Angiotensin II in the Perioperative Management of Hypotension in Kidney Transplant Recipients

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LIST OF ABBREVIATIONS

ADE	Adverse Drug Event
AE	Adverse Event
AKI	Acute Kidney Injury
ATN	Acute Tubular Necrosis
BP	Blood Pressure
CrCl	Calculated Creatinine Clearance (via Cockcroft Gault equation)
DBP	Diastolic Blood Pressure
RAAS	Renin-Angiotensin-Aldosterone system
EKG	Electrocardiogram
GFR	Glomerular Filtration Rate
KDPI	Kidney Donor Profile Index
MAP	Mean Arterial Blood Pressure
PHI	Protected Health Information
SBP	Systolic Blood Pressure
HR	Heart Rate
SCr	Serum Creatinine
UIHHSS	University of Illinois Hospital and Health Sciences System
HIPAA	Health Insurance Portability and Accountability Act
PHI	Protected Health Information
PI	Principal Investigator

1.0 PROJECT SUMMARY/ABSTRACT:

The current standard of catecholamine vasopressor management of perioperative hypotension in kidney transplant patients carries significant risks and falls short in many ways. Currently, there is an absence in the scientific literature and research describing the hemodynamic effectiveness and safety of novel pharmacologic agents such as angiotensin II (Giazpreza – Ang II) in perioperative kidney transplant patients. Phase 3 registrational trials have demonstrated the superior safety and efficacy of Ang II (Giapreza) in distributive shock patients compared to traditional vasopressor agents and the novel mechanism of action may provide additional protection in renal transplant patients. The pilot study entails giving informed and consenting kidney transplant recipients Ang II (Giapreza) as their first vasopressor if the need for vasopressors emerge either intraoperatively or postoperatively in kidney transplant recipients. The primary objective is to evaluate the safety and hemodynamic effects of Ang II (Giapreza) in the renal transplant population.

2. BACKGROUND/SCIENTIFIC RATIONALE

The inability to meet blood pressure (BP) goals in the intraoperative and postoperative period of kidney transplantation carries significant consequences, the most serious of which is hypoperfusion to the newly transplanted organ leading to graft failure (Aulakh 2015, Campos 2012, Toth 1998). Following kidney transplant, it is of utmost importance to maintain adequate perfusion to the kidney allograft for optimal function. This adequate perfusion is maintained by the maintenance of adequate systemic blood pressure. Periods of hypotension in the recipient in the intraoperative and postoperative period can have detrimental effects such as acute tubular necrosis (ATN) leading to delayed graft function or even allograft loss (Walsh 2013). In the intraoperative and postoperative setting of kidney transplantation fluid-refractory hypotension (i.e. distributive shock) is primarily reversed by catecholamine vasopressors - phenylephrine, norepinephrine, epinephrine, and dopamine) (Dandan 2019). Unfortunately, animal and human models have demonstrated that the use of catecholamine vasopressors may cause a reduction in renal blood flow, increase in incidence of acute kidney injury (AKI), and worsen clinical outcomes (Busse 2019). It is known that catecholamine vasopressors predominantly vasoconstrict the afferent arteriole of the kidneys and this vasoconstriction can lead to ischemia at the kidney and in a perioperative kidney transplant patient, putting the new allograft at risk for injury and failure by decreasing blood flow to the new allograft. It has been found that perioperative catecholamine usage is associated with decreased urine output after kidney transplantation (Choi 2016), slower normalization of recipient serum creatinine (Day 2014), delayed graft function in recipients (Robert 2010, Day 2014), increased rate of rejection (Choi 2016), increased rate of tachycardias (Robert 2010), increased length of stay, and increased mortality (Choi 2016, Ciapetti 2009). Despite these known risks, no advances have been made in the pharmacologic treatment of intraoperative or perioperative hypotension in decades. As such, there is an urgent need to identify safer and more effective pharmacologic therapies to manage intra- and post-op hypotension/hypoperfusion in the renal transplant population.

