INTRODUCTION
Thank you for noting this application’s strengths including the importance of the clinical problem, the potential of the candidate and career development plan, the excellent mentors, and outstanding institution. I have noted the cited areas that diminish enthusiasm for the research plan including limited innovation and an unclear approach that could be strengthened by a more mechanistic approach and in-depth discussion of confounding factors. These concerns and others are addressed below, and I have bracketed and italicized the according changes in the research plan.

1. **Limited innovation:** Importantly, ET-1 and vascular resistance have previously been measured in intradialytic hypertension patients. My prior research identified that intradialytic hypertension patients have increased ambulatory blood pressure and abnormal ambulatory blood pressure patterns. I clarified the innovation section (4B Aims 2&3) to emphasize that this research plan addresses a major gap in our comprehension of the association of intradialytic hypertension with increased morbidity and mortality: the effect that intradialytic ET-1 and vascular resistance changes have on ambulatory blood pressure. As ambulatory blood pressure measurements are the best predictors of outcomes in ESRD patients, understanding how it is that events during dialysis independently influence ambulatory blood pressure between dialysis treatments will provide novel insight for devising more targeted approach to hypertension management in ESRD patients.

2. **To clarify the approach rationale and impact on study outcomes:** I changed our inclusion criteria by removing the matching of post-dialysis blood pressure between cases and controls. I included more demographic information on intradialytic hypertension and justified our inclusion criteria of case and control subjects having blood pressure increases or decreases ≥10 mmHg based on prior data (4A, paragraph 3). I also addressed how blood pressure variability might limit our study (4C3d, paragraph 1). In Aim 1, I changed the outcome to the ratio of extracellular water to total body water, instead of to weight (Specific Aim 1, 4C3b #4, and 4C3c Aim 1) to better adjust for body composition. I also specified the accuracy and limitations of bioimpedance spectroscopy (4C3d Aim 1). In Aim 3, I changed the comparator drug for carvedilol to prazosin, instead of placebo (Specific Aim 3, 4C1 Aim 3, 4C3b Aim 3) to 1) eliminate α-adrenergic inhibition as a confounding effect on the ET-1 mediated changes in vascular resistance and blood pressure and 2) better facilitate blinding of the study medications regarding blood pressure change. The primary outcome for Aim 3 is now change in ET-1 from pre to post-HD, not ambulatory blood pressure (Specific Aim 3, 4C3c Aim 3). This outcome requires a smaller sample size (even with a 25% dropout rate) which should improve the overall feasibility of this aim while retaining the scientific validity. Justification for a crossover design in Aim 3 is included (4C3d Aim 3).

3. **For a more mechanistic approach to study expected intradialytic changes in ET-1 and to address possible confounding factors.** I have included a more detailed ascertainment of the type, timing, and dose of potentially confounding medications received before and during dialysis (ESA, antihypertensives, iron, vitamin D) in the Methods section (4C3b Aim 1 #1, 4C3c Aims 1-2, 4c3d Aim 2). In addition to patient interviews, I will obtain prior records to determine presence and severity of comorbidities (heart failure, ventricular hypertrophy, coronary artery disease) if available. In addition to ET-1 and Ang II, I will now measure asymmetric dimethylarginine (ADMA) before and after dialysis and will measure Ang II and ADMA on the non-HD day (4C3b Aim 2, Table 4). This will better establish how these individual mediators influence blood pressure both during dialysis as well as during the interdialytic time period. Using prazosin in Aim 3, instead of placebo, will better differentiate whether carvedilol's effects on blood pressure and vascular resistance are mediated by ET-1 changes independent of α-adrenergic inhibition (4C1 Aim 3).

In response to criticisms of the candidate and training plan, my inpatient clinical workload has been reduced to one month (3D7), my fellow supervision in CKD clinic significantly reduced (3D7) and my co-investigator role in clinical trials reduced to only SPRINT(3D2). I have included a new RAC member, Tyler Miller, and further specified the activities of the RAC (3D1, final paragraph).

Please note that Dr. Julia Inrig remains a co-mentor to guide my experience in conducting clinical research studies in ESRD patients. She is currently employed as a Medical Director of Quintiles Global Clinical Research Organization, instead of UT Southwestern. She continues to live in Dallas, TX and we can communicate via in-person meetings on a bi-weekly basis in additional to phone conferences.

In summary, I have specified the innovative aspects of this project and modified the research plan to provide a more mechanistic approach that also better addresses potential confounding variables. Thank you again for your criticisms and the opportunity to resubmit this application.
1. Candidates Background:

My overall career goal is to be an independent clinical researcher at an academic medical center studying hypertension in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients. I aim to better understand and manage these disease processes through patient-oriented and translational research.

My clinical research interests began during residency at UT Southwestern as clinical experiences generated questions that could not be answered from my medical training alone. My first research experience was an elective month with Dr. Robert Toto in 2007. I analyzed blood pressure (BP) changes from a randomized trial studying dual renin-angiotensin-aldosterone system blockade in diabetic nephropathy to determine the efficacy of antihypertensive regimens in this population. This sparked my interest in hypertension in CKD, but I became particularly interested in the high cardiovascular morbidity in ESRD patients as a resident in the intensive care unit. During fellowship, I also managed ESRD in outpatient settings and became specifically interested in associations between hypertension and clinical outcomes.

Because of my clinical interests and the positive experience with this project, I devoted 3 years following my clinical training to a clinical research fellowship studying hypertension in ESRD patients. I chose Dr. Toto as a mentor based on our prior positive interactions and his experience studying hypertension and CKD. I chose Dr. Jula Inrig as a co-mentor because of her experience in intradialytic hypertension, a phenomenon of increasing BP during hemodialysis that is associated with high mortality. I designed and conducted a case-control study in intradialytic hypertension as part of my training program which was funded by an individual NIH F32 grant, recognition of my commitment to an academic career. I enrolled in a Master's in Clinical Sciences program and applied concepts from didactic courses to design and conduct an epidemiological study to identify the prevalence of intradialytic hypertension. These projects fortified my interest in designing new research studies to better understand the mechanisms of hypertension in ESRD patients. Hypertension in CKD and ESRD is the focus of my early career research career, and I intend to make new discoveries that will benefit patients suffering from this catastrophic illness.

In fellowship I also encountered challenges and rewards. For example, my first attempt at obtaining an F32 failed, but through perseverance, motivation, and dedicated mentoring I succeeded in obtaining the grant which jump started my career in patient-oriented research. Also, I seized opportunities to present my research at regional and national meetings and wrote papers on topics relevant to my research interests (Table 1).

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<th>Table 1: Presentations-Manuscripts during research fellowship (bolded are topics related to hypertension and kidney disease)</th>
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<td><strong>Year</strong></td>
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Further, I developed leadership and organization skills as the chief nephrology fellow at UT Southwestern for 2 years. I met with the fellows regularly and met with the program director monthly to ensure the program provided optimal education, adherence to ACGME regulations, and sufficient coverage of clinical services.

I believe I am an ideal candidate for a career development award. I built a strong foundation in clinical research from research projects and coursework, and have shown my scholarly devotion to clinical research by presenting and publishing my work. [Since my initial application, I completed fellowship, became faculty at UT Southwestern and obtained an American Heart Association Fellow to Faculty Transition Award. I was selected as a UT Southwestern Clinical Research Scholar and Dedman Family Scholar in Clinical Care, which can provide further access to didactic training in clinical research, interaction with other early career clinical researchers, resources for additional exploratory studies and mentorship from experienced investigators committed to training aspiring researchers.] I will commit 75% of my time to research and research training to obtain the necessary experience to become an independent investigator and be competitive for an RO1 grant. In the remaining time I will refine my clinical and teaching skills in the hospital, clinic, and dialysis units.
2. Career Goals and Objectives: Scientific Biography

In the 1st stage of my research career I have obtained grant funding, research experience, and didactic training; presented my research findings; and received dedicated mentoring. I aim to independently conduct clinical research in hypertension in CKD and ESRD patients. I require more training to design prospective studies, a deeper scientific background of hypertension in ESRD, and translational research exposure to expand my expertise from intradialytic hypertension to studying all hypertensive ESRD patients. Ultimately, I will be well prepared to study: 1) effects of various antihypertensive drugs on physiologic parameters mechanistically linked to BP in ESRD patients and 2) long-term effects of these therapies on clinical end-points in large trials. This career development award will enhance my background outlined below to achieve this.

2-A Funding

As a clinical nephrology fellow in 2008, I pursued an opportunity for career development and exposure to the mechanisms responsible for hypertension in ESRD patients. My mentors and I designed a case-control study in patients with intradialytic hypertension as a vehicle to achieve my goals. I hypothesized that intradialytic hypertension was associated with increased endothelial cell dysfunction and increased ambulatory BP. That year, I submitted grants to the NIH, National Kidney Foundation, and American Heart Association. Although not funded, I received positive reviewer feedback. I refined the project, and the NIH (F32DK085965-01A1) and NKF resubmissions were accepted. This experience taught me the significance of resource utilization to design a feasible yet relevant proposal. I also learned perseverance and how to further develop my ideas from constructive criticism. This prepared me for the grant submission process that will be essential throughout my academic career. I require more mentoring from individuals with diverse research backgrounds to help me recognize which of my research ideas have the highest impact and will most likely produce meaningful results.

2-B Research Experience

During my fellowship, I gained hands-on research experience in design and conduct of case-control studies, epidemiologic studies, and large randomized trials in hypertension and CKD.

