Supplement

Table S1. Dialyzability of study beta blockers – primary literature summary

Beta blocker	Molecular Weight (Daltons)	Protein binding (%)	Volume of Distribution (L/kg)	Elimination $t_{1/2}$ with normal GFR (hours)	Elimination $t_{1/2}$ in stage V CKD (hours)	Elimination $t_{1/2}$ during hemodialysis (hours)	Clearance during hemodialysis (mL/min)	Plasma reduction during hemodialysis (%)	Recommendation for use in hemodialysis
Bisoprolol	325	30	3.0	10 - 12.1[1,2]	23.7 - 37.2 [2]	--	50.8 – 69.6 [3]	25.4 – 34.8 [3]	Limit the total dose given to patients receiving chronic hemodialysis.[2,3]
Propranolol	259	90	4.9	4.3 [4]	2.2 – 3.5 [4,5]	4 – 5 [4]	--	--	Alternation of the dose is not needed in patients receiving hemodialysis. [4]
Acebutolol	336	26	1.2	3.5 – 8.8 [6]	7.0 – 7.5 [6]	3.2 [6]	42.6 [6]	--	The dose and timing of administration should be adjusted in patients receiving chronic hemodialysis.[6]
Atenolol	266	10	4.2	5.9 – 6.3 [7,8]	73.4 [9]	4.3 – 7.5 [5,8-10]	42.6 [9]	34 [10]	It is necessary to adjust the dose and frequency of dosing in patients receiving chronic hemodialysis.[9]
Metoprolol	267	10	3.2	3.5	4.2 – 5.8 [5,11]	5.0 [11]	--	--	--

Table S2. Limitations of the available pharmacokinetic studies of beta blockers in hemodialysis.		
Beta blocker	**References**	**Limitations**
Bisoprolol	Payton, *et al* [2]	Published in 1987. Dialysis prescription not described. Half-life and clearance rates not determined.
	Kanegae, *et al* [3]	Clearance estimated by the A-V difference method only. Variances about the mean clearance rates not reported.
Propranolol	Wood, *et al* [4]	Published in 1980. Dialysis prescription not described. Half-life estimated but not clearance rates.
	Niedermayer, *et al* [5]	Published in 1978. Half-life estimated with tritiated drug. Dialysis prescription not described.
Acebutolol	Roux, *et al* [6]	Published in 1980. Dialysis prescription was 2 – 3 times per week for 5 – 7 hour treatments with a bed-side canister machine using a cuprophane membrane. The average Qb was 238 ml/min. Ultrafiltration rate was 2 ml/min. Clearance estimated by the A-V difference method only. Wide ranges of dialysis clearance rates (21.6 – 65.4 ml/min).
Atenolol	Campese, *et al* [10]	Published in 1985. Dialysis prescription was for 5 hours with cellulose dialyzers, but no other details provided. Half-life estimated but not clearance rates.
	Flouvat, *et al* [9]	Published in 1980. Clearance estimated by the A-V difference method only. Wide ranges of dialysis clearance rates reported (17.4 – 92.7 ml/min). Dialysis prescription was for 5 – 7 hours, mean Qb of 236 ml/min with a coil kidney using a cuprophane dialyzer. Ultrafiltration rate was 2 ml/min.
	Kirch, *et al* [8]	Published in 1981. Half-life estimated but not clearance rates. Two of five hemodialysis patients had undetectable drug levels. Dialysis prescription not described.
	Niedermayer, *et al* [5]	Published in 1978. Half-life estimated with tritiated drug. Dialysis prescription not described.
Metoprolol	Seiler, *et al* [11]	Published in 1980. Dialysis prescription not described. Dialysis started 20 hours following drug ingestion – only the dialysis half-life of drug metabolites could be assessed.
	Niedermayer, *et al* [5]	Published in 1978. Half-life estimated with tritiated drug. Dialysis prescription not described.