Need for the Study

As described above, the current standard of care of catecholamine vasopressors is associated with significant, detrimental adverse effects associated with the mechanism of vasoconstriction of these agents. The renin–angiotensin–aldosterone system (RAAS) is an essential hormonal regulator responsible for maintenance of BP via the actions of angiotensin II (AT2). In 2017, the FDA approved pharmacologic angiotensin II (Giapreza – Ang II) for patients with septic shock or distributive shock from other causes (Giapreza prescribing information). Distributive shock is defined as hypotension refractory to appropriate fluid resuscitation, which occurs frequently during the perioperative renal transplant period. After fluid resuscitation is unsuccessful, the use of catecholamine vasopressor agents are the mainstay of therapy for subsequent blood pressure support. As discussed, the narrow therapeutic window and significant risks associated with current vasopressor agents leave a crucial unmet medical need for safer and more effective therapies. In the ATHOS-3 Phase 3 clinical trial Ang II (Giapreza) was shown to have a more optimal pharmacodynamic profile compared to catecholamine vasopressors. It was found that Ang II (Giapreza) more frequently led to mean arterial pressure (MAP) goal attainment than the standard of care (i.e. norepinephrine) and the median duration of MAP goal attainment was 5 minutes for patients on Ang II (Giapreza); an effect that was sustained throughout the study period. Additionally, the usage of concurrent vasopressors was significantly decreased in subjects using Ang II (Giapreza) compared to the standard of care. Lastly, it was found that Ang II (Giapreza) was a safe medication with the most common ADE (> 4% and > 1.5 x placebo) being: thromboembolic events, thrombocytopenia, tachycardia, fungal infection, delirium, acidosis, hyperglycemia, and peripheral ischemia. Despite the commonality of distributive shock in the intraoperative and postoperative period

of renal transplants, there are no data available evaluating Ang II (Giapreza) in this population. The more balanced vasoconstriction of AT2 within the kidney vasculature yields a net result of increased filtration fraction and can preserve kidney function (Fehrer 2012). This has been confirmed with animal and clinical human investigations in patients with the highest known risk of developing acute kidney injury (AKI): septic shock (Lankadeva 2018, Tumlin 2018). Thus, it is hypothesized that the use of Ang II (Giapreza) in the intraoperative and perioperative period for renal transplant patients may lead to improved BP management and more optimal safety outcomes compared to the current standard of care conventional catecholamine vasopressors. Therefore, the purpose of this study is to evaluate the safety and efficacy of Ang II (Giapreza) in improving hypoperfusion among renal transplant patients during the critical peri-op period.

The following section is designed to describe the current peri-op processes of renal transplant patients at UI Health in order to clearly delineate how this specific research protocol will deviate from the standard of care.

The normal care process for deceased donor kidney transplants (DDKT) at University of Illinois Hospital and Health Sciences (UIHHSS) includes the following:

PRE-TRANSPLANT

- Patient is end-stage renal disease (ESRD) on dialysis meeting set criteria for kidney transplant
- Patient obtains medical and social clearance for kidney transplant including blood tests (SCr, LFTs, Thyroid studies, CBC w/ diff); Diagnostics: chest X-ray; Cardiac clearance: ECHO, ECG, +/- Stress test, +/- Left heart cath; Cancer screening: colonoscopy, skin CA screening, prostate exam (if applicable), gynecological exam (if applicable); pregnancy screening (if applicable); Surgical clearance; and Nephrology clearance
- Once cleared, patient is listed with our institution and placed on our waitlist
- Patient has yearly check-in visits to re-evaluate if still eligible for transplant and medically able to obtain transplant
- If kidney becomes available, patient is notified to urgently come to either the UIHHSS Surgicenter or Emergency Room to be expeditiously admitted to the OR for their transplant (this time is generally limited to 1-3 hours)
    - It should be noted that time is of extreme value as longer time that passes before implantation of donor kidney has been associated with worse renal outcomes in recipient

DURING TRANSPLANT

- The transplant operation begins.
- If intraoperative hypotension occurs (e.g. SBP < 120 mmHg) the attending surgeon and attending anesthesiologist will:
    - Give blood products first if patient bleeding
    - If not bleeding or hypotensive despite blood products, intravenous fluids will be given
    - If hypotensive despite intravenous fluids then the attending surgeon and attending anesthesiologist will assess for cardiogenic shock and if suspected give inotropes
    - If not in cardiogenic shock and hypotensive despite fluids (+/- inotropes) then catecholamine vasopressors will be given for the treatment of distributive shock.
        - Vasopressor medications will be titrated intraoperatively to achieve goal BP
        - If the patient is unable to be titrated off the catecholamine vasopressors intraoperatively, they will be continued postoperatively in the Intensive Care Unit (ICU) and titrated until the patients' blood pressure is stable without vasopressor support.