First, I conducted a case-control study on intradialytic hypertension where I screened, enrolled, and obtained informed consent from subjects. A Design and Analysis course that I took reinforced principles of strategic recruitment of cases and controls. I learned the methods and procedures to measure ambulatory BP, flow mediated vasodilation (to assess endothelial cell dysfunction), and pulse wave velocity (to assess arterial stiffness). While studying these physiologic parameters, I pondered how other factors such as vascular resistance and extracellular volume (ECV) had impacted ambulatory BP in patients with intradialytic hypertension. I applied concepts from a Biostatistics course to analyze the data and found that patients with intradialytic hypertension had an average ambulatory BP that was 13 mmHg higher than controls[2]. I also found surprising between-group differences in ambulatory BP patterns. These findings provoked a novel research question about whether differences in vascular resistance and ECV could explain the different patterns. Transitioning my research findings into a new hypothesis was a defining moment of my fellowship. However, I need further guided experience in transitioning a hypothesis into a well-designed and implemented prospective study. I also require collaboration with a translational scientist to enhance my understanding of cardiovascular physiology and teach me techniques to measure parameters such as vascular resistance. Furthermore, I need statistical mentoring to learn the appropriate analysis of ambulatory BP measurements. This training experience will define my background in hypertension in ESRD and distinguish my expertise from others in the field. My future plans are to conduct prospective studies in hypertensive ESRD patients investigating the associations of ambulatory BP patterns with outcomes and response to interventions. With this award, I will learn skills from the appropriate experts so I may ultimately utilize them independently.

Second, when I presented my research findings at a conference, my peers offered criticisms which I addressed with further research. They questioned the prevalence of intradialytic hypertension with extended follow-up and its association with ECV. I used principles from Epidemiology and Biostatistics courses to design a retrospective analysis of our screening database, write a protocol, and gather data. From my analysis, I published the first documentation of the prevalence of intradialytic hypertension over extended periods of time[5]. I found no difference in the average interdialytic weight gain between patients with frequent intradialytic hypertension and other HD patients. Despite these novel findings, I recognize the major limitations of this retrospective study are the lack of ambulatory BP and ECV measurements. A prospective study addressing such limitations requires dedicated time to develop skills in operating equipment to obtain these measurements. With such skills, I can continue to study relationships between ECV and BP in hypertensive ESRD patients in future studies. This award will provide time and mentorship to learn these skills.

Third, I was a co-investigator in 3 long-term randomized clinical trials at UT Southwestern studying antihypertensive and other pharmaceutical interventions for hypertension and diabetic nephropathy. This
introduced me to concepts in multi-center clinical trials in my field related to recruitment, retention, long-term BP management, and reporting adverse events. I still require experience in appropriately designing a clinical trial. This award will enable me to design and conduct a randomized study, while working with an experienced mentor who has been involved in numerous large scale trials.

### 2.C Didactic Training

I completed curriculum for a Masters in Clinical Sciences degree. The courses (Table 2) provided a broad exposure to clinical research principles. I require advanced instruction in developing strategies for hypothesis generation, determining the optimal methods to test hypotheses, and selecting appropriate statistical techniques to analyze results. I require didactic exposure to translational research methods to complement my clinical research background. Further instruction on research ethics will ensure that I am prepared to responsibly conduct patient oriented research independently. This award offers the time and resources to take such courses as I conduct my research and to obtain an advanced Masters with Distinction degree.

#### 2.D Research Productivity:

**Table 1** (Candidate’s Background Page) details my fellowship presentations and publications from which I developed oral and written communication skills. I also learned to handle criticism from peer review to enhance the presentation of my research.

While preparing this work, I extensively read literature and published several review articles related to hypertension and CKD/ESRD including one on intradialytic hypertension. I developed a knowledge base that requires expansion for me to recognize and address gaps in my field. This can be accomplished from the future findings of my proposed study and continued review of emerging literature. I also need to attend and present at national meetings to integrate my ideas into the scientific community. The award will provide the time to generate data and ensure me opportunities to attend and present at meetings.

### 2.E Mentorship

I regularly met with my mentors to discuss my projects and career, and to continue my exposure to the peer-review process. Each month we reviewed manuscripts submitted to high impact journals including *New England Journal of Medicine* and *Journal of the American Society of Nephrology*. I submitted a review of each manuscript prior to our discussions. My mentors challenged me to think critically, which has 1) broadened my exposure to the research of others; 2) introduced me to the strengths and weaknesses of various study designs, analyses, and interpretations; and 3) promoted self-critique of my own work. Furthermore, I used these skills to develop my own mentoring abilities with pre-medical students, medical students, and residents on research electives. I lectured on principles of renal function, blood pressure, and hemodialysis. I discussed articles with them so they could confidently present their critiques at lab meetings. I taught medical students how to format abstracts and co-authored posters they successfully presented at local and national meetings.

I require further development of critical thinking skills to become an independent researcher. This award will provide an environment where I can seek guidance from mentors with extensive experience in conducting and presenting research. I will simultaneously interact with trainees at various scientific and clinical levels so that I can offer lessons from my own experiences to promote their research careers. This bi-directional flow of perspective will serve as a formal transition from mentee to mentor.
3. Career Development/Training Activities During Award Period

My career development plan includes components to expand my background and promote my development into an independent clinical researcher. I aim to 1) develop and refine skills in clinical research study design and implementation, 2) learn statistical models for analyzing ambulatory BP, 3) gain experience in translational research related to cardiovascular physiology in ESRD patients, and 4) transition into an independent investigator. The plan involves direct research experience, didactic training, presentation and publication of my findings, and intensified mentorship focused on independent career development and obtaining an R01 grant.

3.A Develop and Refine Skills in Clinical Research Design and Implementation in ESRD patients

3.A.1 Direct Research Experience

3.A.1.a Design: I will gain experience in transitioning a novel idea into a prospective clinical research study. I will select the design, population, procedures, and statistical analysis for all aims. From this, I will acquire skills in developing a comprehensive strategy to validly test a hypothesis and answer a research question. In years 1-5, I will enroll subjects and execute study procedures for a case-control study and a randomized study. In years 3-5, I will develop ideas for post hoc analyses and begin designing an independent prospective study for an R01 application. I will meet with Dr. Toto weekly to achieve these aims.

3.A.1.b Implementation: I will develop skills to coordinate and implement research in ESRD patients. I will communicate with subjects and HD-unit staff to conduct procedures without obstructing the unit schedule. I will learn to maximize subject retention and minimize obstacles. This will provide a framework to continue studying ESRD patients. In years 1-5, Dr. Toto and I will meet weekly to discuss the study schedule, complications, and potential modifications. I will discuss these issues with Dr. Inrig on a biweekly basis.

3.A.1.c Randomized Study: In Aim 3, I will gain hands-on experience in conducting a randomized trial. I will determine the design, randomization methods, population, and end points. This unique experience will be paramount for my preparation to study pharmacologic interventions in the future. Dr. Toto has extensive experience in randomized clinical trials involving pharmacologic treatment of hypertension and diabetic nephropathy. We will meet weekly to discuss appropriate titration and any adverse effects. Dr. Inrig has studied carvedilol in patients with intradialytic hypertension; we will discuss this titration on a biweekly basis.

3.A.2 Didactics/Conferences: I will enroll in Advanced Clinical Research Design and Analysis (Year 1, 4 month course 2 hrs/wk). The course involves critical discussion of study design/analysis from all medical fields. I will learn the strengths and limitations of all research designs and recognize which designs optimally obtain the information necessary to answer a research question. Monthly journal clubs in the Renal division and within my lab will provide additional experience in critiquing others’ research.

3.A.3 Research Presentation: I will present my research plan and progress to researchers and clinicians in the nephrology division annually during “Research in Progress” lectures and [to clinical researchers from other backgrounds during annual Clinical Scholar Forums.] Their feedback will help me identify potentially modifiable aspects of the project, recognize additional clinically relevant implications of my work, and ensure that my ideas are clear and of high impact. This will also refine my oral presentation skills.

3B. Learn statistical models for analyzing ambulatory BP in ESRD patients:

3.B.1 Research Experience: I will obtain training in quantitative thinking and learn in-depth methods to analyze BP patterns in ESRD patients during the interdialytic time period with Dr. Guanghua Xiao, PhD, as my statistical mentor. I will learn linear and non-linear regression models that account for repeated measures and will learn to identify differences in ambulatory BP slopes. In Year 1 and as needed in years 2-3, we will meet monthly to learn the theory and application of these models to ambulatory BP using my preliminary data. In years 4-5, we will meet monthly to incorporate the models into our analysis. Ultimately, I can incorporate these methods to effectively design future studies investigating how BP patterns relate to clinical endpoints in cohorts of HD patients and how pharmacologic interventions modify these BP patterns in future clinical trials.

3C. Gain Expertise in Translational Research

3.C.1 Research Study: I will gain a deeper understanding of cardiovascular physiology in ESRD patients. I will learn to operate equipment using bioimpedance spectroscopy to measure extracellular and thoracic fluid content to determine ECV and vascular resistance. Dr. Wanpen Vongpatanasin, M.D., in the Division of Cardiology is an expert in using impedance cardiography and will instruct me to use the Cardiodynamics BioZ (thoracic fluid) and the Impedimed SFB7 (extracellular water). I will learn to analyze plasma ET-1 through lab resources in the George O’Brien Kidney Center. With her experience in translational research, Dr. Vongpatanasin will guide my understanding of the clinical relevance of ECV, vascular resistance, ET-1, and Ang II in hypertension. In Year 1, we will meet weekly as I learn to use the equipment. In Years 2-4, we will meet monthly to discuss study progress, analysis, and implications for future research. In years 1-5, Dr. Toto and I will meet weekly to discuss the relevance of these measurements in ESRD patients.
3.C Didactics/Conferences: I will take a course on Genetic and Molecular Science for the Clinical Investigator (Year 2, 6 month course, twice weekly). Topics include proteomics, pharmacogenomics, biomarkers, and acquisition of samples. The course will provide a basis for identifying which biologic systems (renin-angiotensin-aldosterone, endothelin) predominate in hypertensive ESRD patients and hypothesizing which drugs should be studied in the future. [As a Clinical Research Scholar, I can audit any other graduate courses, including Signal Transduction and Mechanisms of Drug Pharmacology to better understand how various antihypertensive medications exert their actions.]

