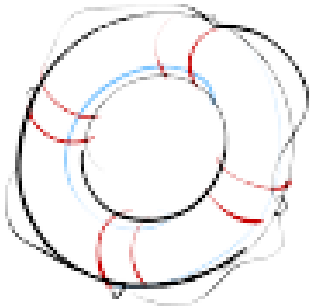
VA COOPERATIVE STUDY # 578 PREVENTION OF SERIOUS ADVERSE EVENTS FOLLOWING ANGIOGRAPHY (PRESERVE)



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A DEPARTMENT OF VETERANS AFFAIRS COOPERATIVE STUDY

VA COOPERATIVE STUDY # 578
PREVENTION OF SERIOUS ADVERSE EVENTS FOLLOWING ANGIOGRAPHY (PRESERVE):

A DEPARTMENT OF VETERANS AFFAIRS COOPERATIVE STUDY

TABLE OF CONTENTS

APPENDICES

EXECUTIVE SUMMARY

The intravascular administration of iodinated contrast media for diagnostic imaging is a common cause of acute kidney injury (AKI) and a leading cause of iatrogenic renal disease. Multiple studies have demonstrated that contrast-induced AKI (CIAKI) is associated with increased short-term mortality, prolonged hospitalization, increased medical resource utilization, and adverse long-term outcomes. CIAKI is a unique form of renal disease in that it is universally iatrogenic, its risk factors and pathophysiology are well-characterized, and its inciting event is highly predictable. All of these characteristics make CIAKI particularly amenable to preventive interventions.