- If distributive shock does NOT occur intraoperatively, no continuous infusion catecholamine vasopressors will be initiated

AFTER TRANSPLANT

- If the patient is unable to be titrated off the catecholamine vasopressors intraoperatively, they will be continued postoperatively in the Intensive Care Unit (ICU) and titrated until the patients' blood pressure is stable without vasopressor support.
- If the patient never received continuous infusion vasopressor intraoperatively and postoperative hypotension occurs (e.g. SBP < 120 mmHg) the attending surgeon or ICU team will:
    - Give blood products first if patient bleeding
    - If not bleeding or hypotensive despite blood products, then intravenous fluids will be given
    - If hypotensive despite intravenous fluids then the attending surgeon and attending anesthesiologist will assess for cardiogenic shock and if suspected give inotropes
    - If not in cardiogenic shock and hypotensive despite fluids (+/- inotropes) then catecholamine vasopressors will be given for the treatment of distributive shock.
    - Vasopressor medications will be titrated postoperatively to achieve goal BP and titrated until the patients' BP is stable without vasopressor support.
- If distributive shock does NOT occur postoperatively, no continuous infusion catecholamine vasopressors will be initiated

3.0 OBJECTIVES/AIMS

Study Objectives

Primary: To evaluate the hemodynamic effectiveness of Ang II (Giapreza) for intraoperative and postoperative hypotension in kidney transplant patients. This will be evaluated by the time to reaching BP goal.

Secondary: To evaluate the safety of Ang II (Giapreza) for intraoperative and postoperative hypotension in kidney transplant patients. This will be evaluated by collecting the incidence of common adverse events (ADE) seen from other Ang II (Giapreza) studies in this patient population.

4.0 ELIGIBILITY

- Eligible patients will include adult patients awaiting DDKT at University of Illinois Hospital and Health Sciences needing a kidney transplant as soon as able.

4.1 Inclusion Criteria

- Adult patients $\geq$ 18 years of age
- Receiving deceased donor kidney transplant
- Pre-transplant Ejection Fraction (within past 18 months) $\geq$ 50%
- Intraoperative or postoperative distributive shock (as described above) requiring vasopressor support

4.2 Exclusion Criteria

- Pregnant patients (they would be excluded from receiving a transplant)
- Prisoners
- History of mesenteric ischemia
- History of aortic dissection
- History of abdominal aortic aneurysm

- Allergy to mannitol
- Absolute neutrophil count < 1000 cell/mm3 (within past 18 months)
- Diagnosis of Raynaud's phenomenon, systemic sclerosis or vasospastic disease

4.3 Excluded or Vulnerable Populations

- n/a

5.0 ENROLLMENT

The patients at the top of the adult kidney transplant list awaiting DDKT maintained by UIHHSS Transplant will be used to screen for eligibility. See addendum for Eligibility Checklist. Study personnel will perform the screening. A password protected Microsoft Excel sheet will be provided by the Transplant team at UIHHSS. This sheet will have the MRN for the top patients on the kidney transplant list. If patients are initially eligible via inclusion and exclusion review, they will remain on the password protected Microsoft Excel sheet. If they are not eligible, they will be removed after screening by one of the study personnel. This password protected Microsoft Excel sheet will be maintained on the "H" drive behind the University firewall maintained by the CCTS. It is estimated that 40 subjects will be consented/enrolled in order for 20 patients to receive study drug. Twenty patients are the goal for this study and no more than 20 patients will receive study drug.

All eligible study subjects will receive a Research Letter (see addendum for Research Letter) via the mail. One week after the Research Letter is mailed, the subjects that have not called the primary investigator regarding the study will be called via telephone by study personnel to follow-up and provide any additional information regarding the study. This call is to provide information regarding the study, study enrollment criteria, and answer any questions regarding the study. This call is informational only.

If a kidney transplant is offered to the previously contacted subjects the study personnel will be contacted by the Transplant Coordinator when the kidney transplant is confirmed. Once that subject arrives at UI Health for their transplant, subjects will be approached by study investigators in-person, reminded of the study criteria, have ample time to review study information again and the informed consent document, and will be asked to provide signed consent after the appropriate informed consent process is completed. Researchers participating in the consent process will review the informed consent document (ICD) with the recruited subject in its entirety ensuring the subject understands the research purpose, all risks/benefits and the study components of this research.

Given the urgency surrounding the time course immediately before transplant (as noted in the Background/Rationale section above), it was deemed by the research team that the process of sending a Research Letter and following up via telephone is necessary in order to eliminate delay in the pre-op operations, avoid a coercive environment due to the time dependency of pre-op operations, minimize in-person interactions given the current state of COVID-19, and allow for ample time for information to be exchanged about the study. Additionally, given the lack of routine office visits prior to transplant there is no opportunity to consent these patients in clinic.

6.0 STUDY DESIGN AND PROCEDURES

This will be a single-center, prospective, observational study.

The prospective, observational study will include 20 consecutive patients receiving DDKT requiring intraoperative or postoperative vasopressors to assess the hemodynamic efficacy and safety and efficacy of Ang II (Giapreza).

