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Beta blocker dialyzability and effectiveness in chronic hemodialysis patients

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Abstract

Of the minimal information describing drug dialyzability, the majority was obtained prior to modern hemodialysis membranes. This study characterized the dialyzability of the most commonly prescribed beta blockers in patients undergoing high-flux hemodialysis. Eight subjects were recruited to a pharmacokinetic, 4-way crossover trial. Drug concentrations were measured using mass spectrometry and dialyzability determined by the arterial-venous difference and recovery clearance methods. A provincial-wide retrospective cohort study was designed to determine the effect of dialyzability on adverse clinical outcomes. Beta blocker efficacy can be hindered if substantial clearance occurs during dialysis. Our results demonstrate atenolol and metoprolol are extensively cleared during hemodialysis, while carvedilol displays low dialyzability. Although bisoprolol was previously considered to be minimally dialyzed, we now demonstrate moderate dialyzability. This highlights the importance of conducting dialyzability studies. With recent findings suggesting heightened mortality risk in hemodialysis patients prescribed highly dialyzed beta blockers, dialyzability data is critical to optimize pharmacotherapy.

Keywords

Beta Blocker, Drug Dialyzability, Dialytic Clearance, Pharmacokinetics, Chronic Hemodialysis, End-Stage Renal Disease, Kidney Failure, Cardiovascular Disease, Mass Spectrometry

Co-Authorship Statement

Portions of the introduction and conclusion were reproduced with permission from the following review articles:

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Dedication

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This dissertation is dedicated to my family and friends

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Abbreviations

ACE	Angiotensin Converting Enzyme
A_{conc}	Arterial Plasma Drug Concentration
ACR	Albumin Creatinine Ratio
APD	Automated Peritoneal Dialysis
ARB	Angiotensin Receptor Blocker
AUC	Area Under the Curve
Beta Blocker	Beta Adrenergic Receptor Blocker
BMI	Body Mass Index
CAPD	Continuous Ambulatory Peritoneal Dialysis
CCB	Calcium Channel Blocker
CI	Confidence Interval
CIHI	Canadian Institute of Health Information
CKD	Chronic Kidney Disease
CL_{A-V}	Arterial-Venous Difference Clearance
$CL_{Non-Dialysis}$	Non-Dialytic Clearance
CL_R	Recovery Clearance
CL_{Total}	Total Clearance
CORR	Canadian Organ Replacement Register
COX	Cyclooxygenase
C_t	Plasma Drug Concentration at a Particular Time
CYP	Cytochrome P450
DAD	Discharge Abstract Database
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FDA	Food and Drug Administration
$F_{Dialysis}$	Fraction of Total Clearance due to Dialysis
F_{Drug}	Fraction of Drug Initially in Body Eliminated by Dialysis
F_U	Fraction of Drug Unbound in Plasma
HbA1c	Hemoglobin A_{1C}
HCT	Hematocrit

HD	Hemodialysis
ICES	Institute for Clinical Evaluative Sciences
k_D	Elimination Rate Constant During Dialysis
KDIGO	Kidney Disease Improving Global Outcomes
k_E	Elimination Rate Constant in CKD
Kt/V	Dialysis Adequacy
LHSC	London Health Sciences Centre
LLOD	Lower Limit of Detection
LLOQ	Lower Limit of Quantification
MS	Mass Spectrometer
NCE	New Chemical Entity
NKF	National Kidney Foundation
NSAID	Non-Steroidal Anti-Inflammatory Drug
ODB	Ontario Drug Benefits
OHIP	Ontario Health Insurance Plan
OR	Odds Ratio
Q_B	Blood Flow Rate
Q_P	Plasma Flow Rate
QToF	Quadrupole Time of Flight
RAAS	Renin Angiotensin Aldosterone System
RPDB	Registered Persons Database
RR	Relative Risk
RRT	Renal Replacement Therapy
RSD	Relative Standard Deviation
SD	Standard Deviation
SPE	Solid Phase Extraction
$T_{1/2}$	Elimination Half-life
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UPLC	Ultra-Performance Liquid Chromatography
V_{conc}	Venous Plasma Drug Concentration
V_D	Volume of Distribution

1 INTRODUCTION

1.1 Renal Physiology

Our understanding of renal physiology continues to advance at an accelerated rate, especially due to global trends of a growing renal impairment population. Yet, the basic lessons learned from early measurements and elegant studies still provide the foundation for researchers today. The overarching role of the kidneys to maintain physiological homeostasis is now empirically recognized. Despite only weighing 150 grams each, kidneys receive more than 20% of the cardiac output supplied by the heart (Suzuki and Saruta, 2004). This highlights the responsibility of the kidneys to filter blood and remove excess organic molecules, regulate electrolyte balance, and maintain body fluid volume. All these functions are interrelated to the crucial role of the renal system in regulating long-term systemic blood pressure (Suzuki and Saruta, 2004).

The renin-angiotensin aldosterone system (RAAS) utilizes a negative feedback pathway to control hormone production, which subsequently modulates blood pressure (Gross *et al.*, 1964). In short, insufficient levels of sodium in circulation can be sensed by macula densa cells of the kidneys and lead to the production of renin by juxtaglomerular cells. Angiotensinogen—a plasma protein constitutively produced by the liver—is converted into angiotensin I by renin which serves as the rate limiting enzymatic step in RAAS. Upon reaching the lungs, angiotensin I is further transformed into angiotensin II by angiotensin-converting enzyme (ACE). Angiotensin II is a potent vaso-active hormone that raises blood pressure through direct widespread vasoconstriction. This hormone can also indirectly regulate blood pressure by altering sodium reabsorption and promoting aldosterone secretion. Aldosterone itself can lead to further increase in blood pressure by means of water and sodium retention. It comes as no surprise that

inappropriate activation of RAAS is recognized as one of the main mechanisms for hypertension progression (Campese and Park, 2006). Hence, many pharmacological compounds developed in the last 40 years have utilized this homeostatic system to combat hypertension and cardiovascular disease. ACE inhibitors and angiotensin receptor blockers (ARBs) have now become first-line treatments for many patients today, including those with renal impairment (Becker *et al.*, 2012).

1.2 Overview of Chronic Kidney Disease

1.2.1 Prevalence, Detection, and Progression

Similar to other economically developed nations, Canada is defined by its ageing population. Such a characterization has profound implications on the health care system, requiring greater emphasis on optimizing treatment for chronic diseases (Wiener and Tilly, 2002; Lefebvre and Goomar, 2005). In particular, chronic kidney disease (CKD) has quickly developed into one of the largest national health concerns in recent times. Approximately 12.5% of adults in Canada are living with some form of CKD, which is similarly observed in the USA's population (13.1%) (Coresh *et al.*, 2007; Arora *et al.*, 2013). Focusing specifically on patients over the age of 60, the prevalence of CKD is markedly higher with estimates surpassing 30% in Canada and the USA (Arora *et al.*, 2013; Saran *et al.*, 2016). In both these nations, CKD affects a greater proportion of the population as compared to Europe (4.7–8.1 %), Asia (2.5–6.8 %) and Australia (11.2%) (Zhang and Rothenbacher, 2008). These statistics emphasize the importance of early disease recognition in hopes of preventing CKD progression in North America.

CKD is an irreversible condition that is typically characterized by three or more months of renal abnormalities leading to a progressive decline in estimated glomerular filtration rate (eGFR) (Stevens *et al.*, 2013). With a lower GFR, serum urea and creatinine levels in CKD patients begin to elevate and serve as estimates of renal function (Smith *et al.*, 2006). Outlined by the severity in kidney dysfunction and classified based on eGFR measurements, patients advance through five successive stages of CKD. The most commonly used method to assess patient eGFR is the Modification of Diet in Renal Disease (MDRD) Study equation, which takes into consideration serum creatinine, age, gender and ethnicity of patients (Levey *et al.*, 1999). However, for patients who exhibit an actual measured GFR value greater than 60 mL/min/1.73 m^2, this equation often leads to an over diagnosis of CKD severity due to its frequent underestimation of eGFR (Stevens *et al.*, 2007). Consequently, the National Kidney Foundation has recommended the use of the CKD-EPI method to assess kidney function based on its improved accuracy to correctly categorize patients into their appropriate stage of CKD (Stevens *et al.*, 2010; Stevens *et al.*, 2011). This estimating equation considers the same variables as the MDRD method and defines normal kidney function as having an eGFR of at least 90 mL/min/1.73m^2 with no albuminuria or structural abnormalities (KDIGO CKD Work Group, 2013). Since minimal decline in GFR is observed for patients in early stages of CKD, the albumin to creatinine ratio (ACR) is analyzed in urine samples to assess and diagnose any initial deterioration in renal function. Albumin detection in urine suggests increased glomerular permeability as a result of kidney injury. Patients are categorized into one of the three classifications of ACR: normal (< 30 mg/g creatinine), moderately increased (30–300 mg/g creatinine) or severely increased (> 300 mg/g creatinine). In

clinical practice, combining both eGFR and ACR allows physicians to determine an individual's risk for CKD progression (Table 1.1).

Patients with CKD stage 1 or 2 exhibit normal (≥ 90 mL/min/1.73 m^2) or marginally decreased (60–89 mL/min/1.73 m^2) eGFR with abnormalities in kidney function observed through elevated ACR. Patients with stage 3 CKD (eGFR of 30–59 mL/min/1.73 m^2) account for more than half of the patient population (Coresh *et al.*, 2007). During this stage, accumulation of uremic toxins as a consequence of hindered renal clearance causes the development of uremic syndrome and other comorbidities. The condition of uremia causes physiological changes that affect cognitive function, alter basal metabolic rate, disturb hormonal regulation, and lead to overall imbalances in homeostasis (Depner, 2001; Meyer and Hostetter, 2007). As a result, a substantial increase in risk of death, cardiovascular events and hospitalizations is observed for stage 3 CKD patients with an eGFR of less than 45 mL/min/1.73 m^2 (Go *et al.*, 2004). For some patients, continued decline of eGFR and renal function will ultimately lead to stage 5 CKD (eGFR < 15 mL/min/1.73 m^2), also known as end-stage renal disease (ESRD). If left untreated, the severity of comorbidities and complications amongst ESRD patients result in a nearly 600 percent increase in risk of mortality as compared to CKD patients in stage 1 or 2 (Go *et al.*, 2004). Although preventing disease progression is an important aspect of managing renal insufficiency, more effective treatment plans to address comorbidities and complications are needed to improve the prognosis of CKD patients.

Table 1.1. Grid of eGFR and albuminuria levels reflecting risk for CKD progression by intensity of colouring (green, yellow, orange and red).

				Albuminuria Categories		
				Normal	Moderately Increased	Severely Increased
	CKD Stage	eGFR	Description	ACR < 30 mg/g creatinine	ACR 30–300 mg/g creatinine	ACR > 300 mg/g creatinine
eGFR Categories (mL/min/1.73m^2)	1	≥ 90	Normal	Low Risk	Moderate Risk	High Risk
	2	60–89	Mild ↓GFR			
	3	30–59	Moderate ↓GFR	High Risk	Very High Risk	
	4	15–29	Severe ↓GFR			
	5	<15	Kidney Failure			

Adapted from KDIGO, 2013.

1.3 Causes and Complications in Chronic Kidney Disease

1.3.1 Diabetes in CKD

Diabetes mellitus (henceforth referred to as diabetes) is the primary cause of CKD and accounts for 36% of ESRD patients in Canada (Canadian Institute for Health Information, 2016). With trends suggesting a continued growth in the global burden of diabetes and nearly 5 million Canadians projected to be diagnosed with the condition by 2025, the proportion of CKD attributable to diabetes will inevitably rise (Guariguata *et al.*, 2014; Canadian Diabetes Association, 2015). Accordingly, healthcare professionals can attempt to delay CKD progression by ensuring early detection and creating appropriate treatment plans for diabetic patients. In type 2 diabetes, 39% of patients demonstrate microalbuminuria (ACR of 30–300mg/g creatinine) and 10% are diagnosed with macroalbuminuria (ACR greater than 300 mg/g creatinine)—both of which are powerful risk factors for diabetic nephropathy and cardiovascular disease (Ljungman *et al.*, 1996; Parving *et al.*, 2006; Chronic Kidney Disease Prognosis Consortium *et al.*, 2010). An additional measure to ascertain diabetes severity is the level of glycated hemoglobin (HbA1c) found in patient blood, which estimates the average plasma glucose concentration over the previous three months. Hyperglycemia is the most notable feature of diabetes and the underlying determinant for vascular target organ conditions, including diabetic kidney disease. High blood glucose can lead to damage of renal capillaries causing hyperfiltration by the glomerulus and subsequent microalbuminuria (Kanwar *et al.*, 2008). Hence, the National Kidney Foundation has recommended intensive glycemic control in CKD patients by suggesting a target HbA1c of 7% to reduce albuminuria

progression (KDOQI, 2007). Any further reduction in the target levels of HbA1c should be avoided due to significantly heightened risks for severe hypoglycemia and all-cause mortality (Ismail-Beigi *et al.*, 2010; Shurraw *et al.*, 2011).

In an effort to manage their blood glucose levels, diabetic patients are often prescribed oral antihyperglycemic agents with or without insulin. Unfortunately, difficulty in maintaining appropriate glycemic control in CKD patients arises as a result of dosing adjustments required for many medications. For instance, metformin is a first-line medication for the treatment of type 2 diabetes. The use of metformin in patients with CKD stage 3 or higher is often avoided due to a heightened risk for adverse drug effects, including lactic acidosis (Lalau *et al.*, 2015). Further complicating glycemic management is the development of insulin resistance, and hindered insulin secretion and clearance in CKD patients (Williams and Garg, 2014). Devising appropriate strategies to optimize the management of hyperglycemia slows the progression of CKD, decreases cardiovascular risk, and improves overall patient prognosis (The Diabetes Control Group, 1993; The Diabetes Control Group, 1995; Ray *et al.*, 2009).

1.3.2 Cardiovascular Disease in CKD

Hypertension is the most common comorbidity experienced by CKD patients with a prevalence estimate of up to 75% for those with eGFR less than 60 mL/min/1.73m^2 (stages 3-5) (National Kidney Foundation, 2002). Not surprisingly, renal vascular disease is a main cause for many of the adverse outcomes observed in CKD, including renal failure, early development and augmented progression of cardiovascular disease, and premature mortality (Levey *et al.*, 1998). With a growing awareness that renal impairment patients are more likely to die from an adverse cardiac event than progress to

ESRD (Keith *et al.*, 2004), all CKD patients are now regarded as the highest risk group for cardiovascular disease, irrespective of any risk factors (National Kidney Foundation, 2002). The complicated interaction between CKD and cardiovascular disease can be attributed to the increased risk for both traditional (hypertension, advanced age, diabetes, and hyperlipidemia) and CKD-specific risk factors (inflammation, malnutrition, mineral disorders, and anemia). The aggregate of all such risk factors has resulted in a nearly 70% prevalence estimate of cardiovascular disease among elderly CKD patients—two-fold greater than what is observed in the general elderly population (Saran *et al.*, 2016).

Congestive heart failure and atherosclerotic heart disease are the two primary clinical presentations of cardiovascular comorbidity in the CKD population (Saran *et al.*, 2016). Acceleration in atherosclerotic plaque development has been an evident problem for hemodialysis patients for over 30 years (Lindner *et al.*, 1974). The asymptomatic nature of coronary artery disease combined with increased inflammation and oxidative stress in CKD has created a challenging circumstance for preventing atherosclerosis progression (deFilippi *et al.*, 2003; Ohtake *et al.*, 2005). Correspondingly, recognition that vascular calcification is very common amongst CKD patients supports the finding of a heightened risk for heart failure in this population (Chertow *et al.*, 2002; Moe *et al.*, 2002). In a large population-based study conducted in the USA, the rate of cardiac failure in stage 3-5 CKD patients was 3-fold higher as compared with non-CKD subjects (Kottgen *et al.*, 2007). ESRD patients diagnosed with heart failure at the start of their renal replacement therapy (RRT) are strongly associated with short and long-term mortality. Specifically, the median survival time of dialysis patients diagnosed with baseline heart failure is 36 months, whereas dialysis patients without heart failure has an

estimated survival of 62 months (Harnett *et al.*, 1995). Although significant improvements have been made for the management of cardiovascular disease in the general population, many of the interventions either lack clinical investigation in patients receiving RRT or have been shown to be less effective. For instance, the lipid-lowering class of medications known as statins are the best-selling drugs in history due to their proven efficacy to reduce cardiovascular disease and mortality (Scandinavian Simvastatin Survival Study Group, 1994; Nawrocki *et al.*, 1995; World Health Organization, 2004; Epidemiological Studies Unit, 2005). However, three large randomized, placebo-controlled trials studying the use of statins in dialysis patients did not display any survival benefit (Fellström *et al.*, 2009). These findings have ultimately warranted updates to clinical practice guidelines recommending statin therapy should no longer be initiated for dialysis-dependent CKD (Wanner *et al.*, 2005; Baigent *et al.*, 2011; Tonelli *et al.*, 2014). More prospective trials are required to compare and determine which medications provide the best cardiovascular protection in subjects treated with RRT.

1.4 Renal Replacement Therapy for End-Stage Renal Disease

As kidney function and eGFR continue to decline for CKD patients, those who reach stage 5 will require RRT to prolong survival. A recent report drawing on data from the Canadian Organ Replacement Register (CORR) has shown that the prevalence of ESRD patients being treated with some form of RRT has increased over two and half fold from 13,230 patients in 1995 to 35,281 in 2014 (Canadian Institute for Health Information, 2016). Clinical decisions for the modality and time of RRT initiation still

remain controversial. Treatment regimen can be divided into patients of "early-start" or "late-start" dialysis (Cooper *et al.,* 2010). In early-start, patients are educated and prepared for RRT during stage 4 CKD to ensure immediate commencement of dialysis once stage 5 CKD is reached. In comparison, late-start dialysis is initiated when patient eGFR falls below 15 mL/min/m^2 and begin to experience signs and symptoms of uremia including cognitive decline, fluid overload, electrolyte imbalances, and hormonal disturbances (Depner, 2001). Results from the IDEAL (Initiating Dialysis Early And Late) study—a randomized, controlled trial comparing time of dialysis initiation—has since prompted the National Kidney Foundation to update their guidelines in favour of commencing dialysis once uremic symptoms become apparent (National Kidney Foundation, 2015). However, healthcare professionals and patients must still work together to select an extracorporeal (hemodialysis) or paracorporeal (peritoneal dialysis) method of dialysis, and whether it will be administered continuously or intermittently.

1.4.1 Hemodialysis

Intermittent, institutional hemodialysis is the most frequently elected form of RRT and has consistently represented 77% of all new dialysis patients in Canada over the past decade (Canadian Institute for Health Information, 2016). This mode of RRT is usually administered thrice weekly for 3-4 hours per session. A vascular access location must first be surgically created to allow withdrawal of arterial blood from patients into the hemodialysis machine. Regarding the choice of vascular access, 80% of patients utilize a central catheter despite numerous functional advantages of fistulas (Moist *et al.*, 2014). Specifically, fistulas have lower rates of thrombosis and infections, require fewer interventions, and provide greater longevity in vascular access (Nassar and Ayus, 2001;

Huber *et al.*, 2003; Perera *et al.*, 2004). Most importantly, patients receiving catheters had a nearly two and half fold greater risk for mortality as compared to patients dialyzed with fistulae (Dhingra *et al.*, 2001).

Within the dialyzer, a countercurrent flow of dialysate maintains a concentration gradient across the dialysis membrane and ensures the diffusion of ions, solutes, and excess water out of blood. Fluid removal known as ultrafiltration can also be achieved by varying the hydrostatic pressure of the dialysate to produce a pressure gradient. The filtered blood can then re-enter systemic circulation of patients through the dialysis venous line. Dialysate is a salt solution containing glucose and many different ions. The composition of dialysate is essential for ensuring patients receive effective hemodialysis therapy since it dictates the balance of electrolyte and mineral concentrations in blood. For instance, adequate sodium and water removal during dialysis is crucial in minimizing inter- and intra-dialytic hypertension and edema (Locatelli *et al.*, 2015). Potassium homeostasis is critical for preventing cardiac arrhythmias, and bicarbonate levels stabilize physiological pH in order for optimal protein function.

The physiological goals for hemodialysis can differ between patients and require individualized treatment regimens. Specifically, extracorporeal filtration is dependent on the blood and dialysate flow rate, duration and frequency of dialysis, and the composition of dialysis membrane including pore size, surface area and material (National Kidney Foundation, 2015). Older, conventional dialysis is characterized by low-flux membranes containing small pore sizes. Recently, there has been a widespread trend in opting for use of high-flux dialyzers due to their advantage of removing larger solutes and shorter requirements for dialysis duration (Schneider and Streicher, 1985). Whether high-flux

dialyzers actually improve patient outcomes still remain controversial. Three large-scale randomized, controlled trials demonstrated no difference in mortality between low- and high-flux dialyzers (Eknoyan *et al.*, 2002; Locatelli *et al.*, 2009; Asci *et al.*, 2013). However, the National Kidney Foundation still recommends high-flux dialyzers be preferentially used due to improvements in secondary outcomes including cardiac mortality and hospitalizations (National Kidney Foundation, 2015).

1.4.2 Peritoneal Dialysis

In Canada, peritoneal dialysis accounts for 20% of new ESRD patients requiring RRT (Canadian Institute for Health Information, 2016). Being able to receive peritoneal dialysis treatment while at home provides a lifestyle convenience for many of these patients. The two main approaches for peritoneal dialysis treatment is through automated peritoneal dialysis (APD) or continuous ambulatory peritoneal dialysis (CAPD) (Fleming, 2011). Both methods of dialysis involve surgical implantation of a catheter into the peritoneal cavity to introduce and remove dialysate. APD is characterized by 3 to 6 cycles of dialysate exchange overnight accomplished by a machine, followed by a small residual volume of dialysate during the day. Conversely, CAPD involves multiple manual exchanges of 2–3 litres of dialysate during the day, followed by a longer dwell time overnight (Fleming, 2011). The dialysate composition for either method of peritoneal dialysis requires a hyperosmotic solution to ensure adequate ion, solute, toxin, and water removal from the blood, across the peritoneum and into the dialysate. Many of the complications experienced by patients are due to excessive loss of fluid resulting in hypovolemic shock or hypotension, and increased infection rates as a consequence of the permanent catheter (Mehrotra *et al.*, 2016).