3.C.3 Presentation: In each of Years 1-5, I will attend the American Society of Hypertension Annual Meeting. Each year, I will submit abstracts based on findings from current research and this project to this meeting as an opportunity to present to nephrologists, cardiologists, and other scientists interested in hypertension. A multi-disciplinary, translational component to my project will broaden my interactions with researchers in other fields.

3.D Transition into an Independent Investigator

3.D.1 Mentorship: My mentors have diverse scientific backgrounds and expertise focused on the objectives I aim to achieve. I additionally formed a research advisory committee (RAC) to provide collective research insight, review results, help plan future studies, and provide feedback on my overall performance.

Dr. Robert Toto (primary mentor, RAC member): Professor of Medicine (Nephrology), UT Southwestern. Dr. Toto has more than 25 years of experience conducting patient-oriented research and clinical trials. He is an internationally recognized, NIH-supported researcher in hypertension and CKD who previously received an NIH K24 mentorship grant and has mentored many successful academic nephrologists. As the primary mentor, he will supervise all components of the training plan with specific recommendations for any obstacles encountered in the study and will assist in interpreting my findings and in preparing manuscripts and presentations. He will provide guidance in my developing an independent project in Year 5. We will meet weekly as specified in the previous sections.

Dr. Wanpen Vongpatanasin (translational research mentor, RAC member): Associate Professor of Medicine (Cardiology), UT Southwestern. Dr. Vongpatanasin is the Director of the Human Cardiovascular Physiology Research Laboratory and has NIH funding to study non-invasive measures of vascular health. She has extensive experience in bioimpedance cardiography and in studying endothelial cell dysfunction with flow mediated vasodilation and analysis of plasma levels of ET-1. We will meet weekly when I am training to operate the bioimpedance equipment and monthly during subsequent phases to discuss the relevance of these measurements to the study findings.

Dr. Jula Inrig (co-mentor): [Medical Director, General Medicine Therapeutic Delivery Unit, Quintiles Global Clinical Research Organization.] Dr. Inrig is internationally recognized as an expert in hypertension in ESRD. Her NIH funded research was the first to show associations between intradialytic hypertension and mortality. She will provide insight for implementing studies in ESRD patients and in the relevance of my findings to intradialytic hypertension. We will communicate bi-weekly to discuss subject enrollment, procedures, and overall study progress. She will also assist in the preparation of manuscripts.

Dr. Guanghua Xiao (biostatistical mentor): Assistant Professor of Clinical Sciences (Biostatistics) at UT Southwestern. Dr. Xiao is an NIH funded biostatistician with expertise in the design and biostatistical analysis of clinical trials. He has prior experience in mentoring both pre and postdoctoral trainees. We will meet monthly and as needed to guide my overall understanding of the biostatistical methods and data analysis.

Dr. Tyler Miller (RAC): Professor of Medicine (Nephrology) at UT Southwestern and Assistant Chief of Medicine in research (Dallas VA). Dr. Miller has extensive experience in career guidance of young researchers as the prior co-PI of an institutional training grant at Case Western Medical Center and reviewer for NIDDK-D study section. He will review my progress and offer insight into which novel research strategies coincide with my project and developing ideas to optimize my potential to conduct high impact research. The RAC will meet every 6 months to review my progress and guide my overall career development. I will update the RAC on my productivity each year and submit their formal report with each NIH progress report. The RAC will evaluate project-specific achievements including my 1) proficiency in operating the bioimpedance equipment, 2) efficiency in recruiting and enrolling subjects both by myself and as a research team leader, and 3) ability to interpret data for abstract and manuscript submissions. I will present them ideas for supplemental projects to expand my scientific skills and generate preliminary data intended to complement this study to prepare for a project suitable for an R01 application. Following their evaluation, the RAC can guide me to the appropriate resources within and outside this institution to facilitate such projects.

3.D.2 Research Experience: I will be a co-investigator in the randomized trial Systolic Blood Pressure Intervention Trial (SPRINT, NHLBI). I will spend 2 hrs/wk conducting assessments and exams, managing...
Specific Aims
Hypertension is nearly universal in end-stage renal disease (ESRD) patients on hemodialysis (HD) and contributes to the excessive mortality in this population. Dietary sodium and water ingestion increases extracellular volume (ECV) and elevates blood pressure (BP) in most HD patients ("salt sensitivity"). Accordingly, reductions in ECV via ultrafiltration during HD and restriction of interdialytic dietary sodium are major goals for managing hypertension in HD patients. However, I have identified a subset of hypertensive HD patients that challenge this perception of BP regulation.

Intradialytic hypertension is an increase in systolic BP ≥10 mmHg from pre to post-HD. Patients with intradialytic hypertension have greater morbidity and mortality than HD patients with BP decreases during HD [24,25]. I demonstrated in an NIH funded F32 fellowship project that intradialytic hypertension is associated with increased interdialytic ambulatory BP and increased underlying endothelial cell dysfunction [2,3]. I also demonstrated that these patients have ambulatory BP patterns that deviate from a salt-sensitivity model in that the BP decreases for the initial 24 hours after HD (Figure 1). Other investigators have shown that vascular resistance and plasma endothelin-1 (ET-1), a potent endothelial cell-derived vasoconstrictor, increase from pre to post-HD in patients with intradialytic hypertension. A major unanswered question is how ECV and vasoconstriction independently modify the overall ambulatory BP burden in patients with intradialytic hypertension. Answering this question can provide a mechanism to therapeutically target BP control. My overall hypothesis is that increases in vascular resistance related to surges in ET-1, as opposed to increased ECV, are responsible for the increased ambulatory BP burden in patients with intradialytic hypertension. To test this hypothesis, I propose the following aims:

1. To determine if ECV is similar in patients with intradialytic hypertension and HD controls. I hypothesize that there are no differences in ECV between these groups. I will use a case-control design to measure extracellular water using multifrequency bioimpedance spectroscopy and compare the ratio of post-HD extracellular water to \(\text{total body water}\) between groups. From this aim I intend to establish that a mechanism other than ECV overload is likely responsible for intradialytic hypertension and the associated adverse events.

2. To determine the associations of vascular resistance and ECV with ambulatory BP in patients with and without intradialytic hypertension. I hypothesize that the change in vascular resistance from pre to post-HD is more strongly associated with ambulatory BP than the post-HD ECV is in patients with intradialytic hypertension. Using a case-control design, I will measure pre and post-HD vascular resistance, using impedance cardiography, and interdialytic ambulatory BP. I will compare the independent associations of extracellular water (see Aim 1) and vascular resistance changes with the ambulatory BP and ambulatory BP slopes within and between groups. From this aim, I will establish that an intradialytic vascular resistance surge is the predominant mechanism regulating ambulatory BP in patients with intradialytic hypertension. Exploratory studies will correlate changes in ET-1, angiotensin II, \([\text{asymmetric dimethylarginine}]\), and vascular resistance.

3. To determine if targeting ET-1 with carvedilol, an alpha and beta adrenergic receptor antagonist shown to inhibit ET-1 release in vitro, reduces ambulatory BP [by modifying intradialytic changes in ET-1 and vascular resistance in intradialytic hypertension patients]. I hypothesize that, [compared to the alpha blocker prazosin], carvedilol use [causes significantly smaller increases in ET-1 and vascular resistance during dialysis]. In a randomized crossover study in subjects with intradialytic hypertension, I will compare differences between carvedilol and [prazosin in intradialytic change in ET-1. Additional analyses will compare effects on intradialytic changes in vascular resistance, as well as ambulatory BP and BP slope]. From this aim, I intend to establish that the mechanistic link between [ET-1], vascular resistance and ambulatory BP is a potential target to effectively reduce BP in patients with intradialytic hypertension.

I identified a group of HD patients that challenge the salt-sensitivity concept in an NIH F32 funded project. The proposed research will explore other mechanisms responsible for increased BP in patients with intradialytic hypertension and serve as a vehicle for me to obtain new research skills to continue investigations in this field. Ultimately, the results of this study can be directed to designing a clinical trial as the focus of an R01 award to determine if therapies that target these mechanisms result in efficient interdialytic BP reduction and risk reduction for cardiovascular morbidity and mortality in all hypertensive HD patients.
4. RESEARCH STRATEGY

4.1 SIGNIFICANCE

Hypertension is a major cause of cardiovascular morbidity and mortality in hemodialysis (HD) patients. Hypertension is present in 90% of HD patients[11], a population whose 20% annual mortality rate mainly stems from cardiovascular disease[12]. Systolic blood pressure (BP) >140 mmHg, is associated with increased risk for heart failure, coronary artery disease, and left ventricular hypertrophy in these patients[13], and these complications cost >9 billion dollars per year to manage[12]. Presently, both the underlying mechanisms and optimal treatment of hypertension in HD patients are poorly understood. Studies which elucidate these mechanisms are needed to design treatment regimens which improve BP control and reduce the excessive morbidity and mortality in this high risk group. My research aims to identify novel mechanisms of hypertension in HD patients. To achieve this, I will study the mechanisms and patterns of BP during and between HD in patients with a poorly understood BP pattern, intradialytic hypertension. This phenomenon of intradialytic hypertension challenges the current dogma of how hypertension is induced and sustained in HD patients.