The care process for this study of Ang II (Giapreza) in deceased donor kidney transplants (DDKT) at University of Illinois Hospital and Health Sciences (UIHHSS) will follow the exact same procedure as described above except (in bold and red):

PRE-TRANSPLANT – n/a

DURING TRANSPLANT

- The transplant operation begins.
- If intraoperative hypotension occurs (e.g. SBP < 120 mmHg) the attending surgeon and attending anesthesiologist will:
    - Give blood products first if patient bleeding
    - If not bleeding or hypotensive despite blood products, intravenous fluids will be given
    - If hypotensive despite intravenous fluids then the attending surgeon and attending anesthesiologist will assess for cardiogenic shock and if suspected give inotropes
    - If not in cardiogenic shock and hypotensive despite fluids (+/- inotropes) then **Ang II (Giapreza)** will be initiated as the first vasopressor given for the treatment of distributive shock.
        - **Ang II (Giapreza)** will be titrated intraoperative to achieve goal BP.
        - **Ang II (Giapreza) will be initiated following the FDA approved dosing in the package insert. This dosing includes a starting dose of 20 nanograms ng/kg/min. Titration will occur every 5 minutes by increments of up to 5 ng/kg/min as needed. During the first 3 hours, the maximum dose will not exceed 80 ng/kg/min. Maintenance dose will n exceed 40 ng/kg/min. Administration through a central venous line will be recommended.**
        - **If the maximum dose of AT II (Giapreza) is reached (80 ng/kg/min in the first 3 hours or 40 ng/kg/min thereafter), additional vasopressor selection and management will be at the discretion of the attending surgeon and attending anesthesiologist.**
        - **If additional vasopressors are needed beyond Ang II (Giapreza), all other vasopressors will be titrated off first.**
        - If the patient is unable to be titrated off the **Ang II (Giapreza)** intraoperatively, they will be continued postoperatively in the Intensive Care Unit (ICU) and titrated until the patients' blood pressure is stable without vasopressor support.
- If distributive shock does NOT occur intraoperatively, **Ang II (Giapreza)** will NOT be initiated.

AFTER TRANSPLANT

- If the patient is unable to be titrated off the **Ang II (Giapreza)** intraoperatively, they will be continued postoperatively in the Intensive Care Unit (ICU) and titrated until the patients' blood pressure is stable without vasopressor support.
- If the patient never received **Ang II (Giapreza)** intraoperatively and postoperative hypotension occurs (e.g. SBP < 120 mmHg) the attending surgeon or ICU team will:
    - Give blood products first if patient bleeding
    - If not bleeding or hypotensive despite blood products, then intravenous fluids will be given

- If hypotensive despite intravenous fluids then the attending surgeon and attending anesthesiologist will assess for cardiogenic shock and if suspected give inotropes
- If not in cardiogenic shock and hypotensive despite fluids (+/- inotropes) then **Ang II (Giapreza)** will be given as the first line vasopressor for the treatment of distributive shock.
- **Ang II (Giapreza)** will be titrated postoperatively to achieve goal BP and titrated until the patients' blood pressure is stable without vasopressor support.
    - **Ang II (Giapreza) will be initiated following the FDA approved dosing in the package insert. This dosing includes a starting dose of 20 nanograms ng/kg/min. Titration will occur every 5 minutes by increments of up to 5 ng/kg/min as needed. During the first 3 hours, the maximum dose will not exceed 80 ng/kg/min. Maintenance dose will n exceed 40 ng/kg/min. Administration through a central venous line will be recommended.**
    - **If the maximum dose of AT II is reached (80 ng/kg/min in the first 3 hours or 40 ng/kg/min thereafter), additional vasopressor selection and management will be at the discretion of the attending surgeon and attending anesthesiologist.**
    - **If additional vasopressors are needed beyond Ang II (Giapreza), all other vasopressors will be titrated off first.**
    - **If at any point the treating physician feels there is a safety concern with the study drug it can be discontinued immediately.**
- Ang II (Giapreza) and other vasopressor medications (if applicable) will be titrated postoperatively to achieve goal BP and titrated until the patients' BP is stable without vasopressor support.

- If distributive shock does NOT occur postoperatively, **Ang II (Giapreza) will NOT be initiated**

The study drug will be provided by La Jolla Pharmaceuticals for this study but they are not the study sponsor or providing any other financial support. Drug distribution will be managed by the Investigation Drug Service (IDS) at UI Health who has the capacity to retain all of the study drug in appropriate temperature-controlled settings. IDS will be used as this is a novel medication, not yet on formulary at UIHHSS, and this is a research investigation. They will maintain and dispense the medication for each kidney transplant in which subjects have consented in the event that vasopressors are required. Additionally, the medication will be ordered via Cerner/EPIC as a study medication and will be programmed into the Alaris pumps to be dosed via the dosing protocol listed above. Ang II (Giapreza) will not be used outside of the study protocol at our institution and will only be available under the electronic study order. Verifying pharmacists will be in-serviced regarding the study protocol and will be aware that this medication is only available and should be dispensed under the study order and as such not used in other contexts.