Table S3. Baseline characteristics of the Non-Dialysis Cohort

Baseline Characteristics	Unmatched Cohort			Propensity-matched Cohort		
	High Dialyzability (acebutolol, atenolol, metoprolol)[1]	**Low Dialyzability** (propranolol, bisoprolol)[1]	Standardized Differences (%)	**High Dialyzability** (acebutolol, atenolol, metoprolol)[1]	**Low Dialyzability** (propranolol, bisoprolol)[1]	Standardized Differences (%)
	N = 36,081	**N = 13,607**		**N = 13,586**	**N = 13,586**	
Age, mean (SD)	74.4 (6.4)	74.4 (6.3)	0	74.5 (6.4)	74.4 (6.3)	1
Sex, female (%)	19,174 (53.1)	6,995 (51.4)	3	6,988 (51.4)	6,988 (51.4)	0
Residence, rural (%)	3468 (9.6)	1,108 (8.1)	5	1,299 (9.6)	1,106 (8.1)	5
General measures of comorbidity (measured in the year before the index date[2])						
Distinct prescription drugs, median (IQR)	10 (6 – 15)	11 (7 – 15)	1	11 (7 – 15)	11 (7 – 15)	1
Comorbidities (measured in the 5 years before the index date[2]), n (%)						
Coronary artery disease[3]	18,612 (51.6)	7,100 (52.2)	1	7,052 (51.9)	7,095 (52.2)	1
Coronary revascularization	4,648 (12.9)	1,574 (11.6)	4	1,594 (11.7)	1,573 (11.6)	0
Heart failure	5,111 (14.2)	2,198 (16.2)	6	2,174 (16.0)	2,190 (12.1)	0
Arrhythmia[4]	3,956 (11.0)	1,567 (11.5)	2	1,627 (12.0)	1,559 (11.5)	2
Aortic aneurysm repair or bypass	191 (0.5)	56 (0.4)	2	61 (0.5)	56 (0.4)	1
Peripheral vascular disease	623 (1.7)	218 (1.6)	1	226 (1.7)	218 (1.6)	0
Stroke or TIA	975 (2.7)	321 (2.4)	2	313 (2.3)	321 (2.4)	0
Diabetes mellitus	8,389 (23.3)	3,157 (23.2)	0	3,181 (23.4)	3.154 (23.2)	0
Estimated glomerular filtration rate category, no. (%)						
45 – 59 ml/min/1.73m^2	8702 (24.1)	3208 (23.6)	1	3317 (24.4)	3200 (23.6)	2
60 – 89 ml/min/1.73m^2	23704 (65.7)	9057 (66.6)	2	8928 (65.7)	9047 (66.6)	2
≥ 90 ml/min/1.73m^2	3675 (10.2)	1342 (9.9)	1	1341 (9.9)	1339 (9.9)	0
Beta blocker dose[5] (measured at the index date[2])						
Low dose, n (%)	32,377 (89.7)	12,780 (93.9)	15*	12,763 (93.9)	12,763 (93.9)	0
Medications (measured in the 180 days before the index date[2]), n (%)						
Alpha blockers	1,424 (4.0)	518 (3.8)	13*	222 (6.7)	202 (6.1)	2
ACE inhibitors	15,571 (46.2)	5,945 (43.7)	1	6,010 (44.2)	5,936 (43.7)	1
ARB	7,645 (21.2)	3,384 (24.9)	9	3,259 (24.0)	3,374 (24.8)	2
CCB	12,291 (34.1)	4,773 (35.1)	2	4,736 (34.9)	4,764 (35.1)	0
Digoxin	1,687 (4.7)	801 (5.9)	5	679 (5.0)	799 (5.9)	4
Statins	18,575 (51.5)	7,519 (55.3)	8	7,490 (55.1)	7,502 (55.2)	0
Warfarin	4,278 (11.9)	1,986 (14.6)	8	1,850 (13.6)	1,977 (14.6)	3
Beta blockers						
Acebutolol	1,361 (3.8)	-	-	460 (3.4)	-	-
Atenolol	15,852 (43.9)	-	-	5488 (40.4)	-	-
Metoprolol	18,868 (52.3)	-	-	7638 (56.2)	-	-
Bisoprolol	-	11,318 (83.2)	-	-	11298 (83.2)	-
Propranolol	-	2,289 (16.8)	-	-	2288 (18.8)	-
Propensity Score Probability (propensity of receiving a high dialyzability beta blocker)						
Mean (SD)	0.74 (0.09)	0.69 (0.09)	48*	0.70 (0.09)	0.70 (0.09)	3
Median (IQR)	0.75 (0.68 –0.80)	0.70 (0.63 – 0.77)	48*	0.70 (0.63 – 0.77)	0.70 (0.63 – 0.77)	3

1. “Acebutolol” refers to acebutolol HCl, “metoprolol” refers to metoprolol tartrate, “bisoprolol” refers to bisoprolol fumarate
2. “Index date” is defined as the day of the first new study beta blocker prescription filled during hemodialysis.
3. Coronary artery disease includes myocardial infarction, angina, and percutaneous coronary interventions
4. Arrhythmia includes brady and tachyarrhythmias.
5. Definitions of “high” or “low” dose were based on the recommendations found in each product’s monograph. High doses: acebutolol, ≥ 400 mg per day; atenolol, > 50 mg per day; metoprolol, > 100 mg per day, propranolol, ≥ 160 mg per day; bisoprolol, > 5 mg per day.
calcium channel blocker.
* Denotes significant standardized differences (≥ 10%)