The current paradigm of BP control fails to explain mechanisms of hypertension in all HD patients. Blood pressure in humans is influenced by cardiac output and vascular resistance. The current dogma is that hypertension in HD patients is caused by: 1) inadequate renal sodium and water excretion causing extracellular volume (ECV) expansion and increased cardiac output[14]; and 2) increased vascular resistance due to imbalances in vasoconstrictors and vasodilators. Most HD patients demonstrate “salt sensitivity” and experience increases in BP with salt and water intake during the interdialytic period (Figure 2)[15, 16]. A major goal for BP management in HD patients involves reducing ECV through ultrafiltration during HD and through dietary salt and fluid restriction during the interdialytic period[17, 18]. Patients that remain hypertensive after such strategies require pharmacologic therapy to reduce BP. Thus, major obstacles in controlling BP in HD patients are 1) accurately identifying and successfully achieving a patient’s dry weight and 2) inducing adequate vasodilation with antihypertensive drugs. The assumption that ECV overload is the primary disturbance that raises BP is limited because of 1) unreliability of physical examinations to accurately determine ECV status[19] 2) a lack of studies directly comparing contributions of ECV and vasoconstriction on interdialytic BP. Multifrequency bioimpedance spectroscopy can be used to measure extracellular water as an indication of ECV in HD patients[20]. Biopendence can also be applied to determine vascular resistance[21-23]. Clinical studies utilizing bioimpedance in HD patients will provide a more complete mechanistic assessment of relationships between ECV, vascular resistance and BP.

Patients with intradialytic hypertension have atypical BP patterns during and between HD treatments. Intradialytic hypertension is an increase in systolic BP ≥10 mmHg from pre to post-HD and is associated with increased morbidity and mortality in HD patients[24, 25]. [While there is an intermediate risk for such outcomes among patients with smaller BP increases, the greatest difference in risk is seen between those with BP increases ≥10 mmHg and those with decreases ≥10 mmHg. Blood pressure increases ≥10 mmHg occur intermittently in some HD patients, but a subset of patients experiences this persistently. At least 25% of our HD population experienced episodes of intradialytic hypertension in >30% of their individual treatments during a 6-month period[5]. Eight percent experienced a change in systolic BP ≥10 mmHg from pre to post-HD, when averaged over this time. In that cohort study, no patient-specific or comorbidity-related variables distinguished these patients from other HD patients beyond the BP patterns themselves.]

I recently demonstrated in a case-control study that patients with intradialytic hypertension (n=25) had higher average systolic 44-hr interdialytic ambulatory BP than HD controls (n=25) (Fig 3)[2]. Additionally, the BP slope during the initial 24 hours after HD differed between the groups: BP increased over time in controls and tended to decrease over time in the patients with intradialytic hypertension (Fig 1). The findings in intradialytic hypertension patients are inconsistent with a salt sensitivity model that describes most HD patients (Fig 2). Identifying factors that modify these patterns can identify which mechanisms contribute to increased
ambulatory BP in intradialytic hypertension patients. This is critically important as the 44-hr ambulatory period better predicts mortality than single HD-unit measurements, and higher ambulatory BP is associated with increased mortality[26]. To develop studies aimed at effectively lowering the overall BP burden in HD patients, it is critical to fully understand which factors modify BP throughout the entire interdialytic period.

**Identifying the mechanisms responsible for elevated ambulatory BP in intradialytic hypertension patients will uncover pathophysiologic principles applicable to all hypertensive HD patients.** Two small studies investigated the role of ECV in patients with intradialytic hypertension[27, 28]. They showed that BP and cardiac output increase with the initiation of ultrafiltration, but that both decrease with trials of intense ultrafiltration. The authors concluded that ECV overload caused intradialytic hypertension. Major limitations of these studies include small sample size, absence of control groups, the presence of left ventricular dilation in the subjects, and lack of actual ECV measurements. One randomized trial demonstrated that gradual reduction of dry weight resulted in ambulatory BP[29] reduction and greater BP reduction from pre to post-HD[30]. However, most subjects did not have intradialytic hypertension and there were no ECV measurements. Establishing a clear relationship between ECV and intradialytic hypertension requires a study that obtains adequate measurements of ECV.

Endothelial cell dysfunction is another proposed etiology for intradialytic hypertension[3, 31, 32]. Plasma ET-1, an endothelial cell derived vasoconstrictor, increases during HD in patients with intradialytic hypertension[33-35]. There are also large increases in vascular resistance from pre to post-HD in patients with intradialytic hypertension compared to controls[34]. A study measuring plasma renin activity and catecholamines failed to support the role of the renin-angiotensin-aldosterone system (RAAS) or sympathetic nervous system in intradialytic hypertension[34], which implicates ET-1 as the mediator of increased vascular resistance. However, Ang II, the most potent RAAS vasoconstrictor, has not been studied in intradialytic hypertension. A study differentiating the impact of ET-1 and Ang II on vascular resistance will fortify the association of endothelial cell dysfunction with intradialytic hypertension. More importantly, establishing an association between ET-1, vascular resistance and ambulatory BP in patients with intradialytic hypertension can help determine whether these patients have an increased ambulatory BP burden and such a high mortality risk. [Another novel mediator to be explored is asymmetric dimethylarginine (ADMA) an inhibitor of nitric oxide synthase that accumulates in HD patients with higher levels being associated with increased mortality[36, 37]].

As vasoconstriction is proposed to contribute to hypertension in all HD patients, the implications of this research can be extended more broadly to more effectively reduce BP in all hypertensive HD patients.

**Summary:** Hypertension causes devastating complications in HD patients. Studying patients with intradialytic hypertension whose ambulatory BP patterns challenge our current understanding of hypertension in ESRD provides the opportunity to explore mechanisms for BP control that may be relevant to all HD patients. My research aims to differentiate the effects of ECV and vascular resistance in ambulatory BP. Additionally, my experiments will determine how pharmacologically targeting ET-1 modifies these factors.

4.B INNOVATION

**Aim 1:** I will challenge the proposed association between intradialytic hypertension and increased ECV by directly measuring extracellular water with multifrequency bioimpedance spectroscopy. This is the first study to use this method specifically in intradialytic hypertension patients and will clarify the role of ECV in this phenomenon.

**Aim 2:** I will explore the associations of ECV and vasoconstriction on ambulatory BP and ambulatory BP patterns in patients with intradialytic hypertension and controls by measuring extracellular water and vascular resistance. This novel study will address a major gap in understanding the association between intradialytic hypertension and increased mortality by [establishing independent associations between these measurements with BP measured during the interdialytic time period. Identifying whether ECV overload or augmented vasoconstriction is the mechanism most strongly associated with ambulatory BP patterns will be critical in determining the optimal strategy to effectively reduce ambulatory BP in patients with various intradialytic BP patterns. Furthermore, the detailed ascertainment of intradialytic changes in the vasoconstrictor mediators ET-1, Ang II, and ADMA, as well as the ascertainment of potentially confounding mechanisms such as antihypertensive removal during HD and dosing of erythropoietin stimulating agents will further elucidate the precise mechanisms through which the proposed intradialytic vasoconstriction occurs.]

**Aim 3:** I will conduct the first randomized, controlled study investigating the effects of pharmacologic therapy in patients with intradialytic hypertension. [This will address not only how these therapies influence intradialytic changes in ET-1, vascular resistance and blood pressure, but also how modification of the changes impacts BP during the interdialytic period. By comparing the effects of carvedilol with prazosin, two drugs with alpha
adrenergic antagonistic activity, I will eliminate any potentially confounding effect that this adrenergic activity may have on vascular resistance and BP. The drugs have similar protein binding characteristics so that their removal during dialysis should be similarly limited. However, only carvedilol has been shown to inhibit the production and release of ET-1. This aim will establish the independent role of ET-1 induced intradialytic vascular resistance increases on the BP of HD patients during the interdialytic time period.

4.C APPROACH
4.C.1 Preliminary Data and Overview:
Aim 1: To determine if ECV is similar in patients with intradialytic hypertension and HD controls. In a case-control study, I found that patients with intradialytic hypertension in >4/6 HD treatments and HD controls had a similar percentage of weight gain in a single interdialytic period (3.4 vs. 3.2%, p=0.6) [2]. I also analyzed 6 months of HD treatments in 362 HD patients [5]. Patients with systolic BP increases >10 mmHg from pre to post-HD, when averaged for 6 months, had similar intradialytic weight gain compared to other HD patients. No study has measured extracellular water in these patients. In a case-control study, I will compare the [ratio of extracellular to total body water] in patients with intradialytic hypertension and HD controls.
Aim 2: To determine the associations of vascular resistance and ECV with ambulatory BP in patients with intradialytic hypertension and HD controls. I have shown that interdialytic BP patterns differ between intradialytic hypertension patients and HD controls (Fig 4). For 24 hours after HD, the BP of intradialytic hypertension patients trends down (-0.3 mmHg/hr, p=0.1), but increases in controls (+0.5 mmHg/hr, p=0.002). For the rest of the interdialytic period, there is a trend for BP increases in both groups. The difference in average 44 hr ambulatory systolic BP in intradialytic hypertension patients and controls is entirely accounted for by the initial 24 hr period (p=0.005 for 0-44 hrs, p=0.003 for 0-24 hrs, p=0.3 for 24-44 hrs). These findings are independent of the timing of HD or antihypertensive medication dosing. Given the mortality risk of increased average ambulatory BP, this suggests that mechanisms regulating BP in the initial 24 hr period after HD in intradialytic hypertension patients are critical components of these patients’ overall mortality risk. These patterns also suggest that mechanisms other than ECV are responsible for this increased BP. [Further analysis shows better baseline flow mediated vasodilation predicted steeper decreases in BP for 24 hours after HD. This suggests that this BP slope is influenced by mediators of endothelial cell function, and that targeting these mediators may be the best therapy to effectively lower ambulatory BP in patients with intradialytic hypertension.] In a case-control study, I will compare interdialytic BP and BP slopes between groups of patients with and without intradialytic hypertension and will identify how ECV and changes in vascular resistance, [ET-1, Ang II and ADMA] independently modify BP within these groups during the critical 24 hrs post-HD and the entire interdialytic period. Changes in pre to post-HD BP will also be correlated with changes in ET-1, [ADMA], Ang II, and vascular resistance.
Aim 3: To determine if targeting ET-1 with carvedilol, an alpha and beta adrenergic receptor antagonist shown to inhibit ET-1 release in vitro [38], reduces ambulatory BP [by modifying intradialytic changes in ET-1 and vascular resistance in intradialytic hypertension patients.] Our lab showed in a pilot study in patients with intradialytic hypertension that carvedilol improved endothelial cell dysfunction and reduced intradialytic ET-1 surges, ambulatory BP, and the frequency of intradialytic hypertension [4]. In that uncontrolled study, neither a causal role nor the mechanisms responsible for these effects could be confirmed. In a randomized crossover study, I will compare the effects of [carvedilol and prazosin, an alpha-adrenergic receptor antagonist without known ET-1 lowering properties, on intradialytic change in ET-1 in patients with intradialytic hypertension. I will further explore the effects on intradialytic changes in vascular resistance, and ambulatory BP/BP slope] This will establish the benefits of strategically targeting our proposed mechanism for increased ambulatory BP in intradialytic hypertension patients: ET-1 induced surges in vascular resistance.