FOR STUDIES THAT COLLECT EXISTING OR PROSPECTIVE DATA

Health and laboratory data will be extracted manually from the electronic medical records (i.e. Cerner or Epic) for both arms of the study. Data will be prospectively captured over the course of 3 months after study initiation (i.e. using Ang II (Giapreza) for vasopressor management during kidney transplant) for the pilot. The data will be collected and input into a Redcap database for analysis. Data analysis will be performed using Spss.v25 computer software. Data collection will include the variables below.

Baseline characteristics:

-Age (years of age at the time of transplant)

-Gender (M/F)
-Race
A) White
B) Black
C) Asian
D) Hispanic
E) Other
-Weight (kilograms at time of transplant)
-Height (centimeters at time of transplant)
-Body mass index (kg/m^2 at time of transplant)
-Duration of time on hemodialysis (years)
-Donor baseline serum creatinine (mg/dL)
-Warm/cold ischemia time (hours)
-KDPI
-Baseline systolic/diastolic/mean arterial pressure (mmHg)
-Baseline heart rate (HR)
-Comorbidities
A) Hypertension
B) Hyperlipidemia
C) Heart failure with preserved ejection fraction
D) Arrhythmias
    -Atrial fibrillation
    -Other
E) Peripheral vascular disease
F) Coronary artery disease
G) Pulmonary hypertension
H) Diabetes
-Type I
-Type II

Intraoperative Hemodynamic Data Points:
-Intraoperative BP (SBP, DBP, MAP) every 5 minutes
-Intraoperative heart rate every 5 minutes
-Maximum dose of Ang II (Giapreza) (ng/kg/min)
-Duration of Ang II (Giapreza) (hours)
-Number of intraoperative vasopressors (if applicable)
-Intraoperative agents used in addition to Ang II (Giapreza) (if applicable)
-Dopamine (Y/N)
-Norepinephrine (Y/N)
-Epinephrine (Y/N)
-Phenylephrine (Y/N)
-Vasopressin (Y/N)
-Minimum intraoperative SBP and DBP (mmHg)
-Minimum intraoperative HR (bpm)

-Intraoperative volume resuscitation (L)
-Type of crystalloid and volume: 0.9% NaCl, PlasmaLyte, Lactated Ringers (L)
-Type of colloids and volume: Albumin, Hydroxyethyl Starch, Mannitol (L)
-Intraoperative blood product utilization (volume and type of blood products administered)

Post-operative Hemodynamic Data Points:
-Postoperative BP (SBP, DBP, MAP - mmHg) every 1 hour for the first 72 hours or duration of vasopressors (whichever is longer) after transplant
-Postoperative HR (bpm) every 1 hour for first 72 hours or duration of vasopressors (whichever is longer) after transplant
-Maximum dose of postoperative Ang II (Giapreza) ng/kg/min
-Maximum dose of postoperative other vasopressors (in norepinephrine equivalents – if applicable)
-Starting dose of postoperative Ang II (Giapreza) and other vasopressors (in norepinephrine equivalents – if applicable)
-Duration of postoperative vasopressors (hours – if applicable)
-Number of postoperative vasopressors (if applicable)
-Minimum postoperative BP (SBP, DBP, MAP – mmHg) in first 72 hours after transplant (in first 24hrs, second 24hrs, third 24 hrs, and total 72hrs)
-Minimum postoperative HR (bpm) in first 72 hours after transplant (in first 24hrs, second 24hrs, third 24 hrs, and total 72hrs)
-Maximum postoperative BP (SBP, DBP, MAP – mmHg) in first 72 hours after transplant
-Maximum postoperative HR (bpm) in first 72 hours after transplant
-Postoperative agents used:
-Dopamine
-Norepinephrine
-Epinephrine
-Phenylephrine
-Vasopressin
-Postoperative volume resuscitation (L in the first 24hrs, 48hrs, 72hrs)
-Daily intake volume (milliliters) during ICU admission
-Daily urine output volume (milliliters) during ICU admission
-Postoperative blood product utilization (volume and type of blood products administered during ICU admission after operating room)

Post-operative Clinical Data Points:
-Induction immunosuppression regimen
-Maintenance immunosuppression regimen
-First SCr, CrCl, calculated GFR after operating room (mg/dL)
-Daily SCr, CrCl, calculated GFR after operating room (mg/dL)
-Average SCr, CrCl, calculated GFR during hospitalization (mg/dL)
-First serum lactate after operating room (mmol/L)
-Peak serum lactate after operating room (mmol/L)
-Duration of elevated (> 2 mmol/L) lactate after operating room (mmol/L)
-Discharge SCr, CrCl, calculated GFR from hospital (mg/dL)

