%)			
RAAS inhibitors	1966 (12.5)	2002 (9.6)	<0.001
Calcium channel blockers	882 (5.6)	1261 (6.0)	0.095
Warfarin	215 (1.4)	312 (1.5)	0.328
Statins	2961 (18.9)	3363 (16.1)	<0.001
Digoxin	265 (1.7)	425 (2.0)	0.016
Antiplatelets (aspirin and clopidogrel)	3704 (23.6)	4705 (22.5)	0.014
BB type, n (%)			
Atenolol	5137 (32.7)	0 (0.0)	
Acebutolol	270 (1.7)	0 (0.0)	
Metoprolol	987 (6.3)	0 (0.0)	
Bisoprolol	9305 (59.3)	0 (0.0)	
Betaxolol	0 (0.0)	396 (1.9)	
Carvedilol	0 (0.0)	11171 (53.4)	
Propranolol	0 (0.0)	9337 (44.7)	

[a]Coronary artery disease includes myocardial infarction, history of percutaneous coronary interventions and history of coronary artery bypass surgery.
[b]Tachyarrhythmias included paroxysmal supraventricular tachycardia, atrial flutter and atrial fibrillation.
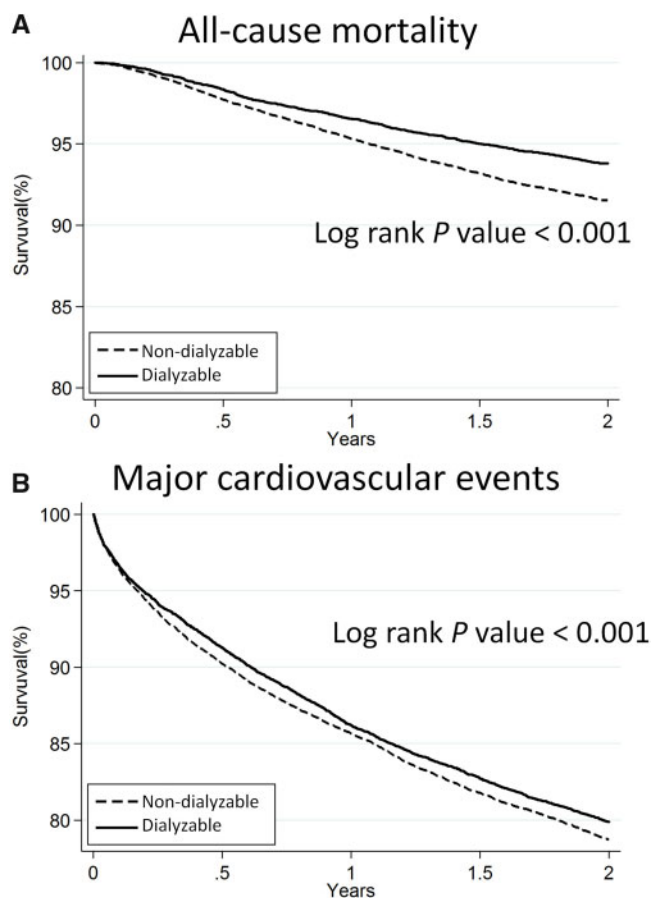
P.-H. Wu *et al.*

FIGURE 3: Kaplan–Meier curves (crude) for the incidence of (**A**) all-cause mortality and (**B**) major CV events according to the initiation of dialyzable or nondialyzable BBs in patients undergoing HD.

Table 2. Outcomes associated with the initiation of dialyzable versus nondialyzable BBs in patients undergoing HD (ITT analysis)

Main outcomes	HR (95% CI)	
	Crude	Multivariable-adjusted model[a]
All-cause mortality		
Dialyzable BBs	0.77 (0.71–0.83)	0.82 (0.75–0.88)
Nondialyzable BBs	1 [Ref]	1 [Ref]
MACE[b]		
Dialyzable BBs	0.84 (0.80–0.89)	0.89 (0.84–0.93)
Nondialyzable BBs	1 [Ref]	1 [Ref]

[a]The multivariable-adjusted model was obtained from Cox regression adjusting for age, sex, comorbidities and concomitant medications.
[b]MACEs included myocardial infarction, heart failure hospitalization and ischemic stroke and analyzed by cause-specific hazard models.
[Ref]: reference.

nationwide study suggests that, clinically, dialyzability does not explain differences in outcome.