Despite early reports from selected nephrologists suggesting that peritoneal dialysis is a "second-class therapy for second-class patients by second-class doctors" (Shaldon *et al.*, 1985), considerable advancements in its application have resulted in survival benefits comparable to that of institutional hemodialysis (Yeates *et al.*, 2012; Heaf and Wehberg, 2014; Marshall *et al.*, 2015; van de Luijtgaarden *et al.*, 2016). The implications of these findings not only allow patients to choose a modality of RRT that may be better suited for their lifestyle, but it also provides a more economically feasible method of dialysis to benefit the healthcare system (Karopadi *et al.*, 2013).

1.4.3 Kidney Transplant

The ultimate goal for any dialysis treatment is to prolong patient survival until an adequate kidney transplant can be received. However, the scarce availability of organs for transplant restricts millions of people worldwide to long-term RRT (Fleming, 2011). In Canada, the number of patients waiting for a kidney transplant is steadily increasing every year but only 40% of those on the waitlist actually receive a kidney (Canadian Institute for Health Information, 2016). Despite more than 35,000 Canadians being treated for ESRD, the median wait time for dialysis patients to receive a kidney is 4 years. Fortunately, living organ donation has greatly improved the outlook for renal transplantation over the past decade and often leads to a healthier, longer-lasting kidney (Davis and Delmonico, 2005).

To date, a successful kidney allograft is the only treatment for improving GFR and reversing CKD. Transplant recipients no longer require dialysis therapy once their kidney begins to function. The risk for heart disease becomes dramatically attenuated, and erythropoietin synthesis commences within a matter of days allowing patients to

reach target levels of hemoglobin in 3 months post-surgery (Joist *et al.*, 2006; Zolty *et al.*, 2008). Accordingly, the quality of life, survival, and long-term prognosis observed in transplant recipients are far better than ESRD patients requiring dialysis (Purnell *et al.*, 2013).

1.5 Pharmacokinetic Studies in CKD Patients

Emerging evidence demonstrate alterations of drug absorption, distribution, and non-renal elimination in renal insufficiency, providing insight as to why CKD patient responses to pharmacotherapy are still widely variable with frequent adverse drug events (Bates *et al.*, 1999; Manley *et al.*, 2005; Naud *et al.*, 2012). Urea retention and its subsequent hydrolysis into ammonia by bacterial urease can increase intestinal pH, leading to changes in absorption of weakly basic drugs (Pappenheimer and Reiss, 1987; Velenosi and Urquhart, 2014). Upon reaching systemic circulation, attenuated production of albumin coinciding with competitive binding by uremic toxins result in elevated free fraction of medications—the outset for drug toxicity (Sakai *et al.*, 2001). Recent preclinical and human studies display reductions in non-renal clearance for CKD, which can ultimately potentiate drug toxicity by prolonging elevated drug concentrations in plasma (Ahmed *et al.*, 1991; Leblond *et al.*, 2001; De Martin *et al.*, 2006; Michaud *et al.*, 2006; Naud *et al.*, 2008; Nolin *et al.*, 2009; Velenosi *et al.*, 2012; Velenosi *et al.*, 2014; Thomson *et al.*, 2015). One possible explanation for this change in drug pharmacokinetics is the accumulation and circulation of uremic toxins as a result of reduced clearance in CKD. It has been proposed that indoxyl sulfate and other uremic toxins can inhibit the function and expression of hepatic drug metabolizing enzymes and

drug transporters—both being essential contributors to drug disposition (Sun *et al.*, 2004; Tsujimoto *et al.*, 2010; Fujita *et al.*, 2014).

Realizing that renal impairment can substantially impact all aspects of drug pharmacokinetics, the FDA Clinical Pharmacology Advisory Committee proposed several important changes to their 1998 FDA Renal Guidance document (Huang *et al.*, 2009). The result of this proposal is an updated draft guidance entitled: *Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing and Labeling*. This draft has developed a detailed algorithm for deciding whether to incorporate patients with renal insufficiency in pharmacokinetic studies of new chemical entities (NCEs) (Huang *et al.*, 2009). In short, if NCEs undergo substantial renal elimination (i.e. if at least 30% of the dose is excreted unchanged in urine), subjects from each stage of CKD must be included in a "full" pharmacokinetic study. For drugs that are primarily non-renally excreted, the new draft guidance recommends implementing a "reduced" study design—an important departure from the 1998 Renal Guidance. This design involves the comparison of drug disposition in healthy versus ESRD patients who have not yet been prescribed RRT. If drug exposure is substantially elevated in ESRD patients (e.g. an increase in the AUC of at least 50%, or a smaller increase for drugs with a narrow therapeutic window), a full renal study must be conducted.

The importance of implementing a reduced design for drugs that may not exhibit renal elimination is evident for the analgesic compound, celecoxib—a selective cyclocooxygenase-2 (COX-2) inhibitor (Swan *et al.*, 2000). It is well-recognized that prescription of conventional non-steroidal anti-inflammatory drugs (NSAIDs) are

accompanied by heightened risks for nephrotoxicity, especially for patients with severe renal insufficiency. However, celecoxib did not undergo any form of renal impairment study during its drug approval process as its development occurred prior to publication of the 1998 Renal Guidance, and its primary route of elimination is through hepatic metabolism. Since then, post-marketing population studies combined with data from FDA's Adverse Event Reporting System has demonstrated associations of celecoxib with acute renal failure (Zhao *et al.*, 2001; Ahmad *et al.*, 2002; Schneider *et al.*, 2006). If overlooked by physicians, lack of appropriate dosage adjustments for CKD patients can lead to an accelerated progression into kidney failure (Perazella and Eras, 2000).

1.6 Drug Dialyzability

1.6.1 Current State of Knowledge

Drug dialyzability is defined as the efficiency of drug removal by dialysis. The 'Dialysis of Drugs,' an annual publication by the renal pharmacy consultants, has become a common source of information regarding the dialytic clearance of drugs (Baillie and Mason, 2013). This excellent resource shows that only 10% of surveyed drugs have definitive dialyzability information for modern, high-flux hemodialysis (Velenosi and Urquhart, 2014). An additional 39% of drugs are classified as likely or unlikely dialyzed based solely on their physicochemical properties with no experimental data, whereas the remaining 50% of drugs have no available data. As a result, our current understanding of drug dialyzability is poor. Information regarding dialyzability currently falls into the following five categories: (1) nonexistent; (2) unsupported statements in product mono-graphs; (3) speculation based on a drug's physicochemical characteristics; (4)

pharmacokinetic studies conducted before the modern era of hemodialysis; and (5) modern pharmacokinetic studies. Case reports of apparently successful dialysis in overdose settings provide some data, but the applicability of these reports to steady-state drug dosing is unknown. Overall, the dialyzability of cardiovascular drugs requires further research to better understand their inherent dialyzability, the clinical ramifications of dialyzability, and steps that can be taken to better the dosage of these important drugs in patients receiving hemodialysis.

1.6.2 Drug Factors

Removal of a drug from the body during hemodialysis depends on how readily the drug crosses the dialyzer and the amount of drug that is accessible in the blood over the course of a typical hemodialysis session. Diffusion across the dialysis membrane is limited primarily by a drug's molecular size, for which molecular weight is a reasonable proxy. While the upper limit for modern high-permeability dialyzers is approximately 12,000 Da, clearance rates decrease logarithmically with increasing size (Cheung and Leypoldt, 1997). Regardless of the physical size of the molecule, this characteristic is meaningful only for the unbound fraction of drug. Binding to serum albumin or erythrocytes increases a drug's effective molecular weight far beyond the threshold of dialyzability. Therefore, the degree of protein binding can greatly reduce a drug's dialyzability; however, protein binding is not a fixed characteristic and the dynamic equilibrium between bound and unbound drug is influenced by factors such as uremia, pH, and clinical circumstances, including whether patients are in a steady state on therapeutic dosing or have overdosed (Vanholder *et al.*, 1988; Sue and Shannon, 1992; Kochansky *et al.*, 2008). A drug's volume of distribution also affects its dialyzability.

This parameter is determined by a drug's lipid solubility and protein binding, and describes the extent to which a drug is distributed throughout the body compartments. Hemodialysis readily accesses contents of the extracellular fluid, particularly the blood compartment. Drugs with low volumes of distribution are largely found in these compartments and are more readily dialyzed than drugs whose large volumes of distribution indicate significant distribution to other tissues.

1.6.3 Dialyzer and Dialysis Prescription Factors

Understanding the role played by dialyzer characteristics and the prescription is important when trying to extrapolate the findings of older dialyzability studies to modern practice. The clearance rates of small-sized and medium-sized molecules are affected by a number of parameters that have changed with the advancement of hemodialysis. Small molecule clearance is largely determined by dialyzer surface area, which is generally larger in modern dialyzers (Daugirdas *et al.*, 2012). Clearance of medium-sized molecules is determined more by dialyzer pore size, which has also increased over time with the introduction of synthetic membrane materials. This also provides higher ultrafiltration coefficients, resulting in better convective clearance (Bouré and Vanholder, 2004). Newer dialysis prescriptions, such as quotidian dialysis protocols and hemodiafiltration, are moving modern hemodialysis practice even further away from the settings in which many drug dialyzabilities were originally determined.

1.6.4 Determining Dialytic Clearance

Further complicating drug dialyzability research is the method selected by investigators to determine dialytic clearance rates. The two main approaches are the arterial–venous (A-V) difference method and recovery clearance method (Lee *et al.*,

1980; Uehlinger *et al.*, 1996; Tieu *et al.*, 2016). The majority of studies have applied the A-V difference method to determine dialyzability. This approach is limited by its inability to account for differences in drug distribution between plasma and red blood cells, as drug levels are generally measured only within the plasma compartment. The recovery clearance method is widely accepted as the superior approach to evaluate dialytic clearance because of its capacity to account for intradialytic hypotension, variations in dialysis membranes, and changes in nonrenal clearance during dialysis (Velenosi and Urquhart, 2014). However, many experimental designs lack analytical techniques sensitive enough to measure highly diluted drugs in total spent dialysate (around 120 L). Nonetheless, the recovery clearance method is accepted as superior to the A-V method and studies evaluating dialytic clearance should employ the recovery clearance method when possible to accurately characterize drug clearance by dialysis.

1.7 Clearance of Cardiovascular Medications During Hemodialysis

1.7.1 Beta-Adrenergic Receptor Blockers

Epinephrine and norepinephrine are endogenous catecholamines that bind and activate adrenergic receptors to mediate different physiological responses. These receptors can be subdivided into alpha and beta receptors (Kidney Disease Outcomes Quality Initiative, 2004). Focusing on the beta subtype, beta-1 adrenoreceptors are primarily expressed in heart muscle and their activation generates an increase in atrioventricular nodal conduction, heart contractility, and heart rate. Localized in the

bronchial and peripheral vascular smooth muscle, activation of beta-2 adrenoreceptors causes dilation of vessels and bronchioles.

Beta-adrenergic receptor antagonists (beta blockers) are an important class of medication for the management of hypertension and cardiovascular disease in patients receiving hemodialysis. The various classes of beta blockers differ in clinical benefit and adverse events, mainly due to their selectivity when binding endogenous receptors (Kidney Disease Outcomes Quality Initiative, 2004). Specifically, selective beta blockers are agents that preferentially antagonize beta-1 receptors (e.g. atenolol, bisoprolol and metoprolol) in order to improve cardiac function. Non-selective beta blockers are those that bind both beta-1 and beta-2 adrenoreceptors, which can lead to additional adverse events including bronchoconstriction and peripheral vascular symptoms. Carvedilol is a non-selective beta blocker that also antagonizes alpha receptors. Left ventricular hypertrophy (Mark *et al.*, 2006) and sudden cardiac death (McCullough, 2004) are common manifestations of heart disease in dialysis patients and the use of beta blockers has been associated with reductions in both the degree of hypertrophy and the risk of death in this patient population (Cice *et al.*, 2003; Abbott *et al.*, 2004; Hampl *et al.*, 2005; Nakao *et al.*, 2009; Matsue *et al.*, 2013). With respect to dialyzability, the clearance of beta blockers during dialysis varies considerably, but the quality of evidence is low (Table 1.2) (Flouvat *et al.*, 1980; Roux *et al.*, 1980; Miki *et al.*, 1991; Kanegae *et al.*, 1999). Minimally dialyzable beta blockers include carvedilol, which is 90% protein-bound and difficult to detect in spent dialysate (Miki *et al.*, 1991), and propranolol, which is also highly protein-bound. Bisoprolol is also likely to be of low dialyzability as outlined by previous review articles and industry sources (Table 1.3). At the more

Table 1.2. Dialyzability of beta blockers.

Beta Blocker	Molecular Weight (Daltons)	Protein binding (%)	Volume of distribution (L/kg)	Dialyzability Data		
				Specified Dialyzability Testing Conditions*	Clearance during hemodialysis (ml/min)	Reference
Acebutolol	336	26	1.2	Recovery method Single dose Dialyzer: cuprophane Q_D: 700 ml/min Q_B: 238 ml/min	42.6	Roux 1980(55)
Atenolol	266	10	4.2	A-V Difference method Single dose Dialyzer: cuprophane Q_D: 700 ml/min Q_B: 236 ml/min	42.6	Flouvat 1980(56)
Bisoprolol	325	30	3	A-V Difference method Single dose Dialyzer: polysulfone Q_D: ? Q_B: ?	50.8	Kanegae 1999(57)
Carvedilol	406	98	1.6	A-V Difference method Single dose Dialyzer: ? Q_D: ? Q_B: ?	"Not dialyzable"	Miki 1991(30)
Metoprolol	267	10	3.2	No data	No data	-
Nebivolol	405	98	?	No data	No data	-

* Clearance of a drug during hemodialysis can be determined by the Recovery Method, in which drug removal is determined from the total spent dialysate, or by the A-V Difference Method, in which clearance is calculated with the Fick Equation using the difference in drug concentrations between the arterial (A) and venous (V) limbs of the dialysis machine and the blood flow rate.
Abbreviations: Q_D, dialysate flow rate; Q_B, blood flow rate.

dialyzable end of the spectrum are a number of beta blockers with minimal protein binding, including acebutolol, atenolol, and metoprolol. A recently published retrospective cohort study compared the 90-day risk of mortality among patients on hemodialysis, who initiated a high versus low dialyzability beta blocker (Weir *et al.*, 2015). This study demonstrated an increase in the risk of mortality among patients initiating one of the highly dialyzable agents (metoprolol, atenolol, or acebutolol) compared to those who started a low dialyzability agent (bisoprolol or propranolol). These findings suggest that dialyzability of beta blockers may be an important determinant of drug effectiveness in people receiving hemodialysis. Although this is thought provoking, shortcomings in the ability to definitively classify dialyzability leaves the door open for debate and is the primary rationale for experiments in this thesis.

1.7.2 Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers

ACE inhibitors are commonly prescribed for hypertension, heart failure, or myocardial infarction because their use improves survival and prevents major cardiovascular events. The dialyzability of ACE inhibitors is incompletely characterized, but from existing data, dialyzability appears to vary significantly within this drug class (Fruncillo *et al.*, 1987; Kelly *et al.*, 1988; Verpooten *et al.*, 1991; Gehr *et al.*, 1993; Guerin *et al.*, 1993; Fillastre *et al.*, 1996; Yamada *et al.*, 2003). Fosinopril is minimally dialyzable with a clearance rate during hemodialysis of only 4 ml/min, whereas enalapril and perindopril are highly dialyzable with clearance rates in excess of 60 ml/min. Other ACE inhibitors appear to have moderate levels of dialyzability (Supplementary Table C1, Appendix C) (Fruncillo *et al.*, 1987; Kelly *et al.*, 1988; Verpooten *et al.*, 1991; Gehr *et*

al., 1993; Guerin *et al.*, 1993; Fillastre *et al.*, 1996; Yamada *et al.*, 2003). The data supporting these categorizations are of reasonable quality with many studies conducted in the modern era using robust pharmacokinetic measurements. However, a significant amount of the data in this class was collected using low-efficiency, low-flux dialyzers and was determined using the inferior arterial-venous (A-V) difference method. Accordingly, it is difficult to compare dialyzability among drugs within this class because of the differences in methodology used to determine clearance. A recent study measured short-term mortality and cardiovascular end-points among patients on hemodialysis, who initiated ACE inhibitors of differing dialyzability (Weir *et al.*, 2015). There was no difference in outcomes, which, among other factors, may have been the result of dialyzability misclassification.

Angiotensin receptor blockers (ARBs) appear to express a more uniform level of dialyzability than ACE inhibitors (Supplementary Table C2, Appendix C) (Sica *et al.*, 1997; Pfister *et al.*, 1999; Sica *et al.*, 2000; Stangier *et al.*, 2000; Tanaka *et al.*, 2009). All commonly prescribed agents show very high levels of protein binding. In pharmacokinetic studies, ARBs are extremely difficult to detect in dialysate, and differences in ARB concentrations between blood entering and exiting the dialyzer are very low. This suggests that ARBs are not dialyzable to any meaningful extent. However, as is frequently the case, most studies with ARBs were not conducted with modern high-flux, high-efficiency dialyzers.

1.7.3 Calcium Channel Blockers

Calcium channel blockers (CCBs) are commonly prescribed antihypertensive medications. Among patients receiving hemodialysis in the United States, approximately

50–65% are prescribed a CCB (St Peter *et al.*, 2013; Shireman *et al.*, 2014). Dihydropyridine CCBs (amlodipine, felodipine, nicardipine, and nifedipine) are much more commonly prescribed than nondihydropyridine CCBs (diltiazem and verapamil) (St Peter *et al.*, 2013). Studies regarding the dialyzability of CCBs are few and were largely conducted prior to the modern era of hemodialysis (Supplementary Table C3, Appendix C) (Martre *et al.*, 1985; Shah and Winer, 1985; Hanyok *et al.*, 1988; Buur *et al.*, 1991; Kungys *et al.*, 2003). However, CCBs likely have minimal dialyzability as a result of high protein binding and large volumes of distribution.

1.7.4 Antiplatelet Agents

Patients receiving hemodialysis have an elevated risk of both thrombotic events and bleeding abnormalities (Rios *et al.*, 2010). The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) recommends the use of antiplatelet agents to prevent cardiovascular events in patients with CKD. Although the associated risk of bleeding is well established, it is out-weighed by reductions in myocardial infarction rates among high-risk patients receiving hemodialysis (Palmer *et al.*, 2013). Understanding the pharmacokinetics of antiplatelet drugs during dialysis is critically important to balance this risk-benefit relationship. However, there is a scarcity of data characterizing the dialyzability of these drugs. Aspirin has been shown to be moderately dialyzable with clearance rates ranging from 30 to 86 ml/min (Supplementary Table C4, Appendix C) (Doolan *et al.*, 1951; Spritz *et al.*, 1959; Kallen *et al.*, 1966; Bern *et al.*, 1980; Jacobsen *et al.*, 1988). These findings were observed in overdose settings, in which aspirin's protein binding was likely to be less than its typical 99%. However, the binding of aspirin to albumin is relatively weak, and this may have contributed to the moderate

dialytic clearance observed (Kallen *et al.*, 1966). No data on dialyzability are currently available for modern antiplatelet agents.

1.7.5 Anticoagulant Agents

Although anticoagulants have a proven benefit in the management of thromboembolic diseases in the general population, for patients with renal disease, there is little data available to guide treatment. With respect to dialyzability, anticoagulants vary considerably. Dabigatran, one of the new oral anticoagulants, is highly dialyzable with whole blood clearance rates in excess of 150 ml/min (Supplementary Table C5, Appendix C) (Ifudu and Dulin, 1993; Robson, 2000; Murray *et al.*, 2004; Kalicki *et al.*, 2007; Wagner *et al.*, 2011; Chang *et al.*, 2013; De Vriese *et al.*, 2015). In contrast, the other oral anticoagulants, including warfarin, apixaban, and rivaroxaban, are minimally cleared by hemodialysis. As shown in Supplementary Table C5 (Appendix C), there is a paucity of dialyzability data for injectable direct thrombin inhibitors, factor Xa inhibitors, and low-molecular-weight heparins. Although argatroban exhibited a 20% increase in clearance during hemodialysis, this difference was deemed to be clinically insignificant (Murray *et al.*, 2004). Fondaparinux, a selective inhibitor of factor Xa, had a minimal dialytic clearance rate of 9.8 ml/min estimated from changes in anti-Xa activity (Kalicki *et al.*, 2007). The lack of available information on anticoagulant removal by hemodialysis implicates a need to conduct further studies using high-efficiency, high-flux dialyzers.

1.7.6 Cholesterol-Lowering Agents

Over the past decade, there has been considerable controversy surrounding the value of cholesterol-lowering medications in patients receiving hemodialysis. Statin or statin and ezetimibe combination therapy is recommended for nondialysis-dependent

CKD patients, while dialysis patients should use these medications only if they were receiving them prior to dialysis initiation (Tonelli *et al.*, 2014). As a class, the dialyzability of statins seems to be consistently minimal, which is reflective of their high protein binding and volumes of distribution. Accordingly, Launay-Vacher *et al.* (2005) has suggested that most statins can be administered at usual dosages any time before or after dialysis sessions. However, rosuvastatin had a dialytic clearance rate of 42 ml/min and pravastatin and its metabolites had higher and more variable rates of clearance, ranging from 38 to 81 ml/min, depending on the method used to determine dialyzability (Supplementary Table C6, Appendix C) (Gehr *et al.*, 1997; Appel-Dingemanse *et al.*, 2002; Lins *et al.*, 2003; Ichimaru *et al.*, 2004; Birmingham *et al.*, 2013). Ezetimibe has no available data but should be a focus of future research given its increasing use (Lu *et al.*, 2014), and the trend toward benefit among patients on dialysis observed in the SHARP trial (Baigent *et al.*, 2011).

1.8 Objectives and Hypothesis

1.8.1 Rationale

Of all comorbidities, cardiovascular disease has the greatest negative impact in CKD accounting for nearly 45% of mortalities in hemodialysis patients—an incidence 10-20 times greater than the general population (Foley *et al.*, 1998; Cheung *et al.*, 2004; Collins *et al.*, 2010). Over the past four decades, there have been vast advancements for the treatment of cardiovascular disease due in part to the emergence of beta blockers. This class of medication promotes cardiovascular improvements by decreasing blood pressure, heart rate, myocardial oxygen demand, arrhythmia, oxidative stress, and

improving left ventricular function (Lopez-Sendon *et al.*, 2004). More importantly, the administration of beta blockers to reduce mortality in cardiovascular disease patients has been observed in numerous prospective randomized clinical trials (Hansson *et al.*, 1999; Cice *et al.*, 2003). It is based on the strength of these findings that beta blockers are administered to 64% of dialysis patients exhibiting cardiovascular complications, and have become a cornerstone treatment in CKD (Frankenfield *et al.*, 2012).

Many studies indicate altered medication pharmacokinetics in CKD, including both renal and non-renal drug elimination (Leblond *et al.*, 2000; Nolin *et al.*, 2009; Velenosi *et al.*, 2012). Accordingly, expectations that beta blockers will deliver similar therapeutic efficacy in hemodialysis patients as compared with the general population is based on very little evidence. Most pharmacologic interventions have not included dialysis patients in their drug development process resulting in a lack of appropriate prescription recommendations (Ishani *et al.*, 2004; Zhang *et al.*, 2009; Frankenfield *et al.*, 2012; Matzke *et al.*, 2015). In particular, drug dialyzability is likely to vary amongst different beta blockers and should be considered when they are administered to hemodialysis patients. For instance, the use of drugs that are highly dialyzable can result in sub-therapeutic plasma concentration during hemodialysis and lead to an increased risk for adverse clinical outcomes (Figure 1.1). The unfortunate circumstance is that there is a paucity of available data to describe the dialyzability of beta blockers and many other currently marketed medications. Of the available information, most were obtained prior to implementation of high-flux, high-efficiency dialysis machines rendering many of the older studies irrelevant. The interdisciplinary approach to bridge pharmacology with clinical epidemiology uniquely positions us to determine conclusively the dialyzability of

beta blockers and its impact on cardiovascular outcomes. Data generated by this project are expected to be translated to future clinical practice guidelines, potentially optimizing pharmacotherapy and improving quality of life for chronic hemodialysis patients.

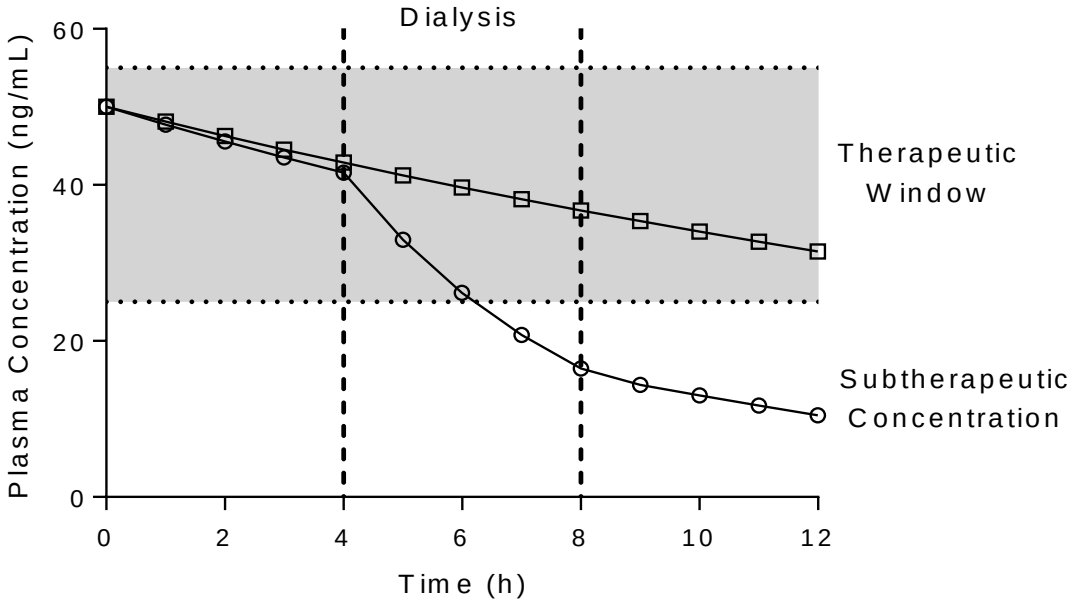


Figure 1.1. Potential effects of dialyzability on plasma drug concentration.

We expect that the dialyzability between medications of the same drug class will differ substantially based on their physicochemical properties. Drugs that are highly dialyzed (○) will result in sub-therapeutic concentrations preventing their ability to mediate their intended pharmacological effect. Conversely, drugs that are minimally dialyzed (□) will remain within their therapeutic window due to lack of clearance during hemodialysis. Consideration to preferentially administer poorly dialyzed drugs to hemodialysis patients should be considered.

1.8.2 Hypothesis

My governing hypothesis is that atenolol and metoprolol will be classified as "high dialyzability" beta blockers, while bisoprolol and carvedilol will be classified as "low dialyzability" beta blockers.

1.8.3 Specific Objective

Determine the pharmacokinetics and degree of dialyzability for the four most commonly prescribed beta blockers: atenolol, bisoprolol, carvedilol and metoprolol.

Prior to investigating the effect of beta blocker dialyzability on clinical outcomes, the dialytic clearance rates were calculated and compared for definitive characterization of drug dialyzability. This was accomplished by conducting a pharmacokinetic, 4-way crossover study with ESRD patients receiving modern, high-flux hemodialysis. Ultra-performance liquid chromatography coupled to mass spectrometry was used to measure plasma drug concentrations.

Hypotheses on which beta blockers would be extensively or poorly dialyzed was determined after reviewing physicochemical properties of the drugs, consulting industry sources, and evaluating review articles. Statements regarding the dialyzability of each beta blocker are summarized in Table 1.3. In summary, we expected to find that atenolol and metoprolol will be extensively cleared by hemodialysis, while bisoprolol and metoprolol will be poorly dialyzed.

Table 1.3. Physicochemical properties and dialyzability statements for study beta blockers.

Beta Blocker	Physicochemical Properties	Industry Statements		Review Articles				Expected Dialyzability
		Product Monographs	Dialysis of Drugs 2013[a]	Levin *et al.* 2010	Chazon and Jean 2006	Chen *et al.*2006	Redon *et al.* 2010	
Atenolol	Molecular Weight: 266 Daltons Water Solubility: 13,500 mg/L Protein Binding: 10% V_D: 4.2 L/kg	Moderately Dialyzable (20–50 %)	Conventional HD: Yes Modern HD: Likely	D	D	D	D	High Dialyzability
Bisoprolol	Molecular Weight: 325 Daltons Water Solubility: 2,240 mg/L Protein Binding: 30% V_D: 3.0 L/kg	Not Dialyzable	Conventional HD: Yes Modern HD: No Data	ND	ND	ND	ND	Low Dialyzability
Carvedilol	Molecular Weight: 406 Daltons Water Solubility: 0.583 mg/L Protein Binding: >98% V_D: 1.6 L/kg	Not Dialyzable	Conventional HD: No Modern HD: Unlikely	ND	ND	ND	ND	Low Dialyzability
Metoprolol	Molecular Weight: 267 Daltons Water Solubility: 16,900 mg/L Protein Binding: 10% V_D: 3.2 L/kg	No Statement	Conventional HD: Yes Modern HD: Likely	D	D	D	ND	High Dialyzability

[a] Annual guidelines published by Renal Pharmacy Consultants, LLC (Saline, Michigan, USA). Dialyzability based on scientific and industry data

V_D	Volume of distribution.
HD	Hemodialysis.
Yes	Dialysis was found to enhance drug clearance from previously published studies.
No	Dialysis was not found to enhance drug clearance from previously published studies.
No Data	No data or assumptions from physicochemical properties exist to describe drug dialyzability.
Likely	Drug is likely to be cleared by hemodialysis based on physicochemical parameters, but no data exists.
Unlikely	Drug is unlikely to be cleared by hemodialysis based on physicochemical parameters, but no data exists.
D	Drug is listed as dialyzable in corresponding review article.
ND	Drug is listed as not dialyzable in corresponding review article.

2 MATERIALS AND METHODS

2.1 Characterizing Beta Blocker Dialyzability

2.1.1 Study Design and Participant Eligibility

Eight hemodialysis patients were prospectively recruited from the London Health Sciences Centre (LHSC) to participate in a clinical pharmacokinetic study on the dialyzability of commonly used beta blockers. This study was approved by the Health Sciences Research Ethics Board at Western University (Approval Number 104909). The sample size was determined based on previously completed dialyzability studies using older, conventional dialyzers (Flouvat *et al.*, 1980; Campese *et al.*, 1985; Payton *et al.*, 1987; Buttazzoni *et al.*, 2006; Sowinski *et al.*, 2008). The study was an open-label, 4-way crossover trial of the four most commonly prescribed beta blockers in Ontario: atenolol (50 mg), bisoprolol (5 mg), carvedilol (6.25 mg), and metoprolol (50 mg). A randomly selected, single oral dose of one of the four beta blockers was administered to the subjects 4 hours prior to hemodialysis initiation. A washout period of at least 2 days was required before subjects received the next beta blocker, and this process continued until all 4 beta blockers were administered to all subjects. Four hours following drug administration, dialysis was initiated according to the patient's regular treatment. During dialysis, blood samples were collected from the arterial and venous ports at 6 different time points for each patient. For subjects who received dialysis for 4 hours, blood was drawn 0.0, 0.5, 1.0, 2.0, 3.0, and 4.0 hours after dialysis initiation. For subjects treated with dialysis for 3.5 hours, blood samples were collected 0.0, 0.5, 1.0, 1.5, 2.5, and 3.5 hours after starting dialysis. Lastly, subjects who were prescribed a 3 hour dialysis duration had blood drawn 0.0, 0.5, 1.0, 1.5, 2.5, and 3.0 hours after dialysis initiation. Total spent dialysate was recovered throughout the entirety of the hemodialysis treatment by diverting the waste

from the drain to a 200 L, food-grade plastic barrel. All samples were obtained for measurement of beta blocker concentrations.

Subject eligibility for study enrollment was determined by the following inclusion criteria: (1) at least 18 years of age, and (2) patients were on standard, thrice weekly hemodialysis for at least 90 days prior to first study session. Subjects were excluded from study enrollment if any of the following exclusion criteria was evident: (1) significant gastrointestinal or liver disease, (2) body mass index greater than 40 kg/m^2, (3) prescription of contraindicated medications (amiodarone, digoxin, phenytoin, quinidine, and others) or prior adverse drug reactions to beta blockers, and (4) bradycardia (heart rate less than 50 bpm) or hypotension (systolic blood pressure less than 100 mmHg) within the last 2 weeks prior to study commencement. Appendix D highlights in greater detail the specific inclusion and exclusion criteria applied to the subject screening process. Patients who did meet the eligibility criteria were enrolled on the provision of informed written consent in accordance with the Declaration of Helsinki.

2.1.2 Clinical Data Collection and Follow-Up

Demographic information was collected at the time of study enrollment. Patient information on their current medications, health status, and hemodialysis treatment plan was obtained by interview and review of medical records. Blood samples from the arterial port before and after the hemodialysis session were obtained for hematocrit assessment conducted by the London Laboratory Services Group using standard methods (London, ON.). Subjects were monitored for adverse events throughout their dialysis session, and adjustments to hemodialysis were made by healthcare professionals

according to standard hemodialysis protocol. The study period was from February 2015 to March 2016.

2.1.3 Chemical Reagents and Drugs

Atenolol (50 mg, Teva Pharmaceuticals Ltd.), bisoprolol fumarate (5 mg, Apotex Inc.), PMS-carvedilol (6.25 mg, Pharmascience Inc.), and metoprolol tartrate (50 mg, Mylan Pharmaceuticals Inc.) administered to subjects in the study were purchased from the pharmacy at London Health Sciences Centre (LHSC, London, ON). Atenolol, bisoprolol hemifumarate, carvedilol, metoprolol, atenolol-d7, bisoprolol-d7 hemifumarate, carvedilol-d3, and metoprolol-d7 standards used for drug level analysis were purchased from Toronto Research Chemicals (Toronto, ON).

2.1.4 Beta Blocker Extraction and Liquid Chromatography

Blood samples were centrifuged at 2000g for 10 minutes within one hour of collection. Plasma was separated from blood cells and subsequently stored with dialysate samples at -80°C until analysis. Plasma and dialysate concentrations of atenolol, bisoprolol, carvedilol, and metoprolol were determined using solid phase extraction (SPE) followed by ultra-performance liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UPLC-QToFMS). Beta blocker extraction from plasma and dialysate samples were conducted with SPE cartridges (C18, Strata-X Polymeric Reversed Phase 33 µm) obtained from Phenomenex (Torrance, CA) and conditioned according to manufacturer's specifications. Atenolol-d7, bisoprolol-d7, carvedilol-d3, and metoprolol-d7, all at 50 ng/mL, were used as internal standards for drug quantification. Plasma, dialysate, and internal standards were passed across the SPE cartridges under a vacuum pressure of less than 250 mmHg. Cartridges were washed with

1 mL of nano-pure water followed by 1 mL of 20% methanol in water, and analytes were eluted into clean glass test tubes with 1 ml of methanol solution containing 0.1% trifluoroacetic acid. Eluents were dried in a 40°C water bath using an Organomation N-EVAP™ nitrogen evaporator (Berlin, MA) which was followed by sample reconstitution in mobile phase. Dried eluents that contained carvedilol from plasma extractions were concentrated 10-fold to ensure adequate compound detection, while samples containing other beta blockers were not concentrated before analysis. Dried eluents from dialysate extractions were concentrated 100-fold to ensure adequate beta blocker signal during analysis. Reconstituted samples were injected at a volume of 5 µL with a flow rate of 0.7 mL/min on a Phenomenex Kinetex C8 column (1.7 µm particle size, 50 x 2.1 mm) for analyte separation. The Waters ACQUITY UPLC™ I-Class system (Waters, Milford, MA) autosampler maintained the column temperature at 40°C. Water (A) and acetonitrile (B), both containing 0.1% formic acid, were the mobile phase solutions used for compound elution. The UPLC elution parameters were as follows: 0.00–0.20 min, 2% B; 0.20–1.50 min, 2–80% B; 1.50–2.50 min, 80% B; and 2.51–3.51 min, 2% B.

2.1.5 Beta Blocker Analysis with Mass Spectrometry

Mass spectrometry was conducted using a Waters Xevo™ G2S-QTofMS. Beta blockers were measured using positive electrospray ionization (ESI) mode. The capillary and cone voltages were set at 0.5 kV and 40 V, respectively and a source temperature of 150°C was maintained. The desolvation gas flow was 1200 L/h at a temperature of 650°C, and the cone gas flow was 50 L/h. The data was acquired in centroid mode using an MS^E method allowing for both MS and MS/MS fragmentation during a single run. Acquisition samples were measured in positive polarity with extended dynamic range and

the analyzer mode set to resolution. Both functions 1 (low energy collision) and 2 (high energy collision) of the centroid method acquired data within a mass range of 50 to 1200 Da and a scan time of 0.05s. Collision energy for function 1 of the MS^E method was set at 0V, while function 2 was ramped from 15–50 V. Function 3 acquired lockspray to maintain accurate mass detection and reproducibility. The lockmass consisted of leucine-enkephalin (1ng/µL) set at a flow rate of 10 µL/min. A lockspray frequency of 10s was applied and data was averaged over 3 scans. Acquisition of data was controlled by Waters MassLynx v4.1 software and peak integration of sample chromatograms were conducted with QuanLynx software (Waters, MA, USA).

2.1.6 Determining Dialytic Clearance

The two main methods to evaluate the clearance of medications during hemodialysis are the arterial-venous (A-V) difference method (1) and recovery clearance method (2), which are described by the following equations (Lee *et al.*, 1980; Uehlinger *et al.*, 1996; Tieu *et al.*, 2016):

$$(1) \quad CL_{A\text{-}V} = Q_P \left[(A_{conc} - V_{conc}) / A_{conc}\right]$$

$$Q_P = Q_B (1 - Hct)$$

Where $CL_{A\text{-}V}$ is A-V difference clearance, Q_P is plasma flow rate, Q_B is blood flow rate, Hct is hematocrit, A_{conc} is arterial plasma drug concentration, and V_{conc} is venous plasma drug concentration.

$$(2) \quad CL_R = R_{drug} / AUC_{0\text{-}T}$$

Where CL_R is dialyzer clearance, R_{drug} is total amount of drug recovered in dialysate calculated by multiplying the dialysate drug concentration by total spent dialysate volume, and $AUC_{0\text{-}T}$ is area under the plasma concentration-time curve during

dialysis. The $AUC_{0\text{-}T}$ was calculated by the trapezoidal method using GraphPad Prism (version 6.01 for Windows; GraphPad Software, San Diego, CA).

2.1.7 Other Pharmacokinetic Parameters

The following pharmacokinetic parameters were determined by applying different equations as outlined by Rowland and Tozer (1995): (3) total clearance, (4) non-dialytic clearance, (5) elimination half-life, (6) fraction of total clearance due to dialysis, (7) fraction of drug eliminated during dialysis, and (8) post-dialysis supplemental dose.

$$(3)\ CL_{Total} = (C_{T=0} * V_D * F_U) / AUC_{0 \rightarrow T}$$

Where CL_{Total} is the total clearance during the hemodialysis session, $C_{T=0}$ is the arterial beta blocker concentration at the beginning of dialysis, V_D is the volume of distribution, F_U is the fraction of drug unbound, and $AUC_{0 \rightarrow T}$ is the area under the plasma concentration-time curve during dialysis.

$$(4)\ CL_{Non\text{-}dialysis} = CL_{Total} - CL_{Dialysis}$$

Where $CL_{Non\text{-}dialysis}$ is drug clearance due to non-dialytic mechanisms, CL_{Total} is total drug clearance, and $CL_{Dialysis}$ is dialytic clearance

$$(5)\ T_{1/2} = 0.693/k_D$$

Where $T_{1/2}$ is the elimination half-life of the drug during hemodialysis, and k_D is the elimination rate constant as determined by calculating the slope of the line after plotting the logarithm of plasma drug levels versus time on hemodialysis.

$$(6)\ F_{Dialysis} = CL_{Dialysis} / CL_{Total}$$

Where $F_{Dialysis}$ is the fraction of total drug clearance occurring by dialysis

$$(7)\ F_{Drug} = F_{Dialysis} * (1 - e^{-K_D * T})$$

Where F_{Drug} is the fraction of drug initially in the body eliminated during hemodialysis, k_D is the elimination rate constant during hemodialysis, and T is the length of the hemodialysis session

$$(8)\ \text{Supplemental Dose} = C_{T=0} * V_D * (e^{-K_E * T} - e^{-K_D * T})$$

Where k_E is the elimination rate constant of the beta blocker in CKD patients

2.1.8 Statistical Analysis

All statistical analysis was performed using GraphPad Prism (version 6.01 for Windows; GraphPad Software, San Diego, CA). Statistical differences between atenolol, bisoprolol, carvedilol and metoprolol treatments were assessed by one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test. Results are presented as mean ± SD and a p-value less than 0.05 was considered statistically significant.

3 RESULTS

3.1 Assay Validation and Performance

In order to determine the concentration of beta blockers found in clinical samples, a UPLC-MS method was developed and validated to quantify atenolol, bisoprolol, carvedilol and metoprolol in plasma and dialysate. Sample preparation with SPE cartridges were assessed for beta blocker recovery by comparing the mean concentration of 5 analytical replicates to the nominal concentration. The percent recovery of atenolol, bisoprolol, carvedilol, and metoprolol were 101%, 112%, 93%, and 112%, respectively.

In plasma, a calibration curve over the concentration range of 0.488–500.0 ng/ml was created. Patient plasma concentrations for each beta blocker were within this range and suitable for sample analysis. Using a signal-to-noise ratio greater than 3:1, the lower limit of detection (LLOD) for atenolol, bisoprolol, carvedilol, and metoprolol in plasma was 0.0153, 0.0305, 0.4883 and 0.0305 ng/mL, respectively. In dialysate, a calibration curve of 0.488–500.0 ng/mL was used for sample analysis. Atenolol, bisoprolol, and metoprolol levels in total spent dialysate were quantifiable using this range of concentrations; however, most dialysate samples containing carvedilol were below the lower limit of quantification (LLOQ) due to minimal clearance by dialysis. As a result, the intra-day accuracy and precision was assessed using 5 analytical replicates of the lowest concentration on the dialysate calibration curve. Accuracy, expressed as a bias percentage, was determined by comparing the mean measured concentration to the nominal concentration. Precision was determined by calculating the coefficient of variation (CV) percentage of the 5 analytical replicates. Using a signal-to-noise ratio of at least 10:1, the LLOQ of the calibration curve displayed acceptable accuracy (< 15%) and precision (< 10%) for all beta blockers. Specifically, the bias and CV were 4.2% and

1.1% for atenolol, 2.0% and 2.7% for bisoprolol, -6.0% and 12.5% for carvedilol, and 1.9% and 1.5% for metoprolol. The LLOD for atenolol, bisoprolol, and metoprolol was 0.0076 ng/mL while carvedilol had a LLOD of 0.0305 ng/mL, all of which were determined using a signal-to-noise ratio of at least 3:1.

3.2 Baseline Characteristics of Subjects

In total, eight ESRD patients requiring chronic hemodialysis were enrolled and each patient had received hemodialysis treatment for greater than three months. Beta blocker treatments were well tolerated by all study participants and no serious adverse drug reactions occurred. No abnormalities in heart rate and blood pressure were observed during the course of the study. Every subject completed the pharmacokinetic 4-way crossover trial and all but one of the patients was male (Table 3.1). The mean age of subjects was 58 years (ranging from 28 to 80 years), mean height was 1.70 m and mean weight was 95.1 kg. The mean body mass index was 32.6 kg/m^2. The primary causes for CKD diagnosis were diabetes mellitus (n=1), hypertension (n=1), rapidly progressive glomerulonephritis (n=1), polycystic kidney disease (n=1), reflux nephropathy (n=1), and a combination of both diabetes and hypertension (n=3). Hemodialysis sessions ranged from 3 to 4 hours with a treatment interval of 3 times per week. Fractional clearance of urea (Kt/V), also known as dialysis adequacy, has been shown to have a strong, positive correlation with patient mortality (Lowrie *et al.*, 1981; Gotch and Sargent, 1985; Shinzato *et al.*, 1997). The National Kidney Foundation has made recommendations for a minimum delivered Kt/V value of 1.2–1.4 as higher target levels do not improve survival, while lower values increase risk for patient morbidity (Lowrie *et al.*, 1981; Shinzato *et*

al., 1997; Eknoyan *et al.*, 2002; National Kidney Foundation, 2015). Four of the eight subjects had Kt/V values below the recommended target (Table 3.1). In regards to vascular access, 4 patients had a central catheter insertion at the right internal jugular vein while the other 4 subjects had an arteriovenous fistula in place for blood removal and return. All but one patient had higher hematocrit levels post-dialysis as compared to their pre-dialysis state.

Table 3.1. Background characteristics of chronic hemodialysis subjects.

Subject ID	BB002	BB003	BB004	BB005	BB006	BB007	BB008	BB009
Sex	Male	Male	Male	Female	Male	Male	Male	Male
Ethnicity	Caucasian	Caucasian	Caucasian	Caucasian	Aboriginal	Black Canadian	Caucasian	Caucasian
Age	42	73	66	28	47	72	80	53
Weight (kg)	94.1	129.1	53.5	81.5	117.3	89.8	89.6	106.4
Height (m)	1.70	1.90	1.67	1.47	1.74	1.63	1.72	1.78
Body Mass Index (kg/m^2)	32.2	35.6	19.2	37.7	38.7	33.8	30.3	33.6
Residual Renal Output (mL/day)	300	425	260	Anuric	Anuric	500	300	300
Cause of CKD	RPGN	DM and HTN	PCKD	Reflux Nephropathy	DM and HTN	HTN	DM and HTN	DM
Dialysis Duration (h)	4	4	3	3.5	4	4	3	4
Dialysis Frequency (Sessions/week)	3	3	3	3	3	3	3	3
Dialyzer Type	FX800	FX1000	FX600	FX600	FX1000	FX800	FX600	Revaclear Max 400
Effective Blood Flow Rate (mL/min)	382	323	354	397	287	385	325	313
Dialysis Adequacy (Kt/V)*	1.48 ± 0.04	1.06 ± 0.12	1.43 ± 0.11	1.62 ± 0.15	1.16 ± 0.02	1.59 ± 0.03	0.97 ± 0.04	1.09 ± 0.03
Vascular Access	Central Catheter	Central Catheter	Fistula	Fistula	Central Catheter	Central Catheter	Fistula	Fistula
Hematocrit, pre-dialysis*	0.27 ± 0.01	0.30 ± 0.01	0.33 ± 0.01	0.29 ± 0.01	0.27 ± 0.01	0.28 ± 0.01	0.29 ± 0.02	0.35 ± 0.01
Hematocrit, post-dialysis*	0.24 ± 0.01	0.34 ± 0.02	0.36 ± 0.01	0.33 ± 0.01	0.28 ± 0.01	0.30 ± 0.01	0.32 ± 0.03	0.37 ± 0.01

Abbreviations: RPGN, rapidly progressive glomerulonephritis; DM, diabetes mellitus; HTN, hypertension; PCKD, polycystic kidney disease. * Mean ± SD

3.3 Dialyzability of Beta Blockers in Chronic Hemodialysis Patients

The effective blood flow rate and pre-dialysis hematocrit measurements for each subject is shown in Table 3.1. These two variables were combined with the difference in beta blocker concentrations in the arterial and venous ports to calculate dialyzability values using the arterial-venous difference equation (Equation 1). As a result, the dialytic clearance rates for atenolol, bisoprolol, and metoprolol are (mean ± SD) 162.1 ± 22.2, 88.9 ± 15.7, and 106.6 ± 18.1 mL/min, respectively (Figure 3.1). The rates of removal for these 3 beta blockers are significantly higher than carvedilol at 17.3 ± 14.8 mL/min ($P < 0.01$). Additionally, the clearance of atenolol during hemodialysis is considerably elevated when compared to bisoprolol and metoprolol ($P < 0.01$), whereas bisoprolol and metoprolol are not significantly different from each other.

Collection and analysis of plasma samples over the duration of the hemodialysis session allowed us to create plasma concentration-time profiles (Figure 3.2) and determine the level of beta blocker exposure for each subject (reported as $AUC_{0\rightarrow T}$). For atenolol, bisoprolol, carvedilol and metoprolol, patient drug exposure was 827.9, 180.7, 150.5, and 106.9 ng·h/mL. The amount of beta blocker measured in total spent dialysate was 3.67 mg, 0.46 mg, 0.00 mg, and 0.56 mg, respectively. AUC values and the total amount of drug recovered in dialysate were applied to the recovery clearance method (Equation 2) to produce comparable dialytic clearance rates between atenolol and metoprolol at 71.8 ± 20.5 and 86.4 ± 27.8 mL/min, respectively (Figure 3.3). The clearance for both of these beta blockers during hemodialysis was considerably higher than bisoprolol at 43.7 ± 8.8 mL/min ($P < 0.05$ compared to atenolol and $P < 0.01$

compared to metoprolol). When compared to the other beta blockers, carvedilol displayed a substantially lower clearance rate at 0.2 ± 0.6 mL/min ($P < 0.01$)

Based on data from the recovery clearance method, atenolol and metoprolol can be classified as beta blockers with “high dialyzability”. Similar findings from both the A-V difference and recovery clearance methods classifies bisoprolol as a drug of “moderate dialyzability”, while carvedilol can be categorized as a “low dialyzability” beta blocker. These beta blocker classifications were incorporated into the study design for a provincial-wide, population-based retrospective cohort study.

Figure 3.1. Clearance rate of beta blockers during hemodialysis calculated using the arterial-venous difference equation.

Dialytic clearance values for the four beta-blockers (atenolol, bisoprolol, carvedilol, and metoprolol) during hemodialysis in end-stage renal disease patients. Plasma concentration of beta blockers were determined using ultra-performance liquid chromatography coupled to a quadrupole time-of-flight mass spectrometer (UPLC-QToFMS) and dialyzability was calculated using the arterial-venous (A-V) difference method. Results are presented as mean ± SD with n=8 for each treatment group. # $P < 0.01$ relative to atenolol, and * $P < 0.01$ for carvedilol relative to all other beta blockers.

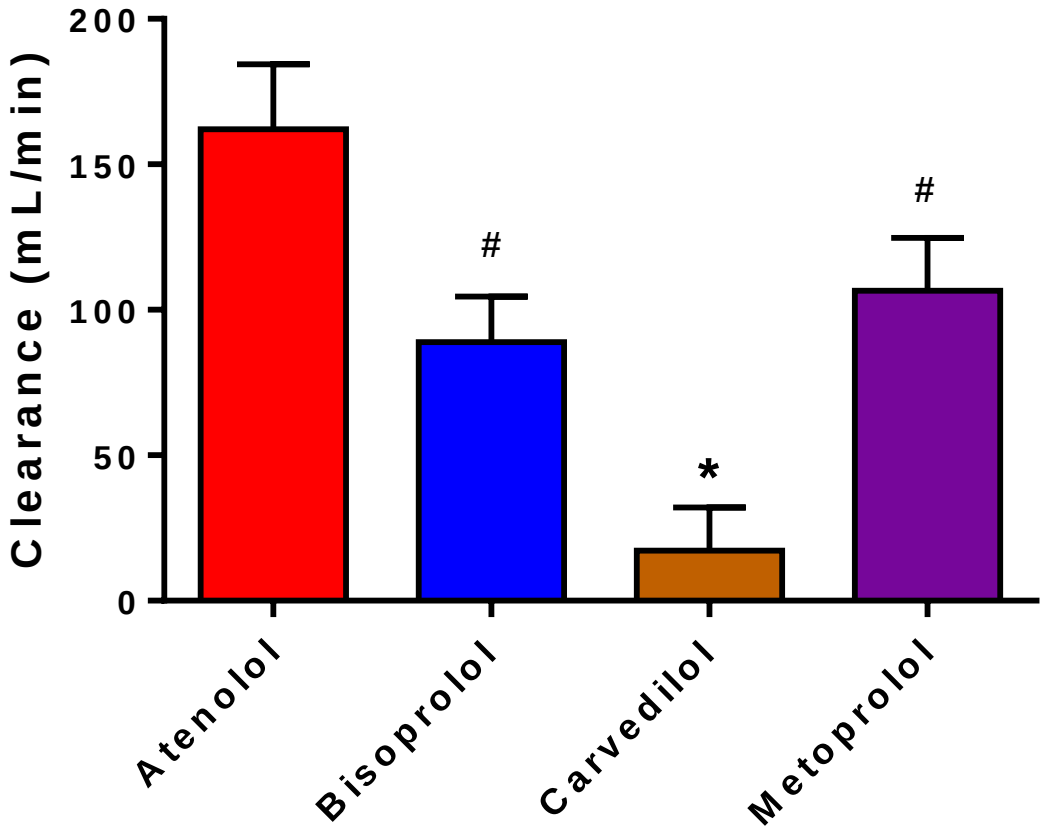

Clearance (mL/min)
200
150
100
50
0
#
#
*
Atenolol
Bisoprolol
Carvedilol
Metoprolol

Figure 3.2. Beta blocker plasma concentration-time profiles of end-stage renal disease patients during hemodialysis.

Plasma concentration-time profiles of atenolol (A), bisoprolol (B), carvedilol (C), and metoprolol (D) during hemodialysis in end-stage renal disease patients. Each subject received a single oral dose of a beta-blocker four hours prior to dialysis onset. Plasma concentration of beta blockers were determined using ultra-performance liquid chromatography coupled to a quadrupole time-of-flight mass spectrometer (UPLC-QToFMS). Results are presented as mean ± SD with n=8 for all treatment groups.

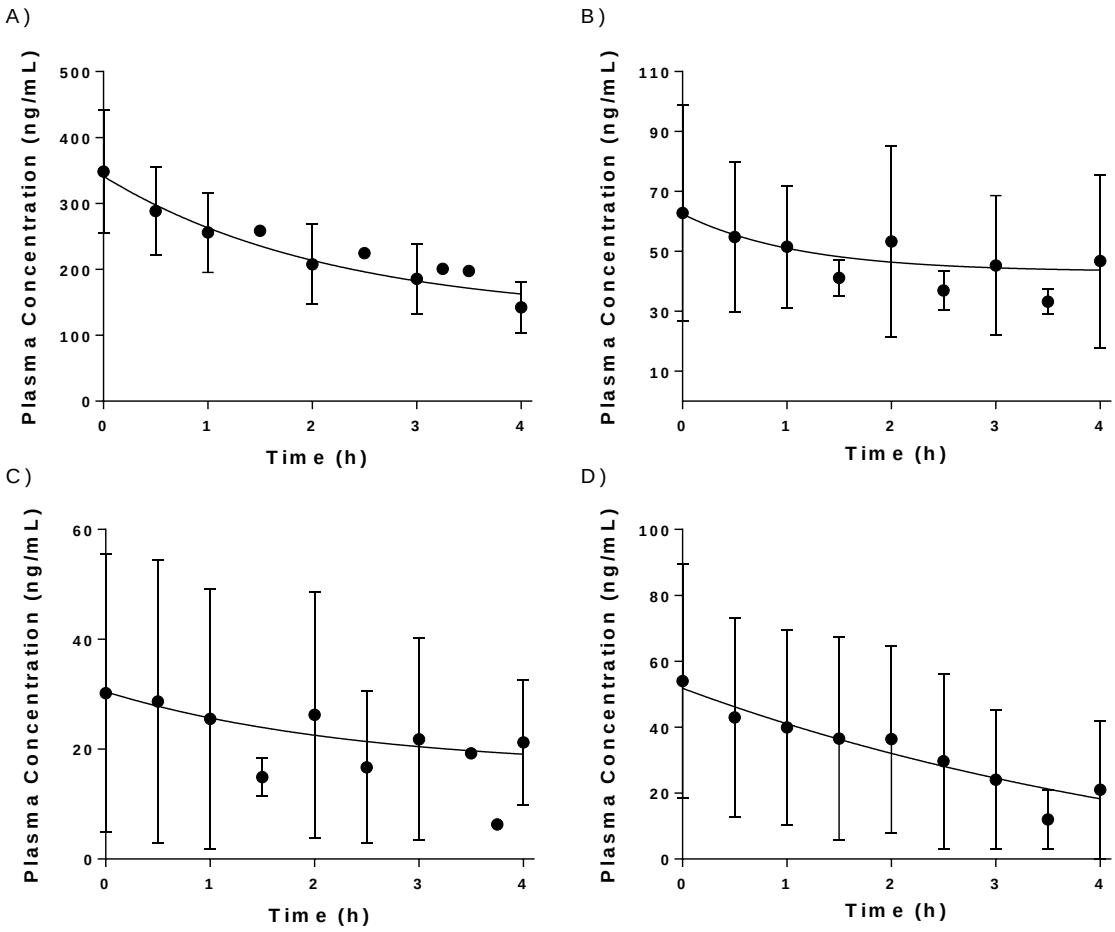
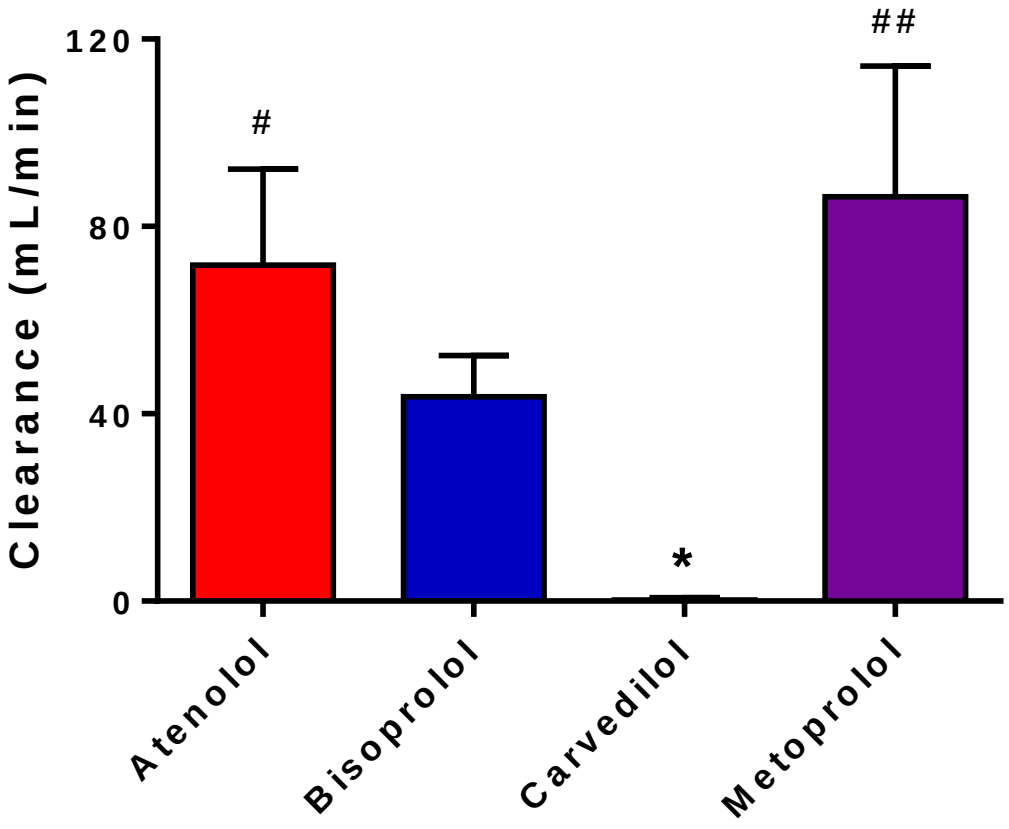

A)
Plasma Concentration (ng/mL)
500
400
300
200
100
0
0
1
2
3
4
Time (h)
B)
Plasma Concentration (ng/mL)
110
90
70
50
30
10
0
1
2
3
4
Time (h)
C)
Plasma Concentration (ng/mL)
60
40
20
0
0
1
2
3
4
Time (h)
D)
Plasma Concentration (ng/mL)
100
80
60
40
20
0
0
1
2
3
4
Time (h)

Figure 3.3. Clearance rate of beta blockers during hemodialysis calculated using the recovery clearance equation.

Dialytic clearance values for the four beta-blockers (A) atenolol, (B) bisoprolol, (C) carvedilol, and (D) metoprolol, during hemodialysis in end-stage renal disease patients. Plasma concentration of beta blockers were determined using ultra-performance liquid chromatography coupled to a quadrupole time-of-flight mass spectrometer (UPLC-QToFMS) and dialyzability was calculated using the recovery clearance method. Results are presented as mean ± SD with n=8 for each treatment group. * $P < 0.01$ for carvedilol relative to all other beta blockers, # $P < 0.05$ relative to bisoprolol, and ## $P < 0.01$ relative to bisoprolol.


Clearance (mL/min)
120
80
40
0
#
*
##
Atenolol
Bisoprolol
Carvedilol
Metoprolol

3.4 Additional Pharmacokinetic Parameters

Additional pharmacokinetic parameters were investigated for each beta blocker during hemodialysis (Table 3.3). Literature values for volume of distribution (V_D), fraction of drug unbound (F_U) and elimination rate constant (k_E) in CKD patients not being treated with HD were used to determine the total clearance of beta blockers. For atenolol, the reported value of V_D is 0.90 L/kg with an F_U of 0.84–0.94 and k_E of 0.0225 h^{-1} (Kirch *et al.*, 1981; AstraZeneca Canada Inc., 2011). The V_D, F_U and k_E of bisoprolol are 1.84 L/kg, 0.70, and 0.0286 h^{-1}, respectively (Kirch *et al.*, 1987; Payton *et al.*, 1987; Apotex Inc., 2004). In non-CKD patients, carvedilol has a V_D of 1.68 L/kg with less than 2% of the drug bound to plasma proteins (von Mollendorff *et al.*, 1987; Auro Pharma Inc., 2013). The k_E observed in patients with advanced renal insufficiency was 0.104 (Gehr *et al.*, 1999). Lastly, the V_D, F_U and k_E for metoprolol are 3.50 L/kg, 0.90 and 0.139 h^{-1}, respectively (Jordo *et al.*, 1980; Novartis Pharma, 2015).

These variables were used to calculate the total clearance of each beta blocker during dialysis (Table 3.2). Metoprolol has a total clearance of 2364.4 mL/min, which is markedly higher when compared to atenolol (524.0 mL/min), bisoprolol (700.3), and carvedilol (810.8 mL/min, $P < 0.01$). The proportion of clearance due to dialytic elimination is 0.14 for atenolol, 0.07 for bisoprolol, 0.00 for carvedilol and 0.04 for metoprolol. During dialysis, the elimination half-life of atenolol was 3.88 hours corresponding to a 54% reduction in plasma concentration. Bisoprolol concentration decreased by 33% over the dialysis session producing a half-life of 7.00 hours, which is considerably longer when compared to the other beta blockers ($P < 0.01$). Plasma concentration of carvedilol decreased by 34%, which corresponds to a half-life of 3.84

hours. Lastly, the half-life of metoprolol during hemodialysis was 2.85 hours which was determined from an overall 61% reduction in plasma concentration.

After the hemodialysis session, the mean supplemental dose for bisoprolol as a percentage of the initial administered dose is 38% (1.9 mg). This is not significantly different from atenolol at 23% (11.4 mg); however, bisoprolol does require a markedly higher post-dialysis dose as compared with carvedilol at 14% (0.87 mg) and metoprolol at 5.5% (2.7 mg, $P < 0.05$).

Table 3.2 Pharmacokinetic parameters of beta blocker treatments during hemodialysis. Hemodialysis time of subjects may vary depending on physician recommendations.

Beta Blocker	**Atenolol (50mg)**	**Bisoprolol (5mg)**	**Carvedilol (6.25mg)**	**Metoprolol (50mg)**
Amount Dialyzed (% of initial dose)	7.34 ± 2.87 Ω	9.30 ± 4.92Ω	0.00 ± 0.00	1.03 ± 0.68
$AUC_{0\rightarrow T}$ (ng·h/mL)	827.9 ± 146.5*	180.9 ± 99.31	89.56 ± 77.84	106.9 ± 90.6
CL_{Total} (mL/min)	524.2 ± 93.1	700.3 ± 170.7	810.8 ± 275.3	2364.4 ± 560.0*
$CL_{Non\text{-}dialysis}$ (mL/min)	452.4 ± 93.2	656.6 ± 170.4	810.6 ± 275.4	2278.0 ± 548.7*
$T_{1/2}$ on hemodialysis (h)	3.88 ± 0.86	7.01 ± 2.12*	3.84 ± 0.85	2.85 ± 0.81
$F_{Dialysis}$	0.14 ± 0.05*	0.07 ± 0.02	0.00 ± 0.00 §	0.04 ± 0.01
F_{Drug}	0.07 ± 0.02*	0.02 ± 0.01	0.00 ± 0.00 §	0.02 ± 0.01
Supplemental Dose as % of initial dose (dose in mg)	22.8 ± 5.6 (11.4 ± 2.8)	38.0 ± 20.6 Ω (1.90 ± 1.03)	13.9 ± 17.1 (0.87 ± 1.07)	5.5 ± 2.9 (2.74 ± 1.45)

$AUC_{0\rightarrow T}$ is the area under the concentration-time curve during hemodialysis
CL_{Total} is total clearance of the drug during hemodialysis (dialytic and non-dialytic components)
$CL_{Non\text{-}dialysis}$ is clearance of the drug due to non-dialytic mechanisms
$T_{1/2}$ on hemodialysis is half-life of the drug during hemodialysis
$F_{Dialysis}$ is fraction of clearance due to hemodialysis
F_{Drug} is fraction of drug initially in body eliminated by hemodialysis
Supplemental Dose is the dose of beta blocker required after hemodialysis to reach the drug level that was observed in the patient prior to dialysis.
Data are presented as mean ± SD with n=8 for each beta blocker group.
Ω $P < 0.01$ relative to carvedilol and metoprolol
* $P < 0.01$ relative to all other beta blockers
§ $P < 0.01$ for carvedilol relative to bisoprolol and metoprolol

4 DISCUSSION

4.1 Summary of Results

4.1.1 Clinical Pharmacokinetic Study

In this thesis, we outlined a dialyzability study design and various pharmacokinetic equations that were applied to a cohort of hemodialysis patients in order to define clinically-relevant parameters pertaining to dialytic elimination of drugs. With only 10% of currently marketed medications having definitive dialyzability information based on experimental data (Velenosi and Urquhart, 2014), this study was conducted with a primary focus on determining the dialytic clearance of the four most commonly prescribed beta blockers in Ontario. Additionally, many of the studies that do exist have become considerably outdated due to the nearly universal switch from "conventional" to "high-flux" dialysis membranes. This study is the first to assess beta blocker dialyzability using the recovery clearance method in ESRD patients during modern, high-flux, high-efficiency hemodialysis treatment.

As expected, our findings demonstrate that both atenolol and metoprolol are extensively removed during hemodialysis. Despite renal excretion accounting for only 5% of metoprolol clearance (Regardh and Johnsson, 1980), both atenolol and metoprolol have physicochemical properties that enable them to be readily dialyzed. For instance, both drugs are only 10% bound to plasma proteins, are highly water soluble, and have similarly low molecular weights at 270 Da—well below the upper limit of 12,000 Da for modern dialyzers (McAinsh, 1977; Regardh and Johnsson, 1980; Cheung and Leypoldt, 1997). Despite metoprolol being the second most frequently used antihypertensive agent in National Health and Nutrition Examination Survey (NHANES) 2009 to 2010 (Gu *et*

al., 2012), no previous studies have been conducted to determine its dialyzability. As for atenolol, the A-V difference method applied by Flouvat *et al.* (1980) produced a clearance rate of 42.6 mL/min for ESRD patients on a coil kidney dialysis with cuprophane membrane. Using the same equation, the contemporary, high-flux polysulfone based dialyzers prescribed to subjects in our study generated a substantially higher dialytic clearance of 162.1 mL/min. When the more reliable recovery clearance equation was applied, the dialyzability of atenolol at 71.8 mL/min was still higher than the value determined by Flouvat and colleagues (1980). These findings support the notion that older dialyzability studies are becoming unreliable in their ability to provide pharmacokinetic information when treating patients with modern dialyzers.

As for carvedilol, its physicochemical properties are highlighted by a larger volume of distribution and decreased water solubility, both of which would suggest minimal or low dialytic clearance (GlaxoSmithKline Inc.). However, the primary factor causing its negligible dialytic clearance is its extensive protein binding at 98% (Varin *et al.*, 1986). This conclusion was also drawn by Miki *et al.* (1991) after finding a non-significant difference in carvedilol levels between the arterial and venous ports of dialysis patients. Although carvedilol displayed a small but measurable value of dialytic clearance when using the A-V difference equation in our study, the recovery clearance method indicated a virtually null contribution from dialysis to its elimination. A low dialyzability was similarly expected for bisoprolol after consulting the dialysis of drugs guidelines and various peer-reviewed articles (Table 1.3). Surprisingly, our study indicates that bisoprolol is moderately dialyzable regardless of the method used to determine its clearance rate. Kanegae *et al.* (1999) found a comparable dialytic clearance of 50.8

mL/min for patients who were also prescribed polysulfone-based dialyzer membranes. This finding of moderate dialyzability is reflective of bisoprolol's intermediate physicochemical properties as compared to carvedilol and atenolol. Specifically, bisoprolol has a mild degree of protein binding (30%) as well as balanced lipophilic and hydrophilic components in its molecular structure (Buhring *et al.*, 1986; Leopold, 1986).

Further evidence showing the impact that modern dialyzers have on drug dialyzability can be derived from comparisons of elimination half-life. For severe renal impairment patients not yet receiving dialysis, the half-life of atenolol, bisoprolol, carvedilol and metoprolol are approximately 70, 24, 7 and 5 hours, respectively (Flouvat *et al.*, 1980; Jordo *et al.*, 1980; Kirch *et al.*, 1987; Gehr *et al.*, 1999). Although very few studies have evaluated dialytic clearance, the half-life for these beta blockers have been previously reported for patients on older conventional dialyzers. The half-life of atenolol is shortened to only 7 hours during conventional hemodialysis (Campese *et al.*, 1985; Fox and Investigators, 2003), which was found to be further reduced to 3.9 hours due to the use of modern dialyzers in our study. In order to maintain the pharmacological effect of atenolol when patients transition from ESRD to dialysis, an increase in dosage is required and changing intake of atenolol to a post-dialysis period should be considered. Plasma concentrations of bisoprolol in patients using a polysulfone dialyzer were reduced by 25% during hemodialysis (Kanegae *et al.*, 1999), similar to what we determined in our study. The resulting half-life was 7 hours—over 70% shorter than what is observed in non-dialysis ESRD patients. For carvedilol and metoprolol, their half-life in CKD patients do not differ largely from the values reported in patients with normal functioning kidneys (Regardh and Johnsson, 1980). However, the modern hemodialyzers used in this

study did result in a minor decrease in metoprolol half-life, which corresponds to more than half of the drug being eliminated within a 4 hour dialysis session.

Plasma concentration-time profiles of each beta blocker during the hemodialysis session were evaluated to assess drug exposure. The variability in plasma drug levels at each time point between patients was noticeably lower for atenolol than other beta blockers. This disparity may be explained by differences in the route of elimination for each drug. Little to none of atenolol clearance can be attributed to hepatic metabolism, suggesting that dialysis is the primary mechanism of atenolol removal in kidney failure patients (AstraZeneca Canada Inc., 2011). Since the hemodialysis treatment plan and dialyzer membranes prescribed between subjects were similar, the more consistent drug levels observed were as expected. In contrast, metoprolol is extensively metabolized by the drug metabolizing enzyme, cytochrome P450 2D6 (CYP2D6), with only 5% of the drug eliminated through renal excretion (Regardh and Johnsson, 1980). Interindividual differences in plasma concentration of metoprolol may be due to the large phenotypic variability in CYP2D6 genotype and the associated categorizations of people into poor, intermediate, extensive or ultra-rapid drug metabolizers (Zanger *et al.*, 2004). Rau *et al.* (2002) demonstrated that poor and intermediate metabolizers on long-term metoprolol treatment had plasma concentrations 6- and 4-fold higher than extensive metabolizers, respectively. A recently completed meta-analysis of CYP2D6 phenotypes similarly showed that poor metabolizers had a 5- and 13-fold increase in metoprolol exposure as compared to extensive and ultra-rapid metabolizers, respectively (Blake *et al.*, 2013). Despite this variability in pharmacokinetics, there still exist controversial findings as to whether CYP2D6 genotyping can offer clinical benefit to metoprolol dosing in patients.

Shin and Johnson (2007) have stated that the overall pharmacological efficacy and toxicity of metoprolol are not influenced by CYP2D6 genotype, while Swen *et al.* (2011) have reported a necessity to alter metoprolol dosage in heart failure patients depending on their CYP2D6 metabolizer phenotype. In our study, individual plasma profiles of study subjects demonstrated good correlation with a one-phase decay model, reaffirming that metoprolol is highly cleared by hemodialysis.

Bisoprolol has a balanced mechanism of clearance with equal contributions from both renal and non-renal pathways (Leopold *et al.*, 1982). The main drug metabolizing enzymes involved in bisoprolol elimination are CYP3A4 and CYP2D6 (Horikiri *et al.*, 1998). However, variations in oral clearance, apparent volume of distribution, and plasma concentration are not well correlated with CYP2D6 genotypes (Nozawa *et al.*, 2005; Taguchi *et al.*, 2005). An *in vitro* study using intestinal epithelial cells indicates temperature and pH dependent alterations in the rate and extent of bisoprolol uptake (Ishida *et al.*, 2013). These findings offer one possible explanation for interindividual variation of bisoprolol levels, but future clinical studies investigating differences in drug bioavailability are required. Lastly, dialysis plays a very minor role in the clearance of carvedilol for ESRD patients whereas hepatic metabolism accounts for more than 98% of carvedilol disposition (Auro Pharma Inc., 2013). In particular, the diversity of genetic polymorphisms for the enzymes responsible for aromatic ring oxidation (CYP2D6 and CYP2C9) and glucuronidation (UGT2B7) have been shown to be important factors in the interindividual pharmacokinetic variability of carvedilol (Takekuma *et al.*, 2007; Pan *et al.*, 2016).

As important as dialytic clearance may be, non-dialytic mechanisms for clearance (e.g. hepatic or biliary excretion) still have a large role in dictating drug elimination during hemodialysis. In particular, almost all of carvedilol clearance was a result of non-dialytic pathways. Metoprolol had a considerably higher total clearance as compared to all other beta blockers, most likely explained by combinations from both high hepatic metabolism and high dialytic clearance. Atenolol and bisoprolol required the largest post-dialysis dose at nearly 23% (11 mg) and 40 % (2 mg) of their initial prescribed dose. For healthcare professionals determining the supplemental dose required to maintain patients within a therapeutic window, both dialytic and non-dialytic means of elimination must be considered. However, regulatory agencies should consider invoking specifications for highly dialyzable drugs to be taken only after dialysis in order to overcome the need for supplemental doses. These additional pharmacokinetic parameters that we examined have never been incorporated in previous dialyzability studies. Nonetheless, other groups investigating drug dialyzability can implement these equations to determine clinically-relevant supplemental information.

4.1.2 Retrospective Cohort Study

A published study by Weir *et al.* (2015) has demonstrated the impact that drug dialyzability can have on clinical outcomes. Atenolol, metoprolol, and acebutolol were classified as “high dialyzability” beta blockers, while bisoprolol and propranolol were categorized as “low dialyzability” drugs. Hemodialysis patients prescribed highly dialyzed beta blockers exhibited a significantly increased risk for all-cause mortality and ventricular arrhythmia. Conversely, patients not requiring dialysis demonstrated no difference in risk for adverse clinical outcomes between dialyzability groups, as

expected. These findings strengthen the idea that beta blocker dialyzability should be considered when constructing future treatment plans. One limitation described by Weir *et al.* (2015) was that classification of dialyzability was based on either data from conventional dialysis membranes or solely on the physicochemical characteristics of the drugs. Indeed, results from our dialyzability study have since recognized that bisoprolol is actually moderately dialyzed, although it has been previously classified as non-dialyzed (Table 1.3). In addition, patients administered carvedilol were omitted from the study due to its limited indications required for prescription in Ontario. Our current data creation plan comparing dialysis patients on carvedilol with those on metoprolol has since been submitted and approved by programmers, and is currently in queue for data analysis (Appendix G). The study objectives and design have been further described in Appendix F. It is unfortunate that a large delay in programming has made this data unavailable for incorporation into this thesis. Although the programming has taken longer than expected, we also delayed the start of the retrospective cohort study until all patient data from the dialyzability study was complete. We felt this was important since our findings in terms of dialyzability were essential in the data creation plan of the retrospective study.

4.2 Research Significance

Despite one study having previously shown that bisoprolol is removed during hemodialysis (Kanegae *et al.*, 1999), it is still widely assumed that this beta blocker is minimally dialyzed. The findings from this clinical pharmacokinetic study demonstrate conclusively that bisoprolol should be re-categorized as having moderate dialyzability.

Although estimations of drug dialyzability can be made based on physicochemical properties, this unexpected discovery highlights the importance of conducting formal, experimental studies to definitively characterize drug dialyzability. CKD patients of all stages, with and without dialysis, must be better represented in the drug discovery process in order to optimize pharmacotherapy in this growing population. This has been acknowledged thus far by the FDA through the implementation of the 1998 FDA Renal Guidance and the current 2010 draft guidance that is pending implementation. A recent survey conducted by Matzke *et al.* (2015) illustrates the positive impact on drug development created by the 1998 Renal Guidance. From 1999–2010, 71.6% of new investigational drugs conducted appropriate renal studies—a significant improvement from 51.6% in the two year span of 1996–1997 (Matzke *et al.*, 2015). As the 1998 Renal Guidance did not emphasize renal studies for non-renally cleared drugs, the involvement of CKD patients were more likely observed in drugs characterized by renal excretion (89.6%) as compared with drugs that primarily display non-renal elimination (65.8%) (Matzke *et al.*, 2015). Nearly 50% of NCEs with low renal clearance exhibited substantial pharmacokinetic changes. However, only one-third of those NCEs resulted in dosage recommendations and proper labeling. With greater emphasis in the 2010 draft guidance to complete renal and dialyzability studies in drugs with non-renal clearance, these results provide an encouraging outlook for future NCEs to standardize the incorporation of CKD patients in pharmacokinetic studies. In turn, accurate clinical information to describe which drugs require a supplemental dose can be determined, and recommendations can be made on preferred medication choices in hemodialysis patients for drugs in the same class.

Current clinical practice guidelines outlined by the National Kidney Foundation make no recommendations on which beta blocker should be prescribed to CKD and dialysis patients. Beta blockers have become a cornerstone treatment to battle cardiovascular disease due to their widespread applicability—from treating heart failure, to post myocardial infarctions, to angina (Kidney Disease Outcomes Quality Initiative, 2004). The dialyzability of beta blockers found in our study can be implemented in future clinical practice guidelines and disseminated to healthcare professionals in order to help their drug selection process. One of the current recommendations by the National Kidney Foundation is to choose a simplified antihypertensive regimen with only a single daily dose requirement if possible (Kidney Disease Outcomes Quality Initiative, 2004). We now know that atenolol, bisoprolol, and metoprolol are all cleared during hemodialysis which indicates that patients may require a post-dialysis dose for their therapy to maintain levels required for efficacy. Conversely, carvedilol removal by dialysis is negligible. Due to renal excretion accounting for less than 2% of its elimination, plasma levels of carvedilol do not accumulate in any form of renal impairment (Deetjen *et al.*, 1995). These combined findings suggest that no dosage adjustments are required for carvedilol when patients progress from normal to reduced kidney function, even if renal replacement therapy is necessary (Miki *et al.*, 1991; Gehr *et al.*, 1999). Hence, the preferential selection of carvedilol over other beta blockers should be considered.

In agreement, the strongest evidence in support of administering carvedilol as opposed to other beta blockers is due its proven efficacy in ESRD patients. Carvedilol is the only beta blocker and one of the only antihypertensive drugs that has been tested in prospective randomized clinical trials in dialysis patients. Cice *et al.* (2001) demonstrated

that for hemodialysis patients with dilated cardiomyopathy, a year-long administration of carvedilol reduces left ventricular volumes and improves overall cardiac function. This cohort of patients was subsequently followed for another 12 months to assess the effect of carvedilol on mortality and morbidity (Cice *et al.*, 2003). When compared to placebo-controlled patients, carvedilol significantly reduced all-cause mortality, cardiovascular mortality, and all-cause hospitalizations. Fatal myocardial infarctions and strokes—two main causes for cardiovascular death in ESRD patients (Saran *et al.*, 2016)—were also considerably reduced in carvedilol-treated subjects.

Although carvedilol is typically reserved for patients with symptomatic heart failure, it may be worth considering expanding the application of carvedilol in dialysis patients. Based on its ideal pharmacokinetic qualities in CKD patients and previous clinical trials indicating its strength to improve patient morbidity, we are hopeful that the administration of carvedilol will become more liberal.

4.3 Limitations and Future Directions

When conducting pharmacokinetic studies to categorize drug dialyzability, the recovery clearance method is widely accepted as the gold-standard approach. One limitation for using this method is the requirement for a sensitive technique when measuring very low drug concentrations in large volumes of dialysate. Despite us concentrating samples 100-fold and our UPLC-MS providing accurate, sensitive detection of small molecules, some dialysate samples containing carvedilol were below our LLOQ. However, negligible dialytic clearance of the beta blocker may have resulted in samples having virtually no carvedilol for detection.

Subjects enrolled in our study had dialysis durations varying from 3 to 4 hours. Patient variability in dialysis time result in differences in how much drug is remaining at the end of dialysis. However, the dialytic clearance values are not affected by shorter or longer dialysis durations since the recovery clearance equation (Equation 2) takes the ratio of amount dialyzed over total drug exposure. Regarding study design, a single oral dose prescription as used in our study may not produce pharmacokinetic parameters reflective of patients on long-term beta blocker therapy. For instance, dialytic clearance is dependent on dialysis prescription factors including blood flow rate, dialysate flow rate, and ultrafiltration rate—all of which can vary from one dialysis session to another. Despite this, the overall categorization of a drug's dialyzability is not expected to change significantly. One proposed future study can examine the dialytic clearance of beta blockers for dialysis patients at steady state. Additionally, plasma concentration of beta blockers at steady state should be compared between normal renal function and chronic hemodialysis patients. If drug dialyzability is an important determinant of therapeutic efficacy, we expect that highly dialyzed drugs would exhibit a substantially lower steady state concentration in subjects on dialysis while poorly dialyzed drugs will show no difference in plasma levels.

Another caveat in our study was the use of literature values to determine additional pharmacokinetic parameters (V_D, F_U, and k_E). The studies used had small sample sizes which may produce values that are not representative for all CKD patients. In addition, the supplemental dose calculated for each beta blocker did not account for post-dialysis rebound of the drugs. Future study designs will attempt to include more sample collection at time points after the dialysis session to characterize any potential

drug distribution out of tissue. Nonetheless, these equations still provide the framework to determine clinically-relevant parameters for any subsequent dialyzability studies.

The unexpected result of bisoprolol having moderate dialyzability prompted us to review other drugs prescribed to subjects during the duration of the study. We compiled a list of different drug classes of interest including narcotics (morphine and codeine), vitamin D supplements (alfacalcidol and calcitriol), cardiovascular medications (ACE inhibitors, ARBs, CCBs and statins), antipsychotics (lorazepam, diazepam, gabapentin, etc.), anticoagulants, and proton pump inhibitors (lansoprazole and rabeprazole). Morphine, codeine, lansoprazole, and warfarin were detected in patient dialysate samples despite the latter 3 drugs being listed as not dialyzble (Figure 4.1) (Baillie and Mason, 2013). This finding confirms the notion that studies involving conventional hemodialysis have become obsolete and drug dialyzability must be further investigated to optimize pharmacotherapy in ESRD patients. Looking forward, similar dialyzability studies should be conducted for other classes of cardiovascular medications (ACE inhibitors, ARBs, CCBs and anticoagulants) in hopes of improving the overall management of cardiac disease in dialysis patients. Results from both present and future investigations will be disseminated to practitioners and regulatory agencies for knowledge translation into clinical practice guidelines.

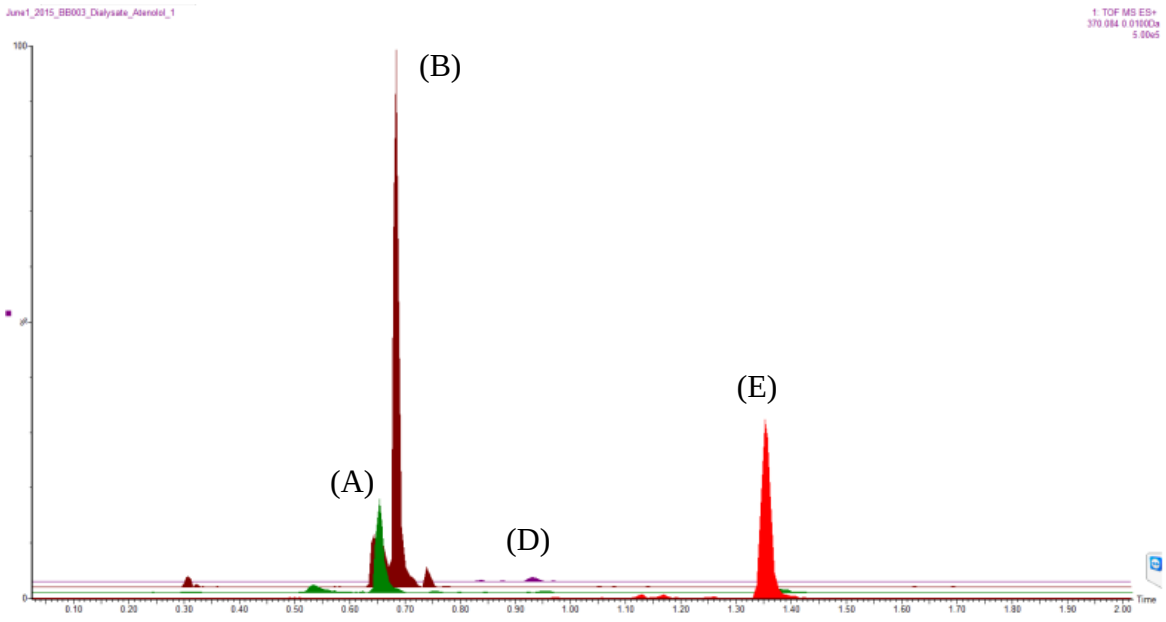


Figure 4.1. Select drugs of interest detected in subject dialysate samples.

A list of drugs of interest was created after reviewing the prescription record of subjects during the study period. Morphine (A), codeine (B), lansoprazole (C), and warfarin (D) were detected in patient dialysate samples using ultra-performance liquid chromatography coupled to quadrupole time-of-flight mass spectrometry (UPLC-QToFMS).

4.4 Conclusions

In much of recent literature, adequacy of dialysis for ESRD patients has been erroneously assumed to be synonymous with adequacy of patient care (National Kidney Foundation, 2015). This concept and approach to healthcare is inaccurate. The overall purpose for renal replacement therapy is to improve the quality of life and prognosis for a vulnerable, globally-growing population. However, many aspects of the treatment plan for ESRD patients are established prior to the renal replacement strategy and are independent or only partially-dependent on dialysis itself. For example, the dosage regimen for drug therapy is often devised in earlier stages of CKD but become extensively intertwined with the daily life of dialysis patients to combat cardiovascular complications and other comorbidities. As such, the importance of dialyzability research has been identified by an international guideline committee for renal disease, Kidney Disease | Improving Global Outcomes (KDIGO) (Atkinson and Umans, 2010; Dager, 2010). When drugs are approved for use in the general population, they must undergo extensive pharmacokinetic evaluation for determination of renal clearance among other parameters. Despite the widespread use of cardiovascular medications in patients receiving hemodialysis and the clear difference between dialytic and renal excretion, there still remains a paucity of data describing drug elimination during dialysis. In this study, we were able to definitively categorize the four most commonly prescribed beta blockers in Ontario into high (atenolol, metoprolol), moderate (bisoprolol) and low (carvedilol) dialyzability drug groups. Clinicians and scientists are encouraged to continue conducting pharmacokinetic studies to characterize drug dialyzability and provide more evidence on the necessity of including dialysis patients in drug

development. When considering study design for future dialyzability studies, it would be ideal to conduct studies in both single-dose and steady-state dosing conditions, use the superior recovery clearance method, and confirm that drug concentrations remain in the therapeutic window following dialysis to ensure efficacy. The clear implications that drug dialyzability has for the efficacy of pharmacotherapy will hopefully improve quality of care and prognosis for all patients receiving chronic hemodialysis.

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Appendices

Appendix A: Ethics Approval

Western Research

Research Ethics

Use of Human Participants - Initial Ethics Approval Notice

Principal Investigator: Dr. Brad Urquhart
File Number:104909
Review Level: Full Board
Protocol Title: Removal of Beta Blocker Drugs by Hemodialysis
Department & Institution: Schulich School of Medicine and Dentistry\Physiology & Pharmacology,Western University
Sponsor:
Ethics Approval Date: March 07, 2014
Ethics Expiry Date: February 28, 2017

Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Western University Protocol	REB Revised Protocol Clean v2_Feb 2014	2014/02/13
Letter of Information & Consent	Revised Letter of Information and Consent Clean	2014/02/13
Other	Revised Case Report Form CLEAN	2014/02/13
Other	Master List	2014/02/13

This is to notify you that the University of Western Ontario Health Sciences Research Ethics Board (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this HSREB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request form.

Member of the HSREB that are named as investigators in research studies, or declare a conflict of interest, do not participate in discussions related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Signature

Ethics Officer to Contact for Further Information

[redacted]

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Appendix B: Copyright Approval

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Wolters Kluwer

Title: Clearance of cardiovascular medications during hemodialysis

Author: Alvin Tieu, Maxwell Leither, Bradley Urquhart, et al

Publication: Current Opinion in Nephrology and Hypertension

Publisher: Wolters Kluwer Health, Inc.

Date: Jan 1, 2016

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Appendix C: Supplementary Information

Supplementary Table C1. Dialyzability of angiotensin converting enzyme (ACE) inhibitors.

ACE Inhibitor	Molecular Weight (Daltons)	Protein binding (%)	Volume of distribution (L/kg)	Dialyzability Data		
				Specified Dialyzability Testing Conditions*	Clearance during hemodialysis (ml/min)	Reference
Fosinoprilat	435	99	"very small"	Recovery method Single dose Dialyzer: cellulose Q_D: 550 ml/min Q_B: 250 ml/min	4	(Gehr *et al.*, 1993)
Ramiprilat	388	56	1.2	A-V Difference method Multiple doses Dialyzer: cellulose Q_D: 500 ml/min Q_B: 250-300 ml/min	21	(Fillastre *et al.*, 1996)
				A-V Difference method Single dose Dialyzer: cellulose Q_D: 500 ml/min Q_B: 250-300 ml/min	32	
Enalaprilat	348	50	1.7	A-V Difference method Multiple doses Q_B: 230 ml/min	39	(Kelly *et al.*, 1988)
				A-V Difference method Single dose Dialyzer: cellulose Q_D: 500 ml/min Q_B: 300 ml/min	68	(Fruncillo *et al.*, 1987)
				A-V Difference method Multiple doses Dialyzer: cellulose Q_D: 500 ml/min Q_B: 300 ml/min	57	
Lisinopril	405	< 1	2.4	A-V Difference method Multiple doses Dialyzer: ? Q_D: ? Q_B: 230 ml/min	40	(Kelly *et al.*, 1988)
Perinoprilat	340	15	0.2	A-V Difference method Single dose Dialyzer: polysulfone Q_D: 500 ml/min Q_B: 300 ml/min	62	(Guérin *et al.*, 1993)
				A-V Difference method Multiple doses Dialyzer: polysulfone Q_D: 500 ml/min Q_B: 300 ml/min	72	
				A-V Difference method Single dose Dialyzer: cellulose triacetate Q_B: 200 ml/min	66	(Verpooten *et al.*, 1991)
				A-V Difference method Multiple doses Dialyzer: polysulfone Q_D: ? Q_B: 200 ml/min	108	(Yamada *et al.*, 2003)

Benazeprilat	396	95	0.1	No data	No data	-
Quinaprilat	428	97	0.4	A-V Difference method Multiple doses Dialyzer: polysulfone Q_D: ? Q_B: 200 ml/min	52	(Yamada *et al.*, 2003)
Trandolaprilat	402	75	0.3	No data	No data	-

* Clearance of a drug during hemodialysis can be determined by the Recovery Method, in which drug removal is determined from the total spent dialysate, or by the A-V Difference Method, in which clearance is calculated with the Fick Equation using the difference in drug concentrations between the arterial (A) and venous (V) limbs of the dialysis machine and the blood flow rate.
Abbreviations: Q_D, dialysate flow rate; Q_B, blood flow rate; UF, ultrafiltration rate.

Supplementary Table C2. Dialyzability of study angiotensin II receptor blockers (ARBs).

ARB	Molecular Weight (Daltons)	Protein binding (%)	Volume of distribution (L/kg)	Dialyzability Data		
				Specified Dialyzability Testing Conditions*	Clearance during hemodialysis (ml/min)	Reference
Candesartan	440	99	0.13	A-V Difference method Multiple doses Dialyzer: polysulfone Q_D: 500 ml/min Q_B: 400 ml/min	1.5	(Pfister *et al.*, 1999)
Irbesartan	429	90	0.75	A-V Difference method Multiple doses Dialyzer: ? Q_D: ? Q_B: ?	"Not removed"	(Sica *et al.*, 1997)
Losartan	423	99	0.49	A-V Difference method Single dose Dialyzer: polysulfone Q_D: 500 ml/min Q_B: 400 ml/min	"Approximately zero"	(Sica *et al.*, 2000)
Olmesartan	447	99	0.24	A-V Difference method Single dose Dialyzer: polysulfone Q_D: ? Q_B: ?	"Not removed"	(Tanaka *et al.*, 2009)
Telmisartan	515	99	>7	Recovery method Single dose Dialyzer: olysulfone Q_D: ? Q_B: ?	"Very little removed"	(Stangier *et al.*, 2000)
Valsartan	436	95	0.24	No data	No data	-

* Clearance of a drug during hemodialysis can be determined by the Recovery Method, in which drug removal is determined from the total spent dialysate, or by the A-V Difference Method, in which clearance is calculated with the Fick Equation using the difference in drug concentrations between the arterial (A) and venous (V) limbs of the dialysis machine and the blood flow rate.
Abbreviations: Q_D, dialysate flow rate; Q_B, blood flow rate.

Supplementary Table C3. Dialyzability of calcium channel blockers.

Calcium Channel Blocker	Molecular Weight (Daltons)	Protein binding (%)	Volume of distribution (L/kg)	Dialyzability Data		
				Specified Dialyzability Testing Conditions*	Clearance during hemodialysis (ml/min)	Reference
Amlodipine	567.1	98	0.3	One time concentration of dialysate Dialyzer: ? Q_D: ? Q_B: ?	No clearance data, but concentration in dialysate very low	(Kungys *et al.*, 2003)
Diltiazem	451	70-80	0.07-0.15	No Data	No Data	-
Felodipine	384.2	>99	0.15	A-V Difference method Single oral dose followed by single IV dose Dialyzer: cellulose Q_D: 500 ml/min Q_B: 200 ml/min	Negligible, but inactive metabolites with clearance of 8.4-13.8	(Buur *et al.*, 1991)
Nicardipine	516	98	0.6-6.8	No Data	No data	-
Nifedipine	346.3	88-95	0.75-1.5	A-V Difference method Single dose Dialyzer: 1.2 m^2 cuprophane Q_D: 500 ml/min Q_B: 200 ml/min	2.8	(Martre *et al.*, 1985)
Verapamil	491.1	90	3.8-5	A-V Difference method Single dose Dialyzer: cuprophane Q_D: ? Q_B: 250-280 ml/min	Negligible	(Hanyok *et al.*, 1988)
				Recovery method Multiple doses Dialyzer: cuprophane Q_D: 500 Q_B: 200 ml/min	Negligible	(Shah and Winer, 1985)

* Clearance of a drug during hemodialysis can be determined by the Recovery Method, in which drug removal is determined from the total spent dialysate, or by the A-V Difference Method, in which clearance is calculated with the Fick Equation using the difference in drug concentrations between the arterial (A) and venous (V) limbs of the dialysis machine and the blood flow rate.
Abbreviations: Q_D, dialysate flow rate; Q_B, blood flow rate, IV, intravenous.

Supplementary Table C4. Dialyzability of antiplatelet agents.

Antiplatelet Agent	Molecular Weight (Daltons)	Protein binding (%)	Volume of distribution (L/kg)	Dialyzability Data		
				Specified Dialyzability Testing Conditions*	Clearance during hemodialysis (ml/min)	Reference
Acetylsalicylic Acid (Aspirin)	180	99.5	0.15-0.20	A-V Difference method Dialyzer: ? Q_D: ? Q_B: 200 ml/min	86**	(Jacobsen *et al.*, 1988)
				A-V Difference method Dialyzer: cuprophane Q_D: ? Q_B: 100 ml/min	30-35**	(Doolan *et al.*, 1951) (Spritz *et al.*, 1959)
				A-V Difference method Dialyzer: cuprophane Q_D: ? Q_B: 250 ml/min	80**	(Kallen *et al.*, 1966)
Dipyridamole	505	91-99	1.0-2.5	No Data	No Data	-
Clopidogrel	321	98	-	No Data	No Data	-
Prasugrel	373	98	-	No Data	No Data	-
Sulfinpyrazone	404	98	0.35	Single dose Dialyzer: cuprophane Q_D: ? Q_B: ?	Negligible	(Bern *et al.*, 1980)
Ticagrelor	340	>99.7	1.25	No Data	No Data	-
Ticlopidine	264	98	-	No Data	No Data	-

* Clearance of a drug during hemodialysis can be determined by the Recovery Method, in which drug removal is determined from the total spent dialysate, or by the A-V Difference Method, in which clearance is calculated with the Fick Equation using the difference in drug concentrations between the arterial (A) and venous (V) limbs of the dialysis machine and the blood flow rate.
** Data derived from overdose settings
Abbreviations: Q_D, dialysate flow rate; Q_B, blood flow rate.

Supplementary Table C5. Dialyzability of anitcoagulants.

Oral Anticoagulants	Molecular Weight (Daltons)	Protein binding (%)	Volume of distribution (L/kg)	Dialyzability Data		
				Specified Dialyzability Testing Conditions*	Clearance during hemodialysis (ml/min)	Reference
Warfarin	308	99	0.14	A-V Difference method Multiple Dialyzer: sulphonated cellulose acetate Q_D: 500 ml/min Q_B: 300 ml/min	31% drop in warfarin concentration during dialysis	(Ifudu and Dulin, 1993)
Acenocoumarol	343	98.7	0.18	No Data	No Data	-
Apixaban	459	>90%	0.3	No Data	18**	-
Dabigatran	627.7	35	0.85-1.0	A-V Difference method Steady State Dialyzer: "high-flux" Q_D: ? Q_B: 350 mL/min	10 ng/mL per hour	(Chang *et al.*, 2013)
				A-V Difference method Multiple doses Dialyzer: Polyflux PF Q_D: 700 mL/min Q_B: 200 mL/min	161	(Khadzhynov *et al.*, 2013)
				A-V Difference method Multiple Dose Dialyzer: Polyflux PF Q_D: 700 mL/min Q_B: 400 mL/min	241	
Rivaroxaban	436	92-95	0.7	A-V Difference method Multiple doses Dialyzer: polysulfone Q_D: 500 mL/min Q_B: 400 mL/min	0	(De Vriese *et al.*, 2015)
Low Molecular Weight Heparin						
Enoxaparin	1117	80	0.07	No Data	No Data	-
Dalteparin	6000	-	0.04	No Data	No Data	-
Nadroparin	4300	-	0.05	No Data	No Data	-
Injectable Direct Thrombin Inhibitors						
Desirudin	6964	-	0.26	No Data	No Data	-
Bivalirudin	2180	-	0.2	Steady State Dialyzer: ? Q_D: ? Q_B: ?	72.8§	(Robson, 2000)

Argatroban	509	54	0.17	Recovery method Multiple doses Dialyzer: Cellulose Triacetate Q_D: ? Q_B: ?	49§	(Murray *et al.*, 2004)
Injectable Factor Xa Inhibitors						
Fondaparinux	1730	94	0.1 – 0.16	Population pharmacokinetics model Multiple doses Dialyzer: High flux Q_D: 500 mL/min Q_B: 388 mL/min	9.8	(Kalicki *et al.*, 2007)
Danaparoid	~6000	-	0.1	No Data	No Data	-

* Clearance of a drug during hemodialysis can be determined by the Recovery Method, in which drug removal is determined from the total spent dialysate, or by the A-V Difference Method, in which clearance is calculated with the Fick Equation using the difference in drug concentrations between the arterial (A) and venous (V) limbs of the dialysis machine and the blood flow rate.
** From Product Monograph.
§ Normalized to 70 kg body weight.
Abbreviations: Q_D, dialysate flow rate; Q_B, blood flow rate

Supplementary Table C6. Dialyzability of cholesterol-lowering medications.

Cholesterol Lowering Drugs	Molecular Weight (Daltons)	Protein binding (%)	Volume of distribution (L/kg)	Dialyzability Data		
				Specified Dialyzability Testing Conditions*	Clearance during hemodialysis (ml/min)	Reference
Atorvastatin	558	≥98	381	Single oral dose Dialyzer: ? Q_D: ? Q_B: ?	Negligible	(Lins *et al.*, 2003)
Rosuvastatin	482	88	134	A-V Difference method Steady State Dialyzer: ? Q_D: ? Q_B: ?	34.8 for Rosuvastatin <42 for metabolites	(Birmingham *et al.*, 2013)
Simvastatin	419	95	--	No Data	No Data	-
Pravastatin	425	50	56	A-V Difference method Multiple doses Dialyzer: Cellulose acetate Q_D: ? Q_B: 200-250 mL/min	38-55	(Gehr *et al.*, 1997)
				Recovery method Multiple doses Dialyzer: Cellulose acetate Q_D: ? Q_B: 200-250 mL/min	49-81	
Fluvastatin	411	98	-	A-V Difference method Dialyzer: pulysulfone Q_D: 500 mL/min Q_B: 180-300 mL/min	Negligible	(Ichimaru *et al.*, 2004)
				Recovery method Dialyzer: ? Q_D: ? Q_B: ?	Negligible	(Appel‐Dingemanse *et al.*, 2002)
Lovastatin	405	>95	-	No data	No data	-
Ezetimibe	409	>90	-	No Data	No data	-

* Clearance of a drug during hemodialysis can be determined by the Recovery Method, in which drug removal is determined from the total spent dialysate, or by the A-V Difference Method, in which clearance is calculated with the Fick Equation using the difference in drug concentrations between the arterial (A) and venous (V) limbs of the dialysis machine and the blood flow rate.
Abbreviations: Q_D, dialysate flow rate; Q_B, blood flow rate.

Appendix D: Screening Criteria for Subject Enrolment

SCREENING PROCESS

EMR review:

1) Over 18 years old
2) No severe gastrointestinal disease
   a. Cirrhosis
   b. Liver transplant
   c. Chronic liver disease
      i. Hepatitis B, Hepatitis C, Primary sclerosing cholangitis, NASH (non-alcoholic steatohepatitis), Wilson's disease, Alpha anti-tripsin 1 deficiency, Alcoholic liver disease
   d. Gastric bypass surgery
   e. Severe peptic ulcer disease
3) No beta blocker related contraindications
   a. Severe symptomatic heart failure (NYHA class III – IV)
   b. Severely depressed left ventricular ejection fraction (< 30%)
   c. Bradycardia (heart rate < 60 beats per minute)
   d. Uncontrolled or severe asthma
   e. Hypoglycemia (glucose < 4 mmol/L in the preceding month)
   f. Ongoing use of:
      i. Amiodarone (Cordarone)
      ii. digoxin (Lanoxin)
      iii. diltiazem (Cardiazem)
      iv. ergotamine (Ergomar)
      v. methyldopa (Aldomet)
      vi. phenytoin (Dilantin)
      vii. quinidine (Quninate)
      viii. quinine
      ix. reserpine
      x. verapamil
4) If already on a beta blocker:
   a. Takes it in the morning
   b. Takes in only on non-dialysis days
   c. Usual dose is 50% higher than proposed study dose
      i. Atenolol: exclude patients on > 75 mg
      ii. Bisoprolol: exclude patients on > 7.5 mg
      iii. Carvedilol: exclude patients on > 10 mg
      iv. Metoprolol: exclude patients on > 75 mg
      v. For other beta blockers, exclude those on > 50% of the recommended starting dose.
5) No beta blocker allergy
6) Dialysis is scheduled for three or four times weekly (exclude those on twice a week or daily dialysis)
7) Started dialysis > 3 months ago

Nurse Practitioner discussion

1) Appropriate transportation (able to arrive 1 hour early)
2) No problems with hypotension (<100 mmHg for systolic blood pressure) or bradycardia (<50 bpm) during dialysis treatments

Paper chart review (last 2 weeks of records)

1) No problems with hypotension in the last two weeks*
2) No problems with bradycardia in the last two weeks*
3) If on a beta blocker already:
   a. Takes it every day
   b. Takes it in the morning

Patient

1) BMI ≤ 40 kg/m^2 (may have to ask them their height)
2) Willing to consider enrolling in the study

Inclusion Criteria

1) Patients on standard thrice weekly hemodialysis for at least 90 days prior to the first study visit.
2) Age > 18 years old.
3) Willingness to sign a letter of informed consent.

Exclusion Criteria

1) Evidence of significant gastrointestinal or liver disease
2) Age < 18 years old
3) Body mass index > 40 kg/m^2
4) Patients with a contraindication to beta blockers or who have had a prior adverse drug reaction to one of the study drugs.
5) Patients who normally take a beta blocker drugs once daily in the evening.
6) Patients who only take a beta blocker drug on non-dialysis days.
7) Patients who normally take a beta blocker drug but their regular dose is 50% higher than the dose of the study drug.

***Intradialytic hypotension and bradycardia**

1) Previous intradialytic bradycardia (heart rate < 50 bpm during hemodialysis treatment in the preceding 6 treatments
2) Previous intradialytic hypotension (any symptomatic hypotension or hypotension requiring treatment with fluid bolus or cessation of ultrafiltration in the preceding 6 treatments; <100 mmHg for systolic blood pressure)

Appendix E: Letter of Information

Western
Schulich MEDICINE & DENTISTRY

The UNIVERSITY *of* WESTERN ONTARIO

Schulich School of Medicine & Dentistry

Brad Urquhart, PhD
Matthew Weir, MD, MSc

LAWSON HEALTH RESEARCH INSTITUTE

London Health Sciences Centre

Letter of Information

Study Title
Removal of Beta Blocker Drugs by Hemodialysis

Investigator(s)

Principle Investigator
Dr. Brad Urquhart, PhD, Department of Physiology and Pharmacology [redacted]
Dr. Matthew Weir, MD, MSc, Department of Medicine, Division of Nephrology [redacted]

Invitation to participate in this research study
You are being invited to voluntarily participate in a research study. The purpose of this study is to determine how well drugs called beta-blockers are removed from the blood by hemodialysis. This study will include 15 people who are on standard three times per week hemodialysis at the London Health Sciences Centre.

Purpose of the Study
Beta-blocker drugs are a class of drug frequently used to decrease the risk of cardiovascular disease. In patients without kidney disease, these drugs have been shown to reduce blood pressure, slow the heart rate and improve the function of the heart. Based on the strength of studies in patients without kidney disease, beta-blocker drugs are now widely prescribed to patients on hemodialysis in an attempt to decrease the risk of cardiovascular disease in this high-risk patient group. Currently, it is unknown what effect the hemodialysis process has on blood levels of the most commonly used beta-blocker drugs. The purpose of this study is to determine which of the most commonly used beta-blocker drugs (atenolol, bisoprolol, carvedilol and metoprolol) are removed from the blood by dialysis. This is important because the amount of drug in the blood determines how well the drug works. The researchers believe that drugs removed from the blood by dialysis may not work as effectively in patients on hemodialysis because the blood levels of drug may be lower than expected by your doctor. Should you choose to participate in this study you will be asked to take a single dose of four different beta blockers (atenolol, bisoprolol, carvedilol and metoprolol) on four different days separated by at least one week. The researchers will determine how well these drugs are removed from your blood by the dialysis machine.

Procedures
All of the following procedures are for research purposes.

Should you agree to participate in this study, you will be asked to arrive to four separate dialysis sessions 2-3 hours earlier than you normally would. If you are already taking a beta-blocker drug as part

of your routine therapy, you will be asked to not take your dose on each of the study days. This is important to ensure that you don't receive too much medication.

When you arrive at the dialysis unit, you will be asked to swallow a single dose of one of the following beta blocker drugs, atenolol (50 mg), bisoprolol (5 mg), carvedilol (6.25 mg) or metoprolol (50 mg). Two or three hours later you will begin your dialysis session as usual. During your dialysis session, the researchers will take two 4 milliliter blood samples when your dialysis session starts (a four milliliter blood sample is approximately equal to one teaspoon). The researchers will also take two 4 millilitre blood samples 30 minutes, 1 hour, 2 hours, 3 hours and 4 hours into your dialysis session (if you usually receive less than 4 hours of dialysis, the last sample will be taken at the end of your usual treatment. In other words, your dialysis treatment **will not** be extended to 4 hours if you are only prescribed 3 and a half hours). These blood samples will be taken from the dialysis tubing, not from your arm. At the same time, the researchers will also collect samples of the dialysate. The dialysate is the fluid that runs through the dialysis machine that allows toxins and drugs to be removed by dialysis. The dialysate usually goes down the drain. Lastly, the researchers will collect the entire volume of dialysate from your dialysis treatment. The blood samples and dialysate will be transported to a laboratory at Western University where the amount of each of the beta-blocker drugs will be determined in your blood and the dialysate. This analysis will allow the researchers to determine how well the dialysis machine removes beta-blocker drugs from your blood.

You will be asked to repeat this process three more times for a total of four sessions, one for each of the beta-blocker drugs (atenolol, bisprolol, carvedilol and metoprolol). Each of the study days will be separated by at least one week. The total amount of blood taken for each study day will be 48 mL (approximately 12 teaspoons, or 1/10 of the amount taken during a standard red cross blood donation). The total amount of blood taken for the entire study is 192 mL. The extra time you will be required to spend in the hospital on each study day will be between 2-3 hours depending on which beta-blocker drug you will be taking. The total additional time you will be required to spend in the hospital for the whole study will be 10 hours.

Confidentiality and Protection of Privacy
Participation in this study requires the researchers to collect some of your personal information. Your name and hospital number will be recorded as part of this research. The researchers will use this information to access other health information that is related to the study. This will include things such as other medical conditions you have, recent lab tests and other medications you are taking. All study participants will be assigned a unique study code. Any data involved with the study including other medical conditions and lab tests will be assigned to this unique study code and not to your name or hospital number. It will be possible only for the researchers to link your unique study code number to your name. All information collected as part of this study will be protected using standard hospital procedures and will be governed by Ontario's Personal Health Information Protection Act, 2004 (PHIPA). Confidentiality will be respected and no information that discloses your identity will be released or published without your consent unless required by law. If the results of the research are published or presented at scientific meetings, your name will not be used and no information that discloses your identity will be released or published without your explicit consent.

Risks and Discomforts
RISKS OF BLOOD DRAWING

The total amount of blood collected is 192 mL (approximately 48 teaspoons) for the entire study. To decrease the discomfort you experience, all blood samples will be taken from your dialysis line and not directly from an arm vein. There is a small risk of infection associated with any blood sampling.

RISKS OF PROVIDING HEALTH INFORMATION FOR RESEARCH USE

We have designed the project with multiple safeguards to protect your privacy and confidentiality. There is, nevertheless, a very small chance your personal information could accidentally become known to employees of this institution or others who are not associated with this study. In this case information could potentially be used to discriminate against you socially, in insurance, employment or other areas.

RISKS ASSOCIATED WITH TAKING BETA-BLOCKERS (ATENOLOL, BISOPROLOL, CARVEDILOL AND METOPROLOL)

The four beta-blockers studied in this research project are not new and are frequently prescribed in to patients on hemodialysis in Ontario. They are typically well tolerated. These drugs are designed to decrease blood pressure and slow your heart rate. An expected side effect of these drugs is therefore low blood pressure and decreased heart rate. The investigators will monitor your blood pressure and heart rate during the study. In addition, the study drugs may have the side effects of headache, nausea, vomiting, diarrhea, constipation or dizziness.

Beta-blockers may cause toxicity to unborn children and therefore females who are pregnant, trying to become pregnant, breast-feeding or not practicing adequate contraception will not be allowed to participate in the study. All females not already taking a beta-blocker drug and of child bearing potential will have a pregnancy test before beginning the study.

Reimbursement
Should you participate in this study you will be reimbursed $100.00 for the extra time you are required to spend in the hospital (approximately 10 hours spread over 4 study days). Should you start the study and decide to not to complete it, you will be reimbursed a pro-rated amount based on the time you spent in the clinic (i.e. $10 per hour for extra spent in the hospital).

Benefits
You should not expect to receive any direct benefit from this research project. New knowledge resulting from this project will be made available to the medical community through publications. No information on an individual participant will be released. If tests or therapies are incorporated into medical practice in the future and physicians make use of that new knowledge it may improve the care of patients. You may experience satisfaction from participating in research that may benefit medical science and other patients receiving hemodialysis.

Withdrawal
Participation in this study is voluntary. You may refuse to participate, refuse to answer any questions or withdraw from the study at any time with no effect on your future care. You do not waive any legal rights by signing the consent form.

Questions and Help
If you have any questions about the research study you may contact Dr. Brad Urquhart, at [redacted] or Dr. Matthew Weir at [redacted]

If you have any questions about your rights as a research participant or the conduct of the study you may contact Dr. David Hill, Scientific Director, Lawson Health Research Institute at [redacted]
For your information, a copy of this research consent form will be given to you before commencement of the study. Representatives of the University of Western Ontario Health Sciences Research Ethics Board may contact you or require access to your study-related records to monitor the conduct of the research.

CONSENT FORM

Study Title: Removal of Beta Blocker Drugs by Hemodialysis

Principal Investigator: Dr. Brad Urquhart, Department of Physiology and Pharmacology
Dr. Matthew Weir, Department of Medicine

I have read the accompanying Letter of Information, have had the nature of the study and the research database explained to me, and my signature below indicates that I agree to participate. All questions have been answered to my satisfaction. A copy of the information and this signed consent form will be given to me to keep.

Printed name of participant	Signature of participant	Date
Printed name of person obtaining consent	Signature of person obtaining consent	Date

Appendix F: Effect of Dialyzability on Clinical Outcomes

Aim: Evaluate the effect of beta blocker dialyzability on risk for all-cause mortality and cardiovascular outcomes.

After categorizing beta blockers into their dialyzability group, a propensity-matched, population-based retrospective cohort study was designed using the linked health administrative databases of Ontario, Canada (Appendix F). To assess the effect of dialyzability on clinical adverse outcomes, chronic hemodialysis patients on a poorly dialyzed beta blocker (carvedilol) were compared to those on a highly dialyzed beta blocker (metoprolol).

A recent study by Weir *et al.* (2015) has shown that elderly hemodialysis patients prescribed highly dialyzed beta blockers had a significant 1.4 fold increase in the risk for all-cause mortality as compared to patients on poorly dialyzed beta blockers. One criticism expressed for this previous study was the omission of carvedilol-treated patients (Shroff and Herzog, 2015). Carvedilol is the only beta blocker with a prospective clinical trial to prove its efficacy in subjects receiving dialysis (Cice *et al.*, 2003). Consequently, the data creation plan for our study compares hemodialysis patients on carvedilol to those on metoprolol. Due to the low dialyzability of carvedilol, we expect that patients receiving this drug will have a comparatively better survival benefit and a decreased risk for cardiovascular outcomes.

Methods

Study design

A provincial-wide retrospective matched cohort study was conducted using health administrative data from April 1, 2002 to September 30, 2014 on all chronic hemodialysis patients who were older than 66 years. One cohort of subjects included only those with evidence of continuous carvedilol use (low dialyzability group), and the other included those with only continuous use of metoprolol (high dialyzability group). Subjects were propensity matched between the two dialyzability cohorts and compared for their risk of all-cause mortality and adverse cardiovascular outcomes using odds ratios. We collected and analyzed all exposure, outcome and covariate data according to a predefined protocol. The study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada, and its design and reporting follow the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guidelines (von Elm *et al.*, 2008).

Setting

Ontario is the most populated province in Canada with nearly 13 million residents in 2011—1.9 million of whom were 65 years of age or older (Statistics Canada, 2012). The Ontario Health Insurance Plan (OHIP) provides all residents of Ontario with universal access to physician and hospital services. Additionally, the Ontario Drugs Benefit (ODB) program allows access for those who are 65 years and older to universal coverage for many prescription medications. The single health insurance payer in Ontario and an emigration rate of less than one percent per year produces a database of health administrative information that is both comprehensive and stable (Ontario Ministry of Finance, 2016).

Sources of Administrative Data

We used Ontario's health administrative data housed at the Institute of Clinical Evaluative Sciences (ICES) to assemble a cohort of patients receiving chronic hemodialysis and determined the impact of dialyzability on mortality and cardiovascular outcomes. We identified patients, exposures, outcomes and covariates using four linked datasets: (1) *Ontario Drug Benefits (ODB) Database*. Information on outpatient medications in the ODB formulary was used to ascertain drug-related baseline characteristics and beta blocker exposure, a covariate in our regression model. (2) *Canadian Institute of Health Information (CIHI) Discharge Abstract Database (DAD)*. This database was used to identify patient baseline characteristics, hospital admission for cardiovascular complications, and potential confounding diagnoses. The causes for hospitalizations were determined based on the codes found in the ninth and tenth editions of the *International Classification of Disease* (ICD-9 and ICD-10). The accuracy of the codes in these databases has been assessed for many diagnoses (Jong *et al.*, 2003; Juurlink *et al.*, 2006). (3) *Ontario Health Insurance Plan (OHIP) Claims History Database*. Most physicians submit billing claims with diagnoses codes that contain information on inpatient, outpatient and laboratory services. This OHIP database ascertained cardiovascular procedures and confounding variables to be included in our regression models. (4) *Registered Persons Database (RPDB).* The RPDB captures information regarding sex, date of birth, postal code and vital status. This database was used to confirm patient mortality. Relative to the CIHI-DAD, the RPDB has a sensitivity of 94% and a positive predictive value of 100% for flagging in-hospital mortality (Jha *et al.*, 1996).

Study Population and Cohorts

In order to ensure that the cohorts of patients were administered one of the two beta blockers during the entirety of their hemodialysis treatment, physician billing records from April 1, 2002 to March 31, 2015 were first used to determine all patients who were treated with long-term hemodialysis. The index date used to identify eligible patients was the date of the first prescription for carvedilol or metoprolol. Subject enrollment was restricted to those older than 66 years old. This minimal age limitation was implemented to guarantee at least 1 year of drug use data since Ontario citizens over the age of 65 years receive universal coverage for prescription medications. Following the age restriction, patients were further filtered by excluding those with greater than one beta blocker prescription and those who did not fill a prescription for one of the two study beta blockers. To identify beta blocker initiation that occurred while receiving hemodialysis, patient prescriptions that were not preceded within 30 days by a long-term hemodialysis code (H540, H740, G325, G326, G860, G862, G863 and G866) were excluded. Furthermore, patients were excluded if they filled any beta blocker prescription within 120 days of their first filled prescription while on hemodialysis. This ensured that enrolled patients were new users of the beta blockers.

Beta blocker dialyzability was the main exposure. Based on findings from the pharmacokinetic, 4-way crossover study (Figure 3.3), patients prescribed carvedilol were categorized into the "low dialyzability" exposure group. Conversely, those prescribed metoprolol were classified as the "high dialyzability" control group.

Propensity Score Computation and Matching

For the hemodialysis cohort, prevalence of baseline characteristics between the high and low dialyzability patient groups was compared. Following this comparison,

carvedilol patients were matched to those on metoprolol in a one-to-two ratio based on age (± 2 years), sex, and propensity score (±0.2 SD). Patients were matched without replacement such that unexposed patients who have been matched can no longer serve as a candidate for comparison with another patient. Propensity score analyses mitigate the effects of imbalances in baseline characteristics on estimates of risk (Rosenbaum and Rubin, 1983). Propensity scores were computed using a logistic regression model in which metoprolol use was the dependent variable. Independent variables for the study included age, year of index, sex, Charlson and John Hopkins comorbidity scores, comorbid conditions (abdominal aortic aneurysm, coronary artery disease, heart failure, peripheral vascular disease, and stroke), general measures of comorbidity (duration of dialysis and number of unique prescriptions within the last year), and concomitant medications (ACE inhibitors, alpha blockers, ARBs, CCBs, diabetes drugs, digoxin, and nitrates).

Outcome Measures

The primary outcome was all cause mortality identified using the RPDB. The secondary outcome is a composite of myocardial infarction, heart failure or ventricular arrhythmia as identified by their corresponding hospitalization outcome codes. All outcomes were specified prior to data analysis and assessed up to 180 days after the index beta blocker prescription. This period of follow-up was chosen on the basis of the findings that the median (interquartile range) duration of continuous use was 471 (85–646) days for high dialyzability beta blockers and 508 (78–752) days for low dialyzability beta blockers. The shorter observation period of 180 days allows for a decreased likelihood of dropout or crossover between exposure groups.

Statistical Methods

The first analysis conducted in this study was to determine imbalances in baseline characteristics between exposure groups using standardized differences. This metric describes differences between group means relative to their pooled standard deviation. An absolute standardized difference of a covariate that is less than 10% is inconsequential, and a 0% difference indicates no imbalance between the two exposure groups for that covariate. Standardized differences that are greater than 10% describe significant imbalances between the cohorts in question (Mamdani *et al.*, 2005; Austin, 2009). After propensity matching patients, comparisons between the two dialyzability groups were conducted. Conditional logistic regression analyses were used to estimate odds ratios and 95% confidence intervals (CIs). Odds ratios were subsequently interpreted as relative risks (RRs), which is reasonable given the low incidence of outcomes. All analyses were completed with SAS software, version 9.2 (SAS Institute Inc., Cary, NC).

Results

Upon completion of the clinical pharmacokinetic study, we were able to decisively conclude that dialysis has a negligible impact on the clearance of carvedilol, while metoprolol is highly dialyzed. These categorizations of beta blocker dialyzability were translated into our data creation plan developed for a provincial-wide retrospective cohort study. Unfortunately, unforeseen delays in programming at the Institute of Clinical Evaluative Sciences (ICES) have hindered completion of this study. Our study design has been approved and is currently in sequence for data analysis. Hemodialysis patients in the

high dialyzability group (metoprolol) are still expected to exhibit an augmented risk for mortality and adverse cardiovascular outcomes as compared with those in the low dialyzability group (carvedilol).

Appendix G: Data Creation Plan – Beta blocker dialyzability: Carvedilol

• **Project Initiation** • **This Section must be Completed Prior to Project Dataset(s) Creation**	
Project Title:	Beta blocker dialyzability: Carvedilol
Project TRIM number:	2016 0906 194 000
Research Program:	KDT
Site:	ICES Western
Project Objectives:	*Insert Project Objectives as listed in the approved ICES Project PIA*
	To determine whether outcomes are better with carvedilol (non-dialyzable) compared to metoprolol (highly dialyzable) in patients on hemodialysis.
ICES Project PIA Initial Approval Date:	*The ICES Employee or agent who is responsible for creating the Project Dataset(s) is responsible for ensuring there is an approved ICES Project PIA and verifying the date of approval prior to creating the Project Dataset(s)*
	2016-Mar-10
Principal Investigator (PI):	Matthew Weir
Check the applicable box if the PI is an ICES Student/Trainee	☐ ICES Student ☐ ICES Fellow ☐ ICES Post-Doctoral Trainee ☐ Visiting Scholar
Responsible ICES Scientist:	*Name the Responsible ICES Scientist if the PI is not a Full Status ICES Scientist*
	Amit Garg
Project Team Member(s) Responsible for Project Dataset Creation and/or Statistical Analysis and date joined (list all):	*All person(s) (ICES Analyst, Appointed Analyst, Analytic Epidemiologist, PI, and/or Student) responsible for creating the Project Dataset(s) and/or statistical analysis on the Research Analytics Environment (RAE) and the date they joined the project must be recorded*
	Stephanie Dixon, [redacted] 2016-Jan-22
Other ICES Project Team Members and date joined (list all):	*All other Research Project Team Members (e.g., Research Administrative Assistants, Research Assistants, Project Managers, Epidemiologists) and the date they joined the project must be recorded*
	Racquel Jandoc, [redacted] Danielle Nash, [redacted] 2016-Jan-22
Confirmation that DCP	*The following individuals must confirm that the ICES Data*

- **Project Initiation**
- **This Section must be Completed Prior to Project Dataset(s) Creation**

is consistent with Project Objectives:	*provided for in this DCP is relevant (e.g., with respect to cohort, timeframe, and variables) and required to achieve the Project Objectives stated in the ICES Project PIA prior to initial Project Dataset creation: 1) PI; 2) Responsible ICES Scientist if the PI is not a Full Status ICES Scientist, or a second ICES Scientist or the Scientific Program Lead if the PI is creating both the DCP and the Project Dataset[s]; 3) ICES Research Practice Staff creating the DCP; and 4) ICES Analytic Staff (ICES Employee or agent responsible for creating the Project Dataset[s]). This may be delegated either verbally or via e-mail.*		
	Principal Investigator: Matthew Weir	☒	2015-Feb-05
	Responsible ICES Scientist or Second ICES Scientist/Lead: Amit Garg	☒	2016-Apr-20
	ICES Research Practice Staff Creating the DCP: Danielle Nash	☒	2015-Feb-05
	ICES Analytic Staff: Stephanie Dixon	☒	2015-Feb-05
Designated ICES Research Practice Staff accountable for Project Documentation:	*The person named (ICES staff) is accountable for ensuring that the approved ICES Project PIA, ICES Project PIA Amendments, and DCP are saved on the T Drive, ensuring ICES Project PIA Amendments are submitted as required, ensuring DCP Amendments are documented, and sharing the final DCP with the PI/Responsible ICES Scientist at project completion*		
	Racquel Jandoc		
DCP Creation Date and Author:	*Date DCP was finalized prior to Project Dataset(s) creation*	*Name of person who created the DCP*	
	Date	***Name***	
	2016-Apr-20	Matthew Weir	

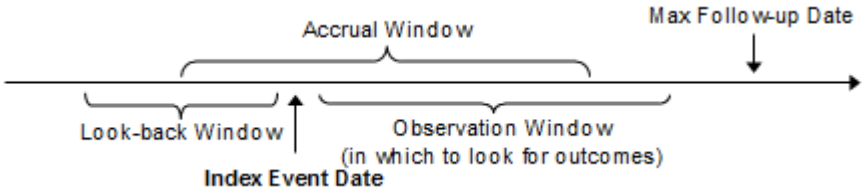
- **ICES Data**
- **This Section must be Completed Prior to Project Dataset(s) Creation**

The ICES Employee or agent who is responsible for creating the Project Dataset(s) must ensure that this list includes only data listed in the ICES Project PIA Changes to this list after initial ICES Project PIA approval require an ICES Project PIA Amendment	*Mandatory for all datasets that are available by individual year*
General Use Datasets – Health Services	***Years (where applicable)***
CIHI DAD	1997-2015
CIHI SDS	1997-2015
NACRS	1997-2015
ODB	2001-2015
OHIP	1997-2015
See list	
General Use Datasets – Care Providers	
IPDB	1997-2013
See list	
General Use Datasets – Population	
RPDB	1997-2015
See list	
General Use Datasets – Coding/Geography	
See list	
See list	
General Use Datasets - Facilities	
See list	
General Use Datasets - Other	
See list	
See list	
Controlled Use Datasets	
See list	
See list	
Other Datasets	

• **Project Amendments and Reconciliation**			
ICES Project PIA Amendment History (add additional rows as needed):	*Privacy approval date*	*Person who submitted amendment*	*Note that any changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment*
	Date	***Name***	***Amendment***
	yyyy-mon-dd		
DCP Amendment History (add additional rows as needed):	*Date DCP amended*	*Person who made the DCP amendment*	*Note that any DCP amendments involving changes to the list of ICES Data or Project Objectives require an ICES Project PIA Amendment*
	Date	***Name***	***Amendment***
	yyyy-mon-dd		
Date Programs/DCP reconciled	*The person(s) creating the dataset and/or analyzing the data are responsible for ensuring that the final DCP reflects the final program(s) when the project is completed*		
	yyyy-mon-dd		

• **Project Cohort**	
Study Design	☐ Cohort study ☒ Matched cohort study ☐ Case-control study ☐ Cross-sectional study ☐ Other (specify):
Index Event / Inclusion Criteria	Inclusion criteria: 1. Patients with evidence of at least 1 chronic hemodialysis code (**Appendix B**) between April 1, 2002 to September 30, 2014, and 2. First evidence of one study drug during the same time period Index date: First prescription for a study drug (**Appendix A**, DCLASS= "S_BBC", "S_BBM")
Estimated Size of Cohort (if known)	Carvedilol (DCLASS= "S_BBC") = 600 Metoprolol (DCLASS= "S_BBM") = 1200 (2:1 matched to carvedilol patients)
Exclusions (in order)	*Step* Description
	1 Data cleaning: a) Patients with missing or invalid IKN b) Patients with missing or invalid age or sex data c) Death on or before index date

• **Project Cohort**		
		d) Non-Ontario residents (individuals without an RPDB variable "prdcddablk" beginning with "35")
	2	Patients ≤66 years old as of index date
	3	Evidence of a hospital discharge or an emergency department visit on or within ≤2 days prior to index date (including index date)
	4	No evidence of a chronic hemodialysis code in the 30 days prior to and including index date (this is intended to eliminate patient who started beta blockers prior to starting hemodialysis) (**Appendix B**)
	5	Evidence of any study beta blocker prescription in the 120 days prior to index date (not including index date) (**Appendix A**, DCLASS= "S_BBC", "S_BBM")
	6	Exclude patients with >1 of any beta blocker prescription on the index date (**Appendix A**, DCLASS= "S_BBC", "S_BBM", "NS_BBL")

• **Project Time Frame Definitions**	
	
Accrual Start/End Dates	April 1, 2002 to September 30, 2014
Max Follow-up Date	March 31, 2015
When does observation window terminate?	First instance of any of the following events: 1. Death 2. 180 days of follow-up 3. March 31, 2015
Lookback Window(s)	Do not include index date in lookback • Comorbid conditions: 2 years • Health care access: 1 year • Baseline medications: 1 year

• **Variable Definitions (add additional rows as needed)**	
Main Exposure or Risk Factor	Beta blocker dialyzability • Exposed group: patients prescribed carvedilol (low dialyzability) (**Appendix A**, DCLASS = "S_BBC")

• **Variable Definitions (add additional rows as needed)**	
	• Control group: patients prescribed metoprolol (high dialyzability) (**Appendix A**, DCLASS = "S_BBM")
Primary Outcome Definition	Look forward 180 days following index date (not including index date) for: • All-cause mortality (**Appendix C**)
Secondary Outcome Definition(s)	Look forward 180 days following index date (not including index date) for: • Myocardial infarction • Heart failure • Ventricular arrhythmia See **Appendix C** for outcome codes
Baseline Characteristics	See **Appendix E** for baseline codes and **Appendix F** for full baseline table
Other Variables	

• **Analysis Plan and Dummy Tables (expand/modify as needed)**	
Descriptive Tables (insert or append dummy tables), e.g.:	
Table 1. Baseline characteristics according to primary/secondary exposure	
Table 2. Outcomes according to primary/secondary exposure	
Table 3. Covariates (baseline characteristics) according to outcomes	
Statistical Model(s)	
Type of model	
Primary independent variable	
Dependent variable	
Covariates	
Sensitivity Analyses	
Type of model	
Primary independent variable	
Dependent variable	
Covariates	

See **Appendix D** for Output tables

1. Cohort selection (**Table 1**)
    a. Report the number of patients in cohort overall, and for each drug group

2. Total event rate (**Table 2**)
    a. Report the total number of events overall

Stop here for discussion

3. Baseline characteristics (**Table 3**)
    a. Report baseline characteristics prior to propensity matching
    b. Calculate the standardized difference between the two study groups: 1) Exposed: carvedilol (DCLASS= "S_BBC") and 2) Unexposed: metoprolol (DCLASS= "S_BBM")

Stop here for discussion

4. Primary analysis: Propensity scores
    a. Propensity scores: calculate propensity score based on all baseline characteristics below. Also report the probability (0 to 1) for pre- and post-weight

(*Note: The propensity score is the probability of exposure (E) conditional on the covariates (baseline characteristics). This score involves a logistic model that estimates the probability of being started on a specific anti-depressant, given these covariates. Thus, patients with similar calculated probabilities will be compared to each other, in an effort to eliminate bias.)*

Include the following variables in the derivation of the propensity score using a multivariable logistic regression model:

- Sex (female* vs. male) – predictor of mortality
- Age (in years, continuous variable) – predictor of mortality
- Abdominal aortic aneurysm (yes vs. no*) – predictor of mortality, probably
- Coronary artery disease (yes vs. no*) – predictor of mortality
- Heart failure (yes vs. no*) – predictor of mortality, requirement for carvedilol (true confounder)
- Peripheral vascular disease (yes vs. no*) -– predictor of mortality
- Stroke (yes vs. no*) – predictor of mortality
- Use of ACE inhibitors (yes vs. no*) – predictor of mortality, requirement for carvedilol (true confounder)
- Use of alpha blockers (yes vs. no*) – measure of HTN, predictor of mortality
- Use of ARBs (yes vs. no*) - predictor of mortality, requirement for carvedilol (true confounder)
- Use of calcium channel blockers (yes vs. no*) - measure of HTN, predictor of mortality
- Use of diabetes drugs (yes vs. no*) – predictor of mortality
- Use of digoxin (yes vs. no*) - predictor of mortality, requirement for carvedilol (true confounder)

- Use of nitrates (yes vs. no*)
- Cardiologist visit (yes vs. no*) – requirement for carvedilol
- Coronary revascularization (yes vs. no*)
- Echocardiogram (yes vs. no*) – requirement for carvedilol
- Comorbidity score (continuous) – predictor of mortality

b. Baselines: Report baseline characteristics after matching and standardized differences (**Table 4**)
   - Calculate the standardized difference between the two study groups: 1) Exposed: carvedilol (DCLASS= "S_BBC") and 2) Unexposed: metoprolol (DCLASS= "S_BBM")

c. Events: Determine aggregate event rates for all outcomes after matching according to each study group: 1) Exposed: carvedilol (DCLASS= "S_BBC") and 2) Unexposed: metoprolol (DCLASS= "S_BBM") (**Table 5**)

Hard & Propensity Score Matching

We will use *greedy matching* with *specified caliper width* of ± 0.2 x the standard deviation of the logit of the propensity score

- Austin, 2010 showed that the above caliper width results in optimal estimation of difference in the risk
- Since we have a specified caliper width, the difference in the logit of the propensity score between exposed and unexposed patients in the matched set is required to be less than the pre-specified maximum caliper width

We will match *without replacement*

- Since we are matching without replacement, matched unexposed patients can no longer serve as a candidate for being matched to another exposed patient

Matching Ratio: We will match <u>1 exposed patient with 2 unexposed patients</u> on:

- The logit of the propensity score
- Age ± 2 years
- Sex

Stop here for discussion

Note: If we lose >80% of carvedilol patients through matching, then will switch to propensity weighting

d. Regression (**Table 6**): Using the matched cohort from above, report the absolute risk difference, odds ratio and 95% confidence interval by performing conditional logistic regression analyses for all outcomes using the exposed (DCLASS = "S_BBC") and unexposed (DCLASS= "S_BBM", referent) study groups (Note: since outcomes are rare we can approximate risk ratios from odds ratios)

Stop here for discussion

- Additional analysis: TBD

• **Quality Assurance Activities**		
RAE Directory of SAS Programs		
RAE Directory of Final Dataset(s)	*The final analytic dataset for each cohort includes all the data required to create the baseline tables and run all the models. It should include all covariates for all models such as patient risk factors, hospital characteristics, physician characteristics, exposure measures (continuous, categorical) and outcomes. It should include covariates that were considered but didn't make the final cut. This would permit an analyst to easily re-run the models in the future.*	
RAE README file available:	☐Yes ☐No	
Date results of quality assurance tools for final dataset shared with project team (where applicable):		
	%assign	yyyy-mon-dd
	%evolution	yyyy-mon-dd
	%dinexplore	yyyy-mon-dd
	%track / %exclude	yyyy-mon-dd
	%codebook	yyyy-mon-dd
Additional comments:		

Appendix A – Drug List

CarvedilolDrugList160201.xlsx

Appendix B – Cohort build

CarvedilolCohort.txt

Appendix C – Outcomes

CarvedilolOutcome.txt

Appendix D – Output tables

CarvedilolOutputTables160205.xlsx

Appendix E – Baseline codes

CarvedilolBaseline-fromKDT.txt

Appendix F – Baseline table

Assume below unless stated:

CIHI-DAD
Source
☒ All
Institution types
☒ Acute care (insttype = 'AP' or 'AT')
Include suspected/questionable diagnoses?
☒ No

OHIP:
Claim Type
☒ NONLAB

NACRS
Source
☒ Emergency Department visits
Include planned visits
☒ No

Characteristic	Code Set	Datasets Used	Other Details
Demographics			
Age		RPDB	Report as mean, SD, median, 25th, 75h percentiles, and N (%) in categories (66-69, 70-74, 75-79, 80-84, 85-89, ≥90)
Sex		RPDB	N (%) female
Rurality		PSTLYEAR Macro: %GETDEMO Var name: RURAL	N (%) rural
Socioeconomic		PSTLYEAR	Report as quintiles

Status – Neighbourhood Income Quintile		Macro: %GETDEMO Var:name: INCQUINT	(1, 2, 3, 4, 5, or missing) Income quintiles using average neighbourhood income on index date as defined by Statistics Canada 1 is lowest quintile (poorest) and 5 is highest quintile (richest)
Year of index event (2002-2014)			Report as N (%) in categories: 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014
Comorbidities (5 year look back except Charlson and John Hopkins scores)			
Abdominal aortic aneurysm		CIHI DAD OHIP	N (%) yes
Arrhythmia		CIHI DAD NACRS OHIP	N (%) yes
Chronic liver disease		CIHI DAD NACRS	N (%) yes
Chronic lung disease		CIHI DAD NACRS OHIP	N (%) yes
Coronary artery disease (without angina)		CIHI DAD OHIP NACRS	N (%) yes
Heart failure		CIHI DAD NACRS	N (%) yes
Implantable defibrillator		CIHI DAD OHIP	N (%) yes
Kidney transplant		CIHI DAD OHIP	N (%) yes
Myocardial infarction		CIHI-DAD	N (%) yes
Pacemaker		CIHI DAD OHIP	N (%) yes
Peripheral vascular disease		CIHI DAD NACRS	N (%) yes

Stroke		CIHI DAD NACRS	N (%) yes
TIA		CIHI DAD NACRS	N (%) yes
Charlson comorbidity score (2 year lookback)		CIHI DAD 1. Identify all acute DAD records for patients in **2 years prior** (do not include index date) 2. Use the %charlson macro and collapse over IKN – read macro definitions 3. Keep the 'charl' variable (weighted sum of the above indicators) and provide frequency results	N (%): 0 or no hospitalization 1 hospitalization 2 hospitalizations 3+ hospitalizations And report as Mean, SD, Median, 25th & 75th percentiles
John Hopkins comorbidity score (2 year look back)		Use %getacg macro to create Johns Hopkins ACG ADG scores, based on ICD-9, ICD-10-CA, OHIP codes	Report as mean, SD, median, 25th percentile, 75th percentile Report as 0-4, 5-9, 10-14, 15-19, ≥20, missing scores missing will be included in the category that contains the median value for the ACG score
Medication use (1 year look back)			
ACE inhibitor	BC_ACE	ODB	N (%) yes
Amiodarone	BC_AMI	ODB	N (%) yes
ARB	BC_ARB	ODB	N (%) yes
Alpha blocker	BC_AAB	ODB	N (%) yes
Calcium channel blocker	BC_CCB	ODB	N (%) yes
Diabetes drugs	BC_DBT	ODB	N (%) yes
Digoxin	BC_DIG	ODB	N (%) yes
Nitrate	BC_NIT	ODB	N (%) yes
Statins	BC_STA	ODB	N (%) yes
Warfarin	BC_WAR	ODB	N (%) yes
Health services utilization (1 year lookback)			

Cardiologist visit		OHIP	N (%) yes Spec = "60" (Cardiology) <u>Count only one claim per patient per day.</u>
Primary care visit		OHIP	N (%) yes Report as 0-4, 5-9, 10-14, 15-19, 20-24, 25-29, ≥30 visits in the previous year Spec = "00" (Family practice and general practice) <u>Count only one claim per patient per day.</u>
Carotid ultrasound		CIHI DAD OHIP	N (%) yes
Coronary angiogram		CIHI DAD OHIP	N (%) yes
Coronary revascularization		CIHI DAD OHIP	N (%) yes
Hemodialysis duration		OHIP	Time from index date back to the date of hemodialysis initiation (days) Initiation of dialysis definition: 1. OHIP feecode R849 (if multiple R849s exist, select the most recent)

			OR (if R849 is not found) Earliest recorded chronic hemodialysis feecode (H540, H740, G325, G326, G860, G862, G863, G866) Report mean, SD, median, 25th & 75th percentile, minimum, maximum
Echocardiogram		CIHI DAD OHIP	N (%) yes
Holter monitoring		CIHI DAD OHIP	N (%) yes
Stress testing		CIHI DAD OHIP	N (%) yes

Curriculum Vitae

Alvin Tieu

EDUCATION

2015–Present — The University of Western Ontario
Master of Science (MSc.) Candidate in Physiology and Pharmacology
Thesis title: Beta-blocker dialyzability and effectiveness in chronic hemodialysis patients.
Supervisor: Dr. Brad Urquhart

2011–2015 — The University of Western Ontario
Bachelor of Medical Science (BMSc.), Western Scholar
Honors Specialization in Pharmacology
Thesis title: Effect of AST-120 on hepatic cytochrome P450 and drug transporter expression in an adenine-fed rat model of chronic kidney disease.
Supervisor: Dr. Brad Urquhart

AWARDS, HONOURS, AND SCHOLARSHIPS

Graduate Education:

2015–2016	Canadian Institutes of Health Research (CIHR) Frederick Banting and Charles Best, Canada Graduate Scholarships – Master's. ($17,500, Accepted)
2015–2016	Ontario Graduate Scholarship. ($15,000, Declined)
2015–2016	Western Graduate Research Scholarship ($4500)

Undergraduate Education:

2014–2015	Dean's Honor List for academic standing
2014	Western's 125th Anniversary Alumni Awards ($1500)
2014	Anne Ferguson Memorial Award in Pharmacology & Toxicology ($450)
2014	Queen Elizabeth II Aiming for the Top Tuition Scholarship ($3500)
2014	Natural Science and Engineering Research Council (NSERC) Undergraduate Student Research Award ($4500, Declined)
2013–2014	Dean's Honor List for academic standing
2013	UWO In-Course Scholarship Year III ($700)
2013	Queen Elizabeth II Aiming for the Top Tuition Scholarship ($3500)
2012	UWO In-Course Scholarship Year II ($700)
2012–2013	Dean's Honor List for academic standing
2012	Lynn Fordham Awards in Science and Engineering ($2500)
2012	Laurene Paterson Estate Scholarships ($1600)
2012	Queen Elizabeth II Aiming for the Top Tuition Scholarship ($3500)
2011–2012	Dean's Honor List for academic standing

2011	The Western Scholarship of Excellence ($2000)
2011	Global Opportunities Award ($1000)
2011	Queen Elizabeth II Aiming for the Top Tuition Scholarship ($3500)

RELATED WORK EXPERIENCE

Sept 2015 – Present — Teaching Assistant
Physiology 2130 – Human Physiology
The University of Western Ontario
Supervisor: Dr. Anita Woods
Responsibility: Promote learning of course material by leading tutorials, discussions, and case studies for 94 undergraduate students

May 2013 – Apr 2015 — Undergraduate Research Assistant
Department of Physiology and Pharmacology
Schulich School of Medicine and Dentistry, London, Ontario
Supervisor: Dr. Brad Urquhart
Responsibility: Clinical investigation of the pharmacokinetic interactions between felodipine and caffeine using UPLC-PDA.

Sept 2012 – Apr 2013 — Undergraduate Research Assistant
Department of Physiology and Pharmacology
Schulich School of Medicine and Dentistry, London, Ontario
Supervisor: Dr. Edmund Lui
Responsibility: Studied medicinal proficiency of natural herbs on the vascular system to combat angiogenesis, cancer, and inflammation.

PUBLICATIONS

1. Gill N, Sirizzotti N, Kucey AS, **Tieu A**, Urquhart BL, Columbus M, Joubert G, Lim R, Rieder M, Mehrotra S, and Poonai N. Endogenous glucocorticoid response to single dose dexamethasone for croup in children: a pharmacodynamic study.
   Paediatric Emergency Care
   Impact Factor: 0.923, **Original Research (In Revision)**
   Role: Collaborator. Contributed to experimental design by preparing patient urine samples, aided in data analysis and manuscript preparation.

2. **Tieu A**, Leither MD, Weir MA, Urquhart BL. Clearance of cardiovascular medications during hemodialysis.
   Current Opinion in Nephrology and Hypertension
   Impact Factor: 3.862, **Invited Review** PMID: 27023840
   Role: Primary author. Contributed to writing and revising this review article as part of my graduate studies.

3. **Tieu A,** House AA, Urquhart BL. Drug disposition in chronic kidney disease: Implications for drug discovery and regulatory approval.
   Advances in Chronic Kidney Disease
   Impact Factor: 2.703, **Invited Review** PMID: 26979144
   Role: Primary author. Developed concepts, wrote, and revised the editorial article during my graduate studies.

4. Velenosi TJ, Hennop A, Feere DA, **Tieu A**, Kucey AS, Kyriacou P, McCuaig LE, Nevison SE, Urquhart BL. Untargeted plasma and tissue metabolomics in rats with CKD given AST-120.
   Scientific Reports 2016 6:22526
   Impact Factor: 5.228, **Original Research** PMID: 26932318
   Role: Collaborator. Contributed in all stages of experimental design, tissue and plasma collection, data analysis, and manuscript preparation.

PRESENTATIONS

Invited Oral Presentations:

1. **Tieu A**, Weir MA, Urquhart BL. Beta blocker pharmacokinetics and dialyzability in chronic hemodialysis patients. Lawson Health Research Institute Talks On Fridays (TOFS), London, Ontario, Canada, November 27, 2015.

Abstracts Presented as Oral Presentations at Local, National, and International Conferences:

2. Velenosi TJ, **Tieu A,** Feere DA, Kucey AS, Urquhart BL. The effect of gut-derived uremic toxins on the expression of hepatic drug metabolizing enzymes in chronic kidney disease. Canadian Society of Pharmacology and Therapeutics in Toronto, Ontario, Canada, June 7–10, 2015.

3. **Tieu A**, Weir MA, Urquhart BL. Beta-blocker dialyzability in chronic kidney disease patients. Western Student Research Conference in London, Ontario, Canada, March 21, 2015.

Abstracts Presented as Posters at Local, National, and International Conferences:

4. **Tieu A**, Velenosi TJ, Kucey AS, McCuaig LE, Weir M, Urquhart BL. Beta-blocker diayzability in chronic hemodialysis patients. Canadian Society of Nephrology in Halifax, Nova Scotia, Canada, May 12–14, 2016.

5. Sirizzotti N, Gill N, Kucey AS, **Tieu A**, Urquhsart BL, Columbus M, Joubert G, Lim R, Rieder M, Mehrotra S, Poonai N. Does a single dose of dexamethasone for croup cause adrenal suppression?: A prospective study. Paediatric Academic Societies Meeting in Baltimore, Maryland, USA, April 30–May 3, 2016.

6. **Tieu A**, Velenosi TJ, Kucey AS, McCuaig LE, Weir M, Urquhart BL. Beta blocker pharmacokinetics and diayzability in chronic hemodialysis patients. London Health Research Day in London, Ontario, Canada, March 29, 2016. **[Top 100 Poster]**

7. **Tieu A**, Velenosi TJ, Kucey AS, McCuaig LE, Weir M, Urquhart BL. Beta-blocker diayzability in chronic hemodialysis patients. American Society of Nephrology in San Diego, California, USA, November 5–8, 2015.

8. Velenosi TJ, **Tieu A**, Feere DA, Kucey AS, Urquhart BL. The effect of gut-derived uremic toxins on the expression of hepatic drug metabolizing enzymes in chronic kidney disease. American Society of Nephrology in San Diego, California, USA, November 5–8, 2015.

9. Kucey AS, Velenosi TJ, **Tieu A**, Nevison S, Urquhart BL. The effect of AST-120 on hepatic and intestinal drug transporter expression in chronic kidney disease. American Society of Nephrology in San Diego, California, USA, November 5–8, 2015.

10. Gill N, Sirizzotti N, Kucey AS, **Tieu A**, Urquhart BL, Columbus M, Joubert G, Lim R, Rieder M, Mehrotra S, Poonai N. Does a single dose of dexamethasone for croup cause adrenal suppression?: A prospective study. American College of Emergency Physicians Scientific Assembly in Boston, Massachusetts, USA, October 26–29, 2015.

11. **Tieu A,** Velenosi TJ, Kucey AS, Urquhart BL. Beta-blocker dialyzability in chronic hemodialysis patients. Canadian Society of Pharmacology and Therapeutics in Toronto, Ontario, Canada, June 7–10, 2015.

12. Kucey AS, Velenosi TJ, **Tieu A,** Urquhart BL. AST-120 and hepatic transport in chronic kidney disease. Canadian Society of Pharmacology and Therapeutics in Toronto, Ontario, Canada, June 7–10, 2015.

13. Velenosi TJ, **Tieu A,** Feere DA, Kucey AS, Urquhart BL. The effect of gut-derived uremic toxins on the expression of hepatic drug metabolizing enzymes in chronic kidney disease. London Health Research Day in London, Ontario, Canada, April 1, 2015.

14. Kucey AS, Velenosi TJ, **Tieu A,** Urquhart BL. AST-120 and hepatic transport in chronic kidney disease. London Health Research Day in London, Ontario, Canada, April 1, 2015

15. **Tieu A,** Feere DA, Velenosi TJ, Urquhart BL. Effect of AST-120 on hepatic cytochrome P450 and drug transporter expression in an adenine-fed rat model of chronic kidney disease. Department of Physiology and Pharmacology Research Day in London, Ontario, Canada, November 4, 2014.