-1-month SCr, CrCl, calculated GFR, 3-month SCr, CrCl, calculated GFR
-Postoperative diuretic utilization (total milligrams of furosemide equivalents)
-Postoperative midodrine usage (total milligram during hospitalization), duration of usage (days), used upon discharge (Y/N)
-Postoperative mannitol utilization (Y/N)
-Baseline serum albumin (mg/dL)
-Need for renal replacement therapy in the first year after transplantation (Y/N)
-Mortality during hospital admission for kidney transplant
-Presumed or definitive allograft rejection rate during hospital admission for kidney transplant
-Biopsy needed to rule out rejection (Y/N)
-Calcineurin inhibitor (in tacrolimus equivalents) serum level at 1 week, 1-month, 3-month, 6-month
-Suspicion for other types of shock (e.g. sepsis, cardiogenic, hemorrhagic – as noted in chart documentation)

Safety data points*:*
Patients will be monitored according to standard monitoring for patients in the peri-operative transplant and collection of ADE will focus on those found in clinical studies using Ang II (Giapreza). The safety endpoints that will be captured will include: incidence of intraoperative arrhythmias for those who receive study drug intraoperatively (confirmed via EKG, flowsheet, or note documentation), incidence of postoperative arrhythmias occurring while receiving study drug postoperatively (confirmed via EKG, flowsheet, or note documentation), incidence of digital or other peripheral/visceral ischemia occurring during hospitalization for kidney transplant (as noted in chart documentation), incidence of venous or arterial thrombosis occurring during the hospitalization for kidney transplant (captured by ultrasound or other diagnostic imaging), incidence of thrombocytopenia while receiving study drug (as defined as platelet count < 50,000), incidence of post-operative fungal infections prior to discharge (as documented by the clinical care team), incidence of delirium while receiving study drug (as documented by the clinical care team), incidence of insulin infusion utilization while receiving study drug , pH values in the ICU at 24hrs, 48hrs, and 72hrs (if available). All of the noted safety variables above are routinely monitored for as part of ICU care.

Data Management
All patients that provide informed consent and receive Ang II (Giapreza) will have their data extracted. These patients will be considered included and associated with an alpha-numeric code that is linked to their medical record number (MRN). This list will be kept in a password protected Excel file on the primary investigator's computer stored on the H drive behind the University firewall on the primary investigator's password protected computer in a locked office. It will be available only to the co-investigators. Lastly, all data collected will not contain PHI and will be stored in Redcap.

All patients that provide informed consent but DO NOT receive Ang II (Giapreza) will be considered a screening failure and NO data will be extracted and they will not be associated with an alpha-numeric code linked to their MRN.

Records retention:
The data will be kept for a minimum of 6 years to meet HIPAA requirements, and after that time the data will be assessed to see if any additional information needs to be collected or any further studies will be conducted. If no further studies will be conducted, the primary investigator will destroy the data at that time.

7.0 EXPECTED RISKS/BENEFITS

The main anticipated benefit is the potential to establish improved hypotension management of future kidney transplant recipients at UIHHSS. This study could also potentially lead to further outcome studies on the effect vasopressors have on post-operative kidney transplant patients or studies directly comparing individual agents. Conversely, the expected risks are low given the existing data in critically ill patients with septic or other distributive shock. In the ATHOS-3 trial patients, the majority of patients evaluated were septic shock patients with a far greater severity of illness than kidney transplant recipients. In that investigation, there were no life-threatening ADE's and minimal that were greater than placebo: most common ADE (> 4% and > 1.5 x placebo) being: thromboembolic events, thrombocytopenia, tachycardia, fungal infection, delirium, acidosis, hyperglycemia, and peripheral ischemia. With all medications, there are risks of adverse reactions. All adverse reactions that occur at an incidence of greater than 4% (and > 1.5 x placebo) in the prescribing information will be discussed individually with the subject prior to informed consent. These data points will be collected as noted above in the data collection section. There is also the risk of poorer outcomes and overall health with this agent. As with all investigations, there is a risk of breach of PHI. However, this risk is very low due to the numerous safeguards in place as described above and from using data collection in Redcap. Additionally, password protection and the hospital firewall security further reduce the likelihood of breach of information.