4.C.2 Study Design
Aims 1-2 will employ a case-control study design in patients with intradialytic hypertension and HD controls. Aim 3 will employ a randomized, double blind crossover study of a subset of case subjects.
4.C.3 Methods
4.C.3.a Patient Population

Research Strategy
Page 99
**Aims 1 and 2:** Using consecutive sampling, I will screen all HD patients from the 3 UT Southwestern-affiliated HD units by reviewing BP measurements from the 6 prior HD treatments. Inclusion criteria for all subjects include age >18 years and hypertension defined as average screening systolic BP >140 mmHg pre-HD or >130 mmHg post-HD. Specific inclusion criteria for case subjects with intradialytic hypertension are systolic BP increases ≥10 mmHg from pre to post-HD in ≥4/6 screening treatments. Specific inclusion criteria for control subjects are systolic BP decreases ≥10 mmHg from pre to post-HD during screening. I will select controls to balance the distribution of age, sex, race, and diabetic status of the case subjects. Exclusion criteria for all subjects include HD vintage <1 month, presence of a cardiac pacemaker or defibrillator, major limb amputation, artificial joint, pregnancy, and failure to achieve dry weight.

**Aim 3:** I will consecutively sample case subjects from Aims 1 & 2. In addition to exclusion criteria from Aims 1 & 2, additional exclusion criteria will be symptomatic coronary artery disease, tachyarrhythmia, pulse <60 beats/minute if not on pulse lowering drugs, and intolerance of α or β blockers will be exclusion criteria.

**4. C. 3.b. Procedures/Variables (Table 4)**

**Aim 1:** Patient information will be collected after obtaining informed consent. Measurements will be obtained at a mid-week HD treatment (Treatment #1) and at the next consecutive treatment (Treatment #2) (Table 4).

1. **Patient Information:** All subjects will undergo a medical history and physical exam (including height). I will ascertain demographics, medical comorbidities, medication doses and time (including medications taking during or before HD), vascular access, monthly laboratory information (serum sodium, creatinine, albumin, potassium, calcium, phosphorus, and hemoglobin), diastolic composition, treatment duration, ultrafiltration rate, and blood flow rate. 

   *I will obtain prior echocardiogram and coronary catheterization reports.*

2. **Weight:** Pre and post-HD weight will be measured on a standing scale. Interdialytic weight gain and ultrafiltration volume will be calculated from differences in weight between and during individual treatments.

3. **Blood Pressure:** HD unit nurses will measure and record the average of 3 BP measurements with an validated Omron HEM-907 XL sphygmomanometer following 5 minutes of rest while the subject is seated with feet on the floor immediately before and after Treatment #1, before Treatment #2, and every 30 minutes during the treatment to monitor hemodynamic stability.

4. **Extracellular Water:** We will measure extracellular ([and total body] water and calculate the ratio of post-HD extracellular water to [total body water] using multifrequency bioimpedance spectroscopy with the Impedimed SFB7 Body Composition Analyzer (Queensland, Australia). This is FDA approved and validated for measuring total body water in healthy subjects[39]. Multifrequency bioimpedance has also been validated in HD patients[40] and is frequently used to study ECV in them[20, 41, 42]. Electrodes placed on the skin emit 256 frequencies (4-1000 kHz) at 200 microamps. This frequency range differentiates extra- and intracellular electric resistance. The SFB7 calculates compartmental water volumes from resistance measurements using Cole-Cole model plots and of measured reactance and resistance at varying frequencies and using the Hanai equation[43, 44]. Measurements will be obtained prior to Treatment #1 and #2 with the patients in the supine position. Electrodes will be placed on the ipsilateral wrist, ankle, foot and hand on the side of the non-access arm, and measurements are obtained within seconds. Post-HD measurements will be obtained 30 minutes after Treatment #1.

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**Table 4: Planned Procedures (See Table 3 for estimated time for individual aims)**

<table>
<thead>
<tr>
<th>AIMS 1-2 All Subjects (n=138)</th>
<th>TABLE 4: Planned Procedures (See table 3 for estimated time for individual aims)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment 1 (Pre and Post)</strong></td>
<td>X X X X X X [X] X X</td>
</tr>
<tr>
<td><strong>Interdialytic Period 1</strong></td>
<td>X X X X X X</td>
</tr>
<tr>
<td><strong>Treatment 2 (Pre)</strong></td>
<td>X X X X X X</td>
</tr>
<tr>
<td><strong>Drug Initiation and Titration</strong></td>
<td>X X X X X X</td>
</tr>
<tr>
<td><strong>Treatment 3 (Pre and Post)</strong></td>
<td>X X X X X X</td>
</tr>
<tr>
<td><strong>Interdialytic Period 2</strong></td>
<td>X X X X X X</td>
</tr>
<tr>
<td><strong>Treatment 4 (Pre)</strong></td>
<td>X X X X X X</td>
</tr>
<tr>
<td><strong>Washout (2 week)</strong></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AIMS 3 Intradialytic Hypertension (n=20)</th>
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</thead>
<tbody>
<tr>
<td><strong>Treatment 5 (Pre and Post)</strong></td>
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</tr>
<tr>
<td><strong>Interdialytic Period 3</strong></td>
<td>X X X X X X X X</td>
</tr>
<tr>
<td><strong>Treatment 6 (Pre)</strong></td>
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</tr>
<tr>
<td><strong>Drug Initiation &amp; Titration</strong></td>
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<td><strong>Treatment 7 (Pre and Post)</strong></td>
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<td><strong>Interdialytic Period 4</strong></td>
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<td><strong>Treatment 8 (Pre)</strong></td>
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</tr>
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</table>

| **Wi=weight; BP=Blood Pressure; ECW=Extracellular Water; ET-1=Endothelin-1; Ang=Angiotensin; [ ADMA=Asymmetric Dimethylarginine; Na=serum sodium** |

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Aim 2: In addition to data from Aim 1, vascular resistance, plasma (ET-1, Ang II, [Asymmetric dimethylarginine (ADMA)]), serum sodium, and ambulatory BP will be measured in all subjects. I expect it will take 4-4 1/2 years to complete Aims 1 & 2.

1. Blood samples will be collected at the HD-unit before and after Treatment #1 (serum sodium only before); on the non-HD day during the interdialytic period at the research clinic (ET-1 and Ang II) and prior to Treatment #2 at the HD-unit (ET-1). Plasma will be collected in an EDTA tube, centrifuged for 15 minutes, pipetted into vials and transported to a -80 degree freezer on dry ice. Serum sodium samples will be collected in a serum separator tube and kept at room temperature. ET-1 (1 mL) will be measured using quantitative sandwich enzyme immunoassay technique with Quantiglo Human Endothelin-1 Immunoassay at UT Southwestern (coefficient of variation [COV] 2.6-3.4% and 4.6-8.9% for intra and interassay precision). ADMA (1 mL) will be measured using competitive enzyme linked immunosorbent assay (BioVendor) with a microtiter plate at UT Southwestern (COV 4.5-7.5% and 4.6-8.9% for intra-assay and interassay precision). Ang II (1 mL frozen) will be measured with immunoassay analysis (Quest Diagnostics). Serum sodium (1 mL) will be measured with Ion Selective Electrode Analysis (Quest) to rule out differences in pre-HD sodium (and thus dialysate-serum sodium gradient) as a confounding factor.

2. Vascular Resistance: We will estimate systemic vascular resistance with impedance cardiography using the Cardiodynamics BioZ (San Diego, CA). This measures change in impedance of an alternating current applied across the thorax to calculate stroke volume, cardiac output and vascular resistance using Digital Impedance Signal Quantifier Technology. These measurements are validated compared to those obtained with invasive catheterization[21-23]. Prior to Treatments #1 and #2, electrodes are placed bilaterally on the neck and chest on a supine subject. Measurements are available within 30 seconds. This procedure will be repeated following HD in Treatment #1 and at mid-day of the non-HD day during the interdialytic time period.

3. Ambulatory Blood Pressure: After Treatment #1, subjects will have an appropriately sized Spacelabs 90207 BP cuff placed on the non-access arm. The subject will wear a monitor for the entire 44 hr interdialytic time period after an initial cuff inflation at the HD unit. The cuff will inflate every 30 minutes from 6 am until 10 pm and every hour from 10 pm until 6 am until the next HD treatment.

Aim 3: A computerized random number generator will randomize subjects in a 1:1 to receive oral carvedilol or [prazosin first. For subjects taking either a or β blocker at baseline, a 2-week washout period will precede any study procedures for Aims 1-3.]

Phase 1: Subjects will begin the study drug after Treatment 2. I will assess the subject's weekly at the HD unit to determine the appropriate titration as tolerated (Table 5). After 8 weeks (with 2 on the max dose), we will repeat Aim 1 & 2 procedures in treatments #3 and #4 (and interdialytic period 2).

Phase 2: A 2-week washout will follow Treatment #4, and procedures from Aims 1 & 2 will be repeated during treatments #5 and #6 (and interdialytic period 3). Following Treatment #6, subjects will begin the crossover drug and repeat the titration protocol. After 8 weeks, we will repeat procedures in Aims 1 & 2 during treatments #7 and #8 (and interdialytic period 4). I expect it will take 3 years to complete Aim 3.