Table S4. Secondary outcomes (hemodialysis cohort, n = 3,294)			
	No. of events (%)	**Relative Risk (95%CI)**	**P value**
Composite of death, myocardial infarction, or heart failure			
High Dialyzability Beta Blockers	269 (8.2)	1.2 (1.0 – 1.5)	0.03
Low Dialyzability Beta Blockers	225 (6.8)	1 (referent)	
Myocardial infarction			
High Dialyzability Beta Blockers	40 (1.2)	1.1 (0.7 – 1.7)	0.82
Low Dialyzability Beta Blockers	38 (1.2)	1 (referent)	
Heart failure			
High Dialyzability Beta Blockers	66 (2.0)	0.9 (0.7 – 1.3)	0.66
Low Dialyzability Beta Blockers	71 (2.2)	1 (referent)	

Table S5. All cause mortality (Conditional Cox Proportional Hazards Model)						
	No. of patients	**Person-years**	**No. of events (%)**	**Event Rate (per 100 patient-years)**	**Hazard Ratio (95%CI)**	**P value**
Hemodialysis cohort						
High Dialyzability Beta Blockers	3294	1578.9	182	11.5	1.3 (1.1 – 1.7)	0.02
Low Dialyzability Beta Blockers	3294	1587.3	135	8.5	1 (referent)	
Non-dialysis cohort						
High Dialyzability Beta Blockers	13,586	6648.6	186	2.7	1.0 (0.8 – 1.3)	0.71
Low Dialyzability Beta Blockers	13,586	6650.3	179	2.8	1 (referent)	

Supplement References

1. Kirch W, Rose I, Demers HG, Leopold G, Pabst J, Ohnhaus EE: Pharmacokinetics of bisoprolol during repeated oral administration to healthy volunteers and patients with kidney or liver disease. *Clin Pharmacokinet* 13: 110–117, 1987

2. Payton CD, Fox JG, Pauleau NF, Boulton-Jones JM, Ioannides C, Johnston A: The single dose pharmacokinetics of bisoprolol (10 mg) in renal insufficiency: the clinical significance of balanced clearance. *European Heart Journal* 8: 12–22, 1987

3. Kanegae K, Hiroshige K, Suda T, Iwamoto M, Ohta T, Nakashima Y, Ohtani A: Pharmacokinetics of bisoprolol and its effect on dialysis refractory hypertension. *Int J Artif Organs* 22: 798–804, 1999

4. Wood A, Vestal RE, Spannuth CL, Stone WJ, Wilkinson GR, Shand DG: Propranolol disposition in renal failure. *Br. J. Clin. Pharm.* 10: 561–566, 1980

5. Niedermayer W, Seiler KU, Wassermann O: Pharmacokinetics of antihypertensive drugs (atenolol, metoprolol, propranolol and clonidine) and their metabolites during intermittent haemodialysis in humans. *Proc Eur Dial Transplant Assoc* 15: 607–609, 1978

6. Roux A, Aubert P, Guedon J, Flouvat B: Pharmacokinetics of Acebutolol in Patients with all Grades of Renal Failure. *Eur J Clin Pharmacol* 17: 339–348, 1980

7. Brown HC, Carruthers SG, Johnston GD, Kelly JG, McAinsh J, McDevitt DG, Shanks RG: Clinical pharmacologic observations on atenolol, a beta-adrenoceptor blocker. *Clin. Pharmacol. Ther.* 20: 524–534, 1976

8. Kirch W, Kohler H, Mutschler E, Schafer M: Pharmacokinetics of atenolol in relation to renal function. *Eur J Clin Pharmacol* 19: 65–71, 1981

9. Flouvat B, Decourt S, Aubert P, Potaux L, Domart M, Goupil A: Pharmacokinetics of atenolol in patients with terminal renal failure and influence of haemodialysis. *Br. J. Clin. Pharm.* 9: 379–385, 1980

10. Campese VM, Feinstein EI, Gura V, Mason WD: Pharmacokinetics of Atenolol in Patients Treated With Chronic Hemodialysis or Peritoneal Dialysis. *J. Clin. Pharmacol.* 25: 393–395, 1985

11. Seiler KU, Schuster KJ, Meyer GJ, Niedermayer W, Wassermann O: The pharmacokinetics of metoprolol and its metabolites in dialysis patients. *Clin Pharmacokinet* 5: 192–198, 1980