8.0 DATA COLLECTION AND MANAGEMENT PROCEDURES

Subjects will be screened for eligibility by the study personnel. The investigators will review a list of kidney transplant patients maintained by the Transplant Coordinators for inclusion in the study. This list will be password protected and stored on the H drive behind the University firewall on the primary investigator's password protected computer in a locked office. If a subject is not eligible after reviewing inclusion and exclusion criteria, they will be removed from this list. All subjects that provide informed consent to receive Ang II (Giapreza) will remain on this list. If a subject is enrolled and receives Ang II (Giapreza), their de-identified data will be extracted and collected in Redcap. Additionally, they will be associated with an alpha-numeric code that is linked to their medical record number (MRN) and placed on a Study Subject list. This Study Subject list will be kept in a password protected Excel file on the primary investigator's computer stored on the H drive behind the University firewall on the primary investigator's password protected computer in a locked office. It will be available only to the co-investigators and research personnel. If a subject is enrolled and does not require Ang II (Giapreza) they will be considered a screening failure and their de-identified data will NOT be extracted or collected and their MRN will NOT be placed on the Study Subject list. All data points collected will be de-identified, containing no PHI and will be stored in Redcap. All study personnel will have access to the Redcap database.

9.0 DATA ANALYSIS

Statistical Analysis:
Continuous data -> Student t-test
Ordinal data -> Wilcoxon-Mann Whitney test
Nominal data -> Chi-square or Fisher's exact test
Multivariate regression analysis for factors associated with duration of vasopressors and worse kidney outcome

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

All personnel collecting data will be taught where to obtain the most accurate information from Cerner and Epic to capture the desired data points. After the first subject of the pilot is enrolled and discharged from the institution, data collected will be audited by the primary and co-investigators. Two additional audits will occur: one after 5 subjects collected and one after 10 subjects collected. If these audits reveal any discrepancies, additional audits will be performed on an as needed basis.

11.0 DATA AND SAFTY MONITORING

The study drug will be given by FDA approved dosing and used within label as perioperative hypotension (when systematically addressed as noted above) is a form of distributive shock. As with all FDA approved medications, adverse events are reported. Patients will be monitored according to standard monitoring for patients in the peri-operative transplant and collection of ADE will focus on those found in clinical studies using Ang II (Giapreza). The safety endpoints that will be captured will include: incidence of intraoperative arrhythmias for those who receive study drug intraoperatively (confirmed via EKG, flowsheet, or note documentation), incidence of postoperative arrhythmias occurring while receiving study drug postoperatively (confirmed via EKG, flowsheet, or note documentation), incidence of digital or other peripheral/visceral ischemia occurring during hospitalization for kidney transplant (as noted in chart documentation), incidence of venous or arterial thrombosis occurring during the hospitalization for kidney transplant (captured by ultrasound or other diagnostic imaging), incidence of thrombocytopenia while receiving study drug (as defined as platelet count < 50,000), incidence of post-operative fungal infections prior to discharge (as documented by the clinical care team), incidence of delirium while receiving study drug (as documented by the clinical care team), incidence of insulin infusion utilization while receiving study drug, pH values in the ICU at 24hrs, 48hrs, and 72hrs (if available). All of the noted safety variables above are routinely monitored for as part of ICU care.

The researchers will assess relatedness of the event to the study drug and will make every attempt to obtain enough information about the event to do so. Relationship of any AE to the use of study drug will be based on available information, using the following definitions:

Not Related: Another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event relative to initiation of study drug; and/or a causal relationship is considered biologically implausible.

Possibly Related: An event that follows a reasonable temporal sequence from administration of the Ang II (Giapreza) and in the investigators estimation follows a response pattern to the drug, but that could readily have been produced by a number of other factors.

Probably Related: An event that follows a reasonable temporal sequence from administration of the Ang II and there is a biologically plausible mechanism for Ang II (Giapreza) to cause or contribute to the AE and the event could not be reasonably explained by the known characteristics of the participant's clinical state.

For reporting purposes, both 'Possibly Related' and 'Probably Related' will be considered **Related**.

Adverse events will also be graded by severity according to CTCAE criteria.

-Grade 1: Mild; Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

-Grade 2: Moderate; Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

-Grade 3: Severe; Medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.

-Grade 4: Life-threatening consequences; urgent intervention indicated.

-Grade 5: Death related to AE.

Given this is a clinical trial a Data Safety Monitoring Board (DSMB) will be established. This board will be composed of two Critical Care Pharmacists (Eljim Tesoro and Keri Kim) with intimate knowledge of Ang II (Giapreza), vasopressors, Ang II (Giapreza) safety endpoints and no relationship to the conduct of the trial. This DSMB will review the safety endpoints collected above after 5, 10, 15, and 20 subjects are enrolled. They will be provided a Safety Summary Report for the allotted number of patients with "Relatedness" and Grading of captured ADE as described above.

Study Halting Criteria: For existing participants study drug will halt dosing immediately until further safety analysis and assessment by the DSMB can be completed and no further enrollment will take place until approved by the DSMB. The halting criteria are as follows:

- Two participants experience the same Grade 4 adverse event considered related to study drug
- 20% of the participants at time of analysis experience the same Grade 3 adverse event
- One participant experiences a Grade 5 AE considered related to study drug

Study can be restarted if the DSMB says it is okay to continue.