4.C.3.c Statistical Analyses and Power Calculations
We will explore the data with histograms, box-plots, scatter plot matrices and Trellis plots. Data not meeting assumptions of normality will be transformed or non-parametric alternatives will be employed as necessary.

Aim 1: Multivariate analysis of variance models will compare between-group differences in post-HD extracellular to [total body water] ratio while controlling for age, gender, race, vascular resistance, [and significant differences in medication use or medical comorbidities. Based on a study of hypertensive HD patients[45], those with and without ECV overload had average ratios of [0.52 and 0.47.] respectively. If there is truly no difference in ECV between groups, then [138 subjects (69 per group)] are required to be 80% sure that the 90% two sided interval will exclude a difference in means of more than 0.05, given the estimated standard deviations of 0.11. We expect 10% dropout and plan to enroll a total of [154] subjects.

Aim 2: To analyze repeated measurements, we will use linear mixed models assuming a first order regressive correlation structure to test between-group differences in ambulatory BP slopes and effects of extracellular water and vascular resistance on these slopes. If this structure assumption does not hold, the generalized estimating equation will be used. If linear mixed models inadequately model hourly BP changes, non-linear models will be used. Missing data will be handled using the generalized-EM algorithm. Regression models will compare associations between extracellular water and ambulatory BP with associations between interdialytic vascular resistance changes and ambulatory BP [while controlling for demographics, comorbidities (including both the presence of and quantification of severity) and medication use.] We will use Pearson or
be a vehicle for my independence based on the skills I will develop and findings I will obtain. Projected studies based on my findings include the following:

**Aim 1:** I anticipate similar post-HD extracellular *to total body* water ratios in cases and controls. If no difference exists, future studies should focus on other mechanisms responsible for intradialytic hypertension and the associated adverse outcomes including effects of endothelial cell dysfunction on vascular resistance. If this ratio is increased in intradialytic hypertension patients, prospective trials should study effects of dry weight reduction on clinical outcomes in this population. **Aim 2:** I anticipate a greater association with vascular resistance and ambulatory BP than with ECV and ambulatory BP in patients with intradialytic hypertension, particularly during the first 24 hrs post-HD. This will justify exploring the prevalence of ambulatory BP patterns that deviate from salt sensitivity in cross sectional studies of HD patients and the association of such patterns with outcomes in prospective studies (**Long Term Objective 1, Fig 5**). I anticipate that some hypertensive HD patients without intradialytic hypertension exhibit such patterns and may be 1) at higher risk for adverse events and 2) ideal candidates for therapies targeting amplified vasoconstriction. **Aim 3:** [Compared to prazosin, I anticipate carvedilol to more effectively blunt the pre to post-HD increase in ET-1 and vascular resistance and reduce ambulatory BP.] Such findings will warrant research into how commonly used antihypertensives affect ET-1 and vascular resistance in other hypertensive HD patients. Ultimately, a large randomized trial can investigate tailored approaches to BP management with antihypertensives that directly target the pathophysiologic mechanism (**Long Term Objective 2, Fig 5**).

**4.C.3.e Study Feasibility:** We have conducted clinical research studies at our DaVita dialysis units for multiple years, as evident by our preliminary data and publications. This includes successful recruitment of intradialytic hypertension patients and Spanish-speaking subjects. Academic nephrologists and HD staff managing these patients are aware and supportive of my work. I have provided instructional sessions to staff at these units on measuring BP and collecting blood. The patients and staff have been very receptive to these studies. We enrolled 50 subjects (25 with intradialytic hypertension) in a prior study over 15 months. We expect 4-4 ½ years to complete enrollment for Aims 1-2 and 2-3 years for Aim 3. [This study has been approved by the UT Southwestern IRB and we already have all the necessary equipment for this project.]
SUMMARY STATEMENT

PROGRAM CONTACT: TRACY RANKIN
(301) 594-4748
rankint@mail.nih.gov

Application Number: 1 K23 DK096007-01A1

Principal Investigator

Applicant Organization: UNIV OF TEXAS SW MED CTR

Review Group: DDK-D
Kidney, Urologic and Hematologic Diseases D Subcommittee

Meeting Date: 03/05/2013
Council: MAY 2013
Requested Start: 07/01/2013

RFA/PA: PA11-194
PCC: KTR KTR

Project Title: Mechanisms of Increased Ambulatory Blood Pressure in Intradialytic Hypertension

SRG Action: Impact Score: 20


Human Subjects: 30-Human subjects involved - Certified, no SRG concerns
Animal Subjects: 10-No live vertebrate animals involved for competing appl.

Gender: 1A-Both genders, scientifically acceptable

Minority: 1A-Minorities and non-minorities, scientifically acceptable

Children: 1A-Both Children and Adults, scientifically acceptable

Clinical Research - not NIH-defined Phase III Trial

The following table shows the requested and estimated costs for each year of the project:

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<tr>
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<tr>
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ADMINISTRATIVE BUDGET NOTE: The budget shown is the requested budget and has not been adjusted to reflect any recommendations made by reviewers. If an award is planned, the costs will be calculated by Institute grants management staff based on the recommendations outlined below in the COMMITTEE BUDGET RECOMMENDATIONS section.

ADMINISTRATIVE NOTE, BIOHAZARD
BIOHAZARD COMMENT

BUDGETARY OVERLAP

SCIENTIFIC REVIEW OFFICER’S NOTES

RESUME AND SUMMARY OF DISCUSSION: This resubmission application was submitted in response to program announcement PA-11-194 entitled “Mentored Patient-Oriented Research Career Development Award (Parent K23)”. The candidate proposes to test the hypothesis that the increases in vascular resistance related to surges in plasma endothelin-1 level are responsible for the increased ambulatory blood pressure in patients with intradialytic hypertension. The proposed studies address an important clinical problem and build on the candidate’s research. Previously noted strengths of the application such as a high potential of the candidate to become an independent scientist; the excellent group of mentors; the well delineated career development plan; the institutional support; and the outstanding environment remain. The significantly improved research plan is supported by additional data and clear rationale; proposes mechanistic studies; and discusses well potential confounding factors. Only minor weaknesses were noted and, overall, this application is rated outstanding.

DESCRIPTION (provided by applicant): This NIH Mentored Patient-Oriented Research Career Development Award proposal describes a 5 year training program with the long-term goal of the candidate developing into an independent academic investigator with a research focus in hypertension in patients with chronic and end-stage kidney disease. The candidate will build on a background in clinical research developed during a comprehensive research fellowship spent studying ambulatory blood pressure and endothelial cell dysfunction in patients with intradialytic hypertension. The career development objectives are to obtain skills in designing and conducting prospective clinical research studies, learn statistical models to analyze ambulatory blood pressure in hemodialysis patients, gain experience in measuring and interpreting cardiovascular physiologic parameters including extracellular water and vascular resistance utilizing bioimpedance analysis, and participate in scholarly activities to facilitate the transition into an independent investigator. These will be applied immediately to investigating how extracellular volume and mediators of vascular resistance affect ambulatory blood pressure in patients with intradialytic hypertension and hemodialysis controls. Aim 1 will use a case control design to compare differences in extracellular water in patients with intradialytic hypertension and hemodialysis controls. Aim 2 will determine how extracellular volume, vasoconstrictor mediators of vascular resistance, and vascular resistance itself modify ambulatory blood pressure and the ambulatory blood pressure slope in these two groups. In aim 3, the candidate will gain experience in designing and conducting a randomized trial by comparing the effects of carvedilol vs. prazosin on ambulatory blood pressure, vascular resistance, and mediators of vascular resistance in patients with intradialytic hypertension. The candidate will develop these skills with the support a primary mentor, 3 co-mentors (including one translational research cardiologist and one biostatistician), and a research advisory committee with extensive experience in multiple research disciplines. The candidate and his advisors are located at the University of Texas Southwestern Medical Center, a leading academic medical center with substantial physical and intellectual resources necessary for the career development of young investigators and the performance of cutting-edge research. The candidate will take advantage of numerous courses and research activities as a Clinical Research Scholar in the Department of Clinical Sciences that will promote the overall development of his career. Consistent with the candidate's long term career goals, the findings from this study can be broadened to studying hypertension in hemodialysis patients in general. Understanding the relationship between extracellular volume, vascular resistance, and ambulatory blood pressure will provide the opportunity to investigate how pharmacologic therapies affect each component and how this can improve cardiovascular outcomes in hemodialysis patients.

PUBLIC HEALTH RELEVANCE: In hemodialysis patients, high blood pressure increases the risk for death and complications related to heart disease. This research studies how hemodynamic changes during dialysis are associated with high blood pressure measured throughout the entire 44 hour period.
between dialysis treatments. Findings from this project will direct future studies that investigate which medications or interventions will most successfully lower blood pressure and reduce adverse events in hemodialysis patients.

CRITIQUES
(Note: The critiques below were prepared by the reviewers assigned to this application. These commentaries and criterion scores do not necessarily reflect the position of the authors at the close of the group discussion, nor the final majority opinion of the group, although reviewers are asked to amend their critiques if their position changed during the discussion. The resume and other initial sections of the summary statement are the authoritative representation of the final outcome of group discussion. If there is any discrepancy between the peer reviewers' commentaries and the priority/impact score on the face page of this summary statement, the priority/impact score should be considered the most accurate representation of the final outcome of the group discussion.)