Using a larger cohort and a similar study design, our results disagree with those of the Canadian report [8]. Our supporting analyses suggest that differences may be attributed to misclassification of bisoprolol as low dialyzable [5] and to variations in the preferences of BBs across our healthcare systems (particularly carvedilol

Table 3. Supporting analyses: outcomes associated with the initiation of dialyzable versus nondialyzable BBs after excluding bisoprolol users or reclassifying bisoprolol as nondialyzable BB and excluding carvedilol users

Main outcomes	HR (95% CI)	
	Crude	Multivariable-adjusted model[a]
Approach 1: excluding bisoprolol users		
All-cause mortality		
Dialyzable BBs	0.83 (0.75–0.92)	0.97 (0.87–1.08)
Nondialyzable BBs	1 [Ref]	1 [Ref]
MACE[b]		
Dialyzable BBs	0.73 (0.69–0.78)	0.87 (0.82–0.94)
Nondialyzable BBs	1 [Ref]	1 [Ref]
Approach 2: reallocating bisoprolol and excluding carvedilol users		
All-cause mortality		
Dialyzable BBs	1.04 (0.93–1.16)	1.16 (1.04–1.30)
Nondialyzable BBs	1 [Ref]	1 [Ref]
MACE[b]		
Dialyzable BBs	0.79 (0.74–0.85)	0.91 (0.85–0.98)
Nondialyzable BBs	1 [Ref]	1 [Ref]

Approach 1: dialyzable BBs include acebutolol, atenolol and metoprolol; nondialyzable BBs include betaxolol, carvedilol and propranolol.
Approach 2: dialyzable BBs include acebutolol, atenolol and metoprolol; nondialyzable BBs include bisoprolol, betaxolol and propranolol.
[a]The multivariable-adjusted model was obtained from Cox regression models adjusted for age, sex, comorbidities and concomitant medications.
[b]MACEs included myocardial infarction, heart failure hospitalization and ischemic stroke and analyzed by cause-specific hazard models.
[Ref]: reference.

use; Supplementary data, Table S12). From an academic point of view, this study opens an interesting discussion about the generalizability of findings across health systems in the context of different patterns or practices and medication use. However, we also note that there are other inevitable differences in patient selection and covariate definition (summarized Supplementary data, Table S13) that should be considered when directly comparing studies.

One possibility is that dialyzing BBs actually reduce the risk of adverse events attributed to their use. In this regard, it would have been valuable to evaluate the incidence of bradycardia or hypotension, but ascertaining such outcomes from ICD diagnoses may not be reliable. However, beyond dialyzability differences, the heterogeneous family of BBs has other varying pharmacologic and pharmacokinetic properties, such as β-adrenergic receptor selectivity, vasodilatory capabilities, lipophilicity/hydrophilicity and other physicochemical factors (i.e. molecular size, plasma protein binding or differences in the volume of distribution) [8, 9, 18, 19]. These may also (and perhaps more strongly) impact on outcome differences.

We note that mortality outcomes were dependent on the classification of bisoprolol, but the MACE outcomes were not. Thus, if we were to assume that the small population taking acebutolol or betaxolol in our study had a limited effect on the findings, a simplified assessment of the results may suggest that prescribing atenolol or metoprolol is associated with reduced MACEs compared with carvedilol or propranolol. Beyond dialyzability, a common feature of atenolol and metoprolol (and bisoprolol) is their β1 cardioselectivity. β1 cardioselective BBs allow reduced cardiac output and heart rate as well as a

lesser tendency to peripheral vasoconstriction [20]. Preceding evidence suggests advantages associated with the use of these over noncardioselective BBs; in trials of heart failure patients (cardioselective), bisoprolol achieved a greater heart rate reduction than carvedilol (a noncardioselective) [21]. Also, in previous observational analyses of persons with ESRD, cardioselective BBs (specifically atenolol and metoprolol) were associated with lower all-cause mortality compared with noncardioselective BBs (carvedilol and labetalol) [22]. Also, in patients on HD, carvedilol was associated with slightly higher rates of death and intradialytic hypotension than metoprolol [9].

Conversely, noncardioselective BBs (mainly carvedilol and propranolol in our study) have been suggested to promote hyperkalemia in patients with ESRD, especially after exercise, and in patients taking mineralocorticoid receptor antagonists [23, 24]. In patients with heart failure with preserved ejection fraction, treatment with carvedilol (versus placebo) did not modify surrogate cardiac biomarkers but instead increased both brain natriuretic peptide and N-terminal proB-type natriuretic peptide levels [25]. We thus speculate prescribing cardioselective BBs may be associated with fewer MACEs compared with noncardioselective BBs and possibly reduced mortality. Although our supporting analyses do not show consistency for the mortality outcome, this may be confounded by either a limited sample size from excluding bisoprolol or a beneficial mortality effect from bisoprolol.

This study has several strengths, including large sample size and national representativeness, comprehensive longitudinal follow-up and outcome analysis applicable to real-world clinical practice. However, this study also has limitations. First, as in any observational study, we cannot presume causality in the associations reported and unmeasured confounding may have persisted despite our efforts. In this regard, we acknowledge the lack of information on echocardiography, smoking habits, body mass index or physical activity. Because of this, the BB dialyzability effect in HD patients with heart failure with preserved ejection fraction could not be evaluated. We also acknowledge that BB prescription does not guarantee that the patient complies with the treatment. Furthermore, we remind the reader that results represent Taiwan's healthcare during a certain time period. As discussed earlier, extrapolation to other periods, health systems, clinical practices and ethnicities other than Asians should be done with caution.

To conclude, we found that initiation of dialyzable BBs was associated with a lower risk of mortality and MACEs compared with nondialyzable BBs initiators. Thus the dialyzability potential of BBs does not seem to consistently explain outcome differences in this nation-representative study. Finally, our observational study favors the use of cardioselective BBs in patients undergoing dialysis for cardiovascular risk prevention.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

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AUTHORS' CONTRIBUTIONS

P.-H.W., Y.-T.L. and J.-J.C. were involved in conceptualization. P.-H.W., Y.-T.L. and Y.-W.C. were involved in data curation. P.-H.W., Y.-T.L., M.-C.K., J.-S.L. and J.-J.C. were involved in the study design and analysis plan. Y.-T.L. was involved in statistical analysis. P.-H.W., Y.-T.L. and Y.-W.C. carried out funding acquisition. P.-H.W. and Y.-T.L. were involved in the investigation. P.-H.W., Y.-T.L. and J.-J.C. were involved in writing the first draft and all coauthors were involved in writing, review and editing.

CONFLICT OF INTEREST STATEMENT

All the authors declare no competing interests.

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Estradiol and mortality in women with end-stage kidney disease

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ABSTRACT

Background. Young women with end-stage kidney disease (ESKD) have early menopause compared with women in the general population and the highest mortality among the dialysis population. We hypothesized that low estrogen status was associated with death in women with ESKD.

Methods. We measured estradiol and sex hormone levels in female ESKD patients initiating hemodialysis from 2005 to 2012 in four Canadian centers. We divided women into quintiles based on estradiol levels and tested for associations between the estradiol level and cardiovascular (CV), non-CV and all-cause mortality. Participants were further dichotomized by age.

Results. A total of 482 women (60 ± 15 years of age, 53% diabetic, estradiol 116 ± 161 pmol/L) were followed for a mean of 2.9 years, with 237 deaths (31% CV). Estradiol levels were as follows (mean ± standard deviation): Quintile 1: 19.3 ± 0.92 pmol/L; Quintile 2: 34.6 ± 6.6 pmol/L; Quintile 3: 63.8 ± 10.6 pmol/L; Quintile 4: 108.9 ± 19.3; Quintile 5: 355 ± 233 pmol/L. Compared with Quintile 1, women in Quintiles 4 and 5 had significantly higher adjusted all-cause mortality {hazard ratio [HR] 2.12 [95% confidence interval (CI) 1.38–3.25] and 1.92 [1.19–3.10], respectively}. Similarly, compared with Quintile 1, women in Quintile 5 had higher non-CV mortality [HR 2.16 (95% CI 1.18–3.96)]. No associations were observed between estradiol levels and CV mortality. When stratified by age, higher quintiles were associated with greater all-cause mortality (P for trend <0.001) and non-CV mortality (P for trend = 0.02), but not CV mortality in older women.

Conclusions. In women with ESKD treated with hemodialysis, higher estradiol levels were associated with greater all-cause and non-CV mortality. Further studies are required to determine the mechanism for the observed increased risk.

Keywords: cardiovascular, end-stage renal disease, mortality, estradiol, women

INTRODUCTION

Women with end-stage kidney disease (ESKD) have an abnormal sex hormone profile characterized by hypothalamic