Subjects can withdraw from the study at any time. This withdrawal will not impact any portion of their care other than not being able to receive the study drug as it is not formulary approved at our institution. If a patient withdraws, their data will not be collected or used for analysis. Confidentiality will be maintained by using password protection for the Excel sheets, password protection for the computers used for storage of those Excel sheets, storing the sheet on the University H firewall behind the firewall and storing de-identified data within Redcap.

12.0 STATISTICAL CONSIDERATIONS

Given it is a sample size of convenience, no sample size calculation was performed.

13.0 REGULATORY REQUIREMENTS

13.1 INFORMED CONSENT

The patients at the top of the adult kidney transplant list awaiting DDKT maintained by UIHHSS Transplant will be used to screen for eligibility. See addendum for Eligibility Checklist. Study personnel will perform the screening. A password protected Microsoft Excel sheet will be provided by the Transplant team at UIHHSS. This sheet will have the MRN for the top patients on the kidney transplant list. If patients are initially eligible via inclusion and exclusion review, they will remain on the password protected Microsoft Excel sheet. If they are not eligible, they will be removed after screening by one of the study personnel. This password protected Microsoft Excel sheet will be maintained on the "H" drive behind the University firewall maintained by the CCTS. It is estimated that patients

will be required to be screened assuming a consent rate of ~50% and vasopressor utilization rate of ~50% of patients that receive a deceased donor kidney transplant. It is estimated that 40 subjects will be consented/enrolled in order for 20 patients to receive study drug. Twenty patients are the goal for this study and no more than 20 patients will receive study drug.

All eligible study subjects will receive a Research Letter (see addendum for Research Letter via the mail. One week after the Research Letter is mailed, the subjects will be called via telephone by study personnel to follow-up and provide any additional information regarding the study. This call is to provide information regarding the study, study enrollment criteria, and answer any questions regarding the study. This call is informational only.

If a kidney transplant is offered to the previously contacted subjects the study personnel will be contacted by the Transplant Coordinator when the kidney transplant is confirmed. Once that subject arrives at UI Health for their transplant, subjects will be approached by study investigators in-person, reminded of the study criteria, have ample time to review study information again, and will be asked to provide signed consent. Researchers participating in the consent process will review the informed consent document (ICD) with the recruited subject in its entirety ensuring the subject understands the research purpose, all risks/benefits and the study components of this research. If a subject does NOT provide informed consent they will be considered a screening failure and NO data will be extracted and they will not be associated with an alpha-numeric code linked to their MRN.

Given the urgency surrounding the time course immediately before transplant (as noted in the Background/Rationale section above), it was deemed by the research team that the process of sending a Research Letter and following up via telephone is necessary in order to eliminate delay in the pre-op operations, avoid a coercive environment due to the time dependency of pre-op operations, and allow for ample time for information to be exchanged about the study. Additionally, given the lack of routine office visits prior to transplant there is no opportunity to consent these patients in clinic.

Given the time-dependent nature of enrollment in the immediate pre-operative setting and the complexity of enrolling patients with interpreting services, in an effort to avoid coercion or misunderstanding, non-English speaking subjects will not be pursued for enrollment.

13.2 SUBJECT CONFIDENTIALITY

The investigators will review a list of the top patients awaiting kidney transplant maintained by the Transplant Coordinators. This list will be password protected. This list will be kept on the primary investigator's computer stored on the H drive behind the University firewall on the primary investigator's password protected computer in a locked office. It will be available only to the co-investigators. If a patient is screened as eligible and is consented they will be associated with an alpha-numeric code that is linked to their medical record number (MRN). This Study Subject list will be kept as a password protected Excel file on the primary investigator's computer stored on the H drive behind the University firewall on the primary investigator's password protected computer in a locked office. It will be available only to the co-investigators. If a patient requires AT II as their vasopressor and is included in the study, their data will be collected prospectively. These data points will be de-identified, containing no PHI and will be stored in Redcap. All study personnel will have access to the Redcap database. It would be impossible to screen for enrollment without using PHI. This PHI (e.g. MRN) will only be on the list provided by the Transplant Coordinators and the alpha-numeric list of patients included. These lists, as mentioned above, will be kept on a password protected computer.

13.3 UNANTICIPATED PROBLEMS

Though many circumstances have been foreseen, if any unforeseen circumstances arise such as any data breaches or other concerns, these will be reported immediately to the IRB by the primary investigator. Subjects will also be informed pending the instruction of the IRB based off of the problem that has occurred.

14.0 REFERENCES

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APPENDICES

- Appendix 1: Eligibility Checklist (attached)
- Appendix 2: Telephone Script (attached)
- Appendix 3: Angiotensin II (Giapreza) Package Insert (attached)
- Appendix 4: Research Letter