CRITIQUE 1:
Candidate: 1
Career Development Plan/Career Goals /Plan to Provide Mentoring: 2
Research Plan: 2
Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1
Environment, Commitment to the Candidate: 1

Overall Impact: This is a resubmission of a K23 award for Dr. [REDACTED] which received a prior priority score of 30. Strengths of the prior application included that the clinical focus, intradialytic hypertension, importance of clinical problem and the candidate’s previous research. The candidate was thought to have a high potential to become an independent scientist; he has an excellent group of mentors; a well delineated career development plan; strong institutional support; and an outstanding environment. The research plan was considered a main weakness with limited innovation; weak rationale and unclear discussion of the proposed underlying mechanism and approach and in depth discussion of confounding factors. In response to these criticisms the candidate has significantly strengthened and clarified the research plan, made explicit the rationale and underlying mechanisms. Overall this application is outstanding, and has few minor weakness.

1. Candidate:

Strengths

- Currently an Instructor at UT Southwestern (appointed since prior submission). BA from UPenn, MD from UT San Antonio, completed residency and fellowship at UT Southwestern.
- Completed the coursework for a Master’s in Clinical Science since the prior submission.
- Has successfully competed for research funding, having been awarded both a NKF fellowship (declined) and F32. Since the last submission, he was awarded an American Heart Association Fellow to Faculty Transition Award through 2017 entitled “Mechanisms of Increased Ambulatory Blood Pressure in Patients With Intradialytic Hypertension”.
- In the last review it was commented that his documented productivity in peer-reviewed papers could be higher. He now reports publication of 6 first author review articles on hypertension in diabetic nephropathy, end-stage renal disease, and intradialytic hypertension, in addition to 3 first author original research publications. This is up from 2 first author papers in the prior submission.
- He is highly commended in the letters for his commitment to research and his skills. His division chief calls him “one of the two best clinical research fellows that our program has produced in
the last twelve years”.

Weaknesses

- Doesn’t address potential overlap between this proposal and the AHA award

2. Career Development Plan/Career Goals & Objectives:

Strengths

- Plans to meet weekly with Dr. Toto, who has an outstanding track record of mentoring, and has added another mentor Dr. Tyler Miller (RAC): Professor of Medicine (Nephrology) at UT Southwestern and Assistant Chief of Medicine in research (Dallas VA) with expertise in career guidance of junior researchers, prior co-PI of an institutional training grant at Case Western Medical Center
- The candidate proposes to meet monthly with Dr. Xiao to learn the theory of modeling ABPM data in ESRD patients and then to use these models to analyze his study data.
- Dr. Vongpatanasin will serve as a co-mentor to study the role of extracellular volume on vascular resistance.
- The candidate will learn to measure ET-1 in the O’Brien Kidney Center laboratory. He will take a course on Genetic and Molecular Science for the Clinical Investigator, which will include proteomics, pharmacogenomics, biomarkers and sample acquisition.
- In response to prior critique that involvement in large RCT’s of mentors may not be in his best interest, this involvement has been minimized in the current proposal to only involvement in SPRINT.
- In response to the prior comment that more discussion about how the mentoring group will work together to ensure career progress is needed the candidate has added q 6 months meetings of the mentoring team.

Weaknesses

- Since the prior application, Dr. Inrig has moved to industry, but plans for ongoing meetings are included. She is now 100% effort devoted to clinical research as the Medical Director, Quintiles Global CRO and Adjunct Associate in Medicine, Division of Nephrology, Duke University.
- The candidate completed coursework for a Master’s of Science degree, states he requires advanced instruction in developing strategies for hypothesis generation, determining the optimal methods to test hypotheses, and selecting appropriate statistical techniques to analyze results and didactic exposure to translational research methods to complement his clinical research background so plans to obtain an advanced Masters with Distinction degree. However only remaining coursework seems to be Research Ethics, in addition to the genetic and molecular science course. This appears appropriately translational, but overall the need for additional didactic training is weak. However, the mentorship and hands on component of training is strong, so this is only a minor weakness.

3. Research Plan:

Strengths

- The main concerns in the prior review were with the research plan, and this has been revised extensively in response to the prior comments. The candidate presents additional preliminary data on the prevalence on intradialytic hypertension in his cohort, yielding more evidence of feasibility.
- Overall hypothesis, stated clearly, is that increases in vascular resistance related to surges in ET-1, as opposed to increased ECV, are responsible for the increased ambulatory BP burden in
patients with intradialytic hypertension. In response to the prior review, the candidate will now look at the ratio of extracellular body water to total body water rather than weight gain.

- For Aims 1 and 2, utilizing a case control design, somewhat modified from the prior proposal, the proposed studies will examine his hypothesis that intradialytic vascular resistance surge is the predominant mechanism regulating ambulatory BP in patients with intradialytic hypertension. In addition to exploring changes in ET-1, angiotensin II, measures of asymmetric dimethylarginine have been added to explore the relationship of these markers and vascular resistance. In response to the prior concern about inconsistency in the development of intradialytic hypertension and the definition of cases, to reduce misclassification bias, case subjects will be selected only if they have repeated intradialytic hypertension (≥4/6 treatments).

- In response to the prior review, the applicant has changed the randomized crossover study in subjects with intradialytic hypertension, and he will now compare differences between carvedilol and prazosin in intradialytic change in ET-1. Prazosin is now chosen as the comparator agent, as an α-adrenergic receptor antagonist without known ET-1 lowering properties. Its use will control for possible sympathetic mechanism that might underlie intradialytic hypertension. He will further explore the effects on intradialytic changes in vascular resistance, and ambulatory BP/BP slope in the trial. The goal is to establish that the mechanistic link between ET-1, vascular resistance and ambulatory BP as a potential target to effectively reduce BP in patients with intradialytic hypertension.

- One of the issues with the prior application was that it was not seen as innovative. In response to this, the candidate states that understanding the effect that intradialytic ET-1 and vascular resistance changes have on ambulatory blood pressure will provide novel insight for devising more targeted approach to hypertension management in ESRD patients. His argument for this that identifying whether ECV overload or augmented vasoconstriction is the mechanism most strongly associated with ambulatory BP patterns will help determine the optimal strategy to effectively reduce ambulatory BP in patients with various intradialytic BP patterns. The detailed ascertainment of intradialytic changes in the vasoconstrictor mediators ET-1, Ang II, and ADMA, as well as the ascertainment of potentially confounding mechanisms such as antihypertensive removal during HD and dosing of erythropoietin stimulating agents will further elucidate the precise mechanisms through which the proposed intradialytic vasoconstriction occurs.

- Another of the issues raised in the prior review was the problem of confounding, the candidate now states, more explicitly, the limitation of confounding factors that may affect ET-1, Ang II, and vascular resistance, and will collect information and adjust for these, including the use of erythropoietin stimulating agents, the removal of antihypertensives during HD and illnesses associated with up-regulation of these systems.

Weaknesses

- The candidate doesn’t address the possibility of carryover effects in the cross-over design that were brought up in the prior review

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- A number of strengths and no weaknesses were cited in the prior review. Dr. Toto, the primary mentor, Associate Dean for Clinical and Translational Research at UT Southwestern has extensive laboratory and clinical research experience. He has a K24, is also the PI of the UT Southwestern CTSA, and has a terrific mentoring track record.

- Dr. Vongpatanasin, co-mentor, is an Associate Professor of Cardiology and directs a NIH-funded laboratory that performs the cardiac output and vascular function measures proposed in this application. She is committed to helping the candidate learn the theory and mechanics of
these measures.

- Dr. Xiao is a statistical mentor with the appropriate expertise to assist with the proposed analyses.

**Weaknesses**

- Dr. Inrig, the prior co-mentor, has moved to industry. She had been a co-mentor on Dr. F32. She has moved to a CRO, but is still in Dallas and can continue to interact with him frequently.

5. **Environment and Institutional Commitment to the Candidate:**

**Strengths**

- Strong letter of commitment and support from the primary mentor and from the Department Chairman and Division Chief. The Department of Clinical Sciences, the CTSA with its Clinical and Translational Research Center are important resources that will help ensure that the candidate can complete his projects. In addition, the O'Brien Center also adds important resources.

- In the prior submission, the candidate proposed clinical and teaching activities that included one month of ward attending, one month of consult service attending, one half day per week of clinic, one dialysis shift, and 14 weeks of supervising fellows in clinic one half day per week which seemed to exceed 25% effort. This has been decreased in the current application.

**Weaknesses**

- In the prior submission, the candidate was to have been appointed as an Assistant Professor in June, 2012, but has been appointed as an Instructor.

**Protections for Human Subjects:**

**Acceptable Risks and Adequate Protections**

**Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):**

Acceptable

**Inclusion of Women, Minorities and Children:**

G1A - Both Genders, Acceptable

M1A - Minority and Non-minority, Acceptable

C1A - Children and Adults, Acceptable

**Vertebrate Animals:**

Not Applicable (No Vertebrate Animals)

**Biohazards:**

Not Applicable (No Biohazards)

**Training in the Responsible Conduct of Research:**

Acceptable

Comments on Format (Required):

- acceptable, online and course

Comments on Subject Matter (Required):

- acceptable
Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):

- acceptable

Comments on Duration (Required):

- acceptable

Comments on Frequency (Required):

- acceptable, annual

Select Agents:

Not Applicable (No Select Agents)

Resource Sharing Plans:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 2:

Candidate: 1

Career Development Plan/Career Goals/Plan to Provide Mentoring: 2

Research Plan: 2

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 2

Environment Commitment to the Candidate: 2

Overall Impact: This is a revised K23 application from an accomplished junior investigator seeking to study the causes and potential treatment of intradialytic hypertension. Major concerns on the last submission were some weaknesses in the research plan and some concern about the institutional commitment to the candidate, particularly the large proposed clinical load. The current proposal has addressed these concerns and is considerably improved. The comparator arm for the study proposed in Aim 2 has been changed from placebo to an active control, and the outcome has been changed to change in ET-1 level, both of which increase the potential impact of the findings. Dr. [redacted] has been promoted to Instructor since the last submission and his proposed clinical responsibilities have been lowered substantially.

1. Candidate:

Strengths

- Dr. [redacted] has been promoted to Instructor since the last submission and has completed the coursework for a Masters in Clinical Science.
- He has successfully competed for research funding, having been awarded both a NKF fellowship, which he declined, and an F32. Most recently he received an American Heart Association Fellow to Faculty award.
- He has demonstrated excellent research productivity, with 6 original articles of which he is first author on 3, plus an additional 9 review articles (8 first author).

Weaknesses

- None noted

2. Career Development Plan/Career Goals & Objectives:
3. Research Plan:

Strengths

- As previously noted, the proposed research builds on the candidate’s prior research, and the research is in an area with important clinical implications.

- The applicant has made some changes to the research plan that should increase the impact of the work. Specifically, adding prazosin as a control treatment rather than placebo in the intervention and changing the primary outcome to change in ET-1 should lead to results that are more interesting and relevant to the candidate’s hypotheses about intradialytic hypertension.

Weaknesses

- None noted

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths

- Drs. Toto, Vongpatanasin, and Xiao are still committed to training and mentoring the candidate during the period of the award. This talented team has the necessary expertise to help him succeed.

- Dr. R. Tyler Miller, an experienced researcher and mentor, has been added to Dr. Research Advisory Committee.

Weaknesses

- Dr. Inrig has moved from UT Southwestern to Quintiles Global Clinical Research Organization. However, she is still based in Dallas, and she writes that she will meet with Dr. on a biweekly basis, and Dr. Toto will still meet weekly to directly advise the candidate on his research endeavors and career trajectory.

5. Environment and Institutional Commitment to the Candidate:

Strengths

- Dr. clinical load has been lessened since the last submission. The letter from the department chair states that his 75% research support is not contingent on receipt of the K23 award.

- Dr. has been selected for and will participate in the UT Southwestern Clinical Research Scholar program, which will give him access to a broader range of clinical research colleagues and biostatistical support.

Weaknesses

- None noted

Protections for Human Subjects:

Acceptable Risks and Adequate Protections
Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):

Acceptable

Inclusion of Women, Minorities and Children:

G1A - Both Genders, Acceptable
M1A - Minority and Non-minority, Acceptable
C1A - Children and Adults, Acceptable

Biohazards:

Unacceptable

- Specific biohazards plans for assays of blood samples were not presented.

Training in the Responsible Conduct of Research:

Acceptable

Comments on Format (Required):

- The candidate has completed formal training and will continue with formal didactics as well as monthly ethics grand rounds presentations.

Comments on Subject Matter (Required):

- The relevant subject matter will be covered.

Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):

- Faculty participation is documented.

Comments on Duration (Required):

- for the duration of the award

Comments on Frequency (Required):

- Frequency is specified.

Resource Sharing Plans:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3:

Candidate: 1

Career Development Plan/Career Goals /Plan to Provide Mentoring: 2

Research Plan: 1

Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s): 1

Environment Commitment to the Candidate: 1

Overall Impact: This is an A1 application previously reviewed and received a score of 30. Weaknesses of the previous submission have been adequately addressed by the candidate. These were primarily with the research plan. The drive and passion the candidate has for becoming an independent clinical investigator is supported by his productivity and letters of recommendations. He has an outstanding mentoring team and is working in an environment that is conducive to his career development. The
area of research, hypertension in dialysis patients, is significant. The research plan is clear and has the potential to provide new insights into our understanding of hypertension in dialysis patients and to foster the career development of the candidate.

1. Candidate:

Strengths

- The candidate graduated from medical school at U of Texas Health Science Center, San Antonio and completed his internal medicine residency and nephrology fellowship at UT Southwestern where he is also enrolled in the Masters of Clinical Sciences. He successfully transitioned from T32 to F32. Since the last submission of this grant he has been made an Instructor with plans for 2013 to become Assistant Professor. He is a UTSW Clinical Research Scholar and has received an AHA Fellow to Faculty Award.

- He has published 6 original articles (two since last submission), first author on three, with three related to this area of research. In addition he has published 9 first author review articles related to hypertension and other complications of CKD.

- The candidate has high potential to develop as an independent and productive researcher.

- Research record includes a case-control study and retrospective database analysis. He has cohesively integrated his course work and research studies together during his fellowship training.

- Letters of reference are outstanding and attest to his potential to develop into an independent investigator.

Weaknesses

- None noted

2. Career Development Plan/Career Goals & Objectives:

Strengths

- This was a weakness of the original submission being considered underdeveloped. The skills the candidate wants to develop are defined and include study design and implementation, statistical models, and experience in translational research. A plan is presented that includes direct research experience, didactic training, intensified mentorship and presentation and publications skills.

- The plan will contribute to the scientific development of the candidate and lead to scientific independence

- Content, scope, phasing and duration are appropriate based on his previous training and objectives

Weaknesses

- The didactic component of the CDP is modest.

3. Research Plan:

Strengths

- The cardiovascular morbidity of dialysis patients is arguably one of the most important problems in nephrology. The role of hypertension, especially intradialytic hypertension, is a very significant area of investigation.

- Research plan builds on the work the candidate did during his fellowship on defining the epidemiology of intradialytic hypertension. Previous studies by the candidate demonstrated that
intradialytic hypertension was associated with increased intradialytic ambulatory BP. It occurred in 25% of the HD population in >30% of treatments in a 6 month period.

- The proposed work is appropriate to the research stage of the candidate and for developing the skills described in career development plan. The candidate will gain experience with case-control and randomized clinical trials. He will learn techniques of impedance cardiography and bioimpedance spectroscopy.
- Previously identified weaknesses have been addressed including confounders, lack of mechanistic studies, and unclear rationale. The experimental plan is well written and rationalized and interpretation and potential experimental problems are nicely addressed.

Weaknesses
- None noted

4. Mentor(s), Co-Mentor(s), Consultant(s), Collaborator(s):

Strengths
- The primary mentor is Dr. Toto, who is an accomplished productive clinical investigator. His mentorship is a major strength of the application. He is the Associate Dean for Clinical and Translational Research at UT Southwestern. He has a K24 award. He directs the Clinical and Translational Core of the O’Brien Center and is PI of the institutional CTSA and KL2 grant.
- The research qualifications of other mentors are excellent. Dr. Inrig will mentor the candidate in clinical trial design, implementation and execution. Since the last submission she has become Medical Director of Quintiles Global CRO. Dr. Vongpatanasin will provide mentoring in the technique of bioimpedance spectroscopy analysis and cardiovascular physiology. Dr. Xiao will provide biostatistical mentoring. Dr. Ty Miller is a new member of the Research Advisory Committee.
- All mentors have provided letters of support confirming their commitment to mentoring the candidate towards independence.
- Mentor’s description of career development plan is excellent including specific benchmarks to be addressed during mentor meetings.
- Previous mentoring experience of Dr. Toto is excellent and includes trainees who have gone on to distinguished careers.

Weaknesses
- None noted

5. Environment and Institutional Commitment to the Candidate:

Strengths
- There is strong commitment towards the candidate as evidenced by 75% protected time; he will be part of the formal mentoring program in the Dept. of Medicine; access to the core facilities of the O’Brien Center;
- The research environment at UTSW is outstanding. Strengths include an outstanding Renal Division under the direction of Dr. Peter Igarashi that is home to an O’Brien Center and its Clinical and Translational Core; DaVita dialysis units; and the Clinical and Translational Research Center.

Weaknesses
- None noted


**Protections for Human Subjects:**

Acceptable Risks and Adequate Protections
- all points addressed

Data and Safety Monitoring Plan (Applicable for Clinical Trials Only):
- Acceptable

**Inclusion of Women, Minorities and Children:**

G1A - Both Genders, Acceptable
M1A - Minority and Non-minority, Acceptable
C1A - Children and Adults, Acceptable
  - children 18-21

**Resubmission:**
- The grant was reviewed 3/12 and received a score of 30. Weaknesses have been addressed as discussed in this review.

**Training in the Responsible Conduct of Research:**

Acceptable

Comments on Format (Required):
- appropriate

Comments on Subject Matter (Required):
- appropriate

Comments on Faculty Participation (Required; not applicable for mid- and senior-career awards):
- appropriate

Comments on Duration (Required):
- appropriate

Comments on Frequency (Required):
- appropriate

**Resource Sharing Plans:**

Not Applicable (No Relevant Resources)

**Budget and Period of Support:**

Recommend as Requested

Recommended budget modifications or possible overlap identified:
- May be overlap with fellow to faculty transition grant

THE FOLLOWING RESUME SECTIONS WERE PREPARED BY THE SCIENTIFIC REVIEW OFFICER TO SUMMARIZE THE OUTCOME OF DISCUSSIONS OF THE REVIEW COMMITTEE ON THE FOLLOWING ISSUES:

- PROTECTION OF HUMAN SUBJECTS (Resume): ACCEPTABLE
- INCLUSION OF WOMEN PLAN (Resume): ACCEPTABLE, G1A
INCLUSION OF MINORITIES PLAN (Resume): ACCEPTABLE, M1A
INCLUSION OF CHILDREN PLAN (Resume): ACCEPTABLE, C1A

Only Children 18-21 years old are included in the studies.

BIOHAZARD COMMENT:
Specific biohazards plans for assays of blood samples were not presented.

BUDGETARY OVERLAP:
There is a potential overlap between this application and the American Heart Association Fellow to Faculty Transition Award.

SCIENTIFIC REVIEW OFFICER’S NOTES
The plans outlined in the application to obtain training in the responsible conduct of research are adequate to satisfy this requirement.

COMMITTEE BUDGET RECOMMENDATIONS: The budget was recommended as requested.
Recommended direct cost levels are estimated and are subject to further adjustment based on the Institute’s standard budget calculation practices.

The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.
MEETING ROSTER

Kidney, Urologic and Hematologic Diseases D Subcommittee
National Institute of Diabetes and Digestive and Kidney Diseases Initial Review Group
NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES
DDK-D 1
March 05, 2013 - March 07, 2013

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* Temporary Member. For grant applications, temporary members may participate in the entire meeting or may review only selected applications as needed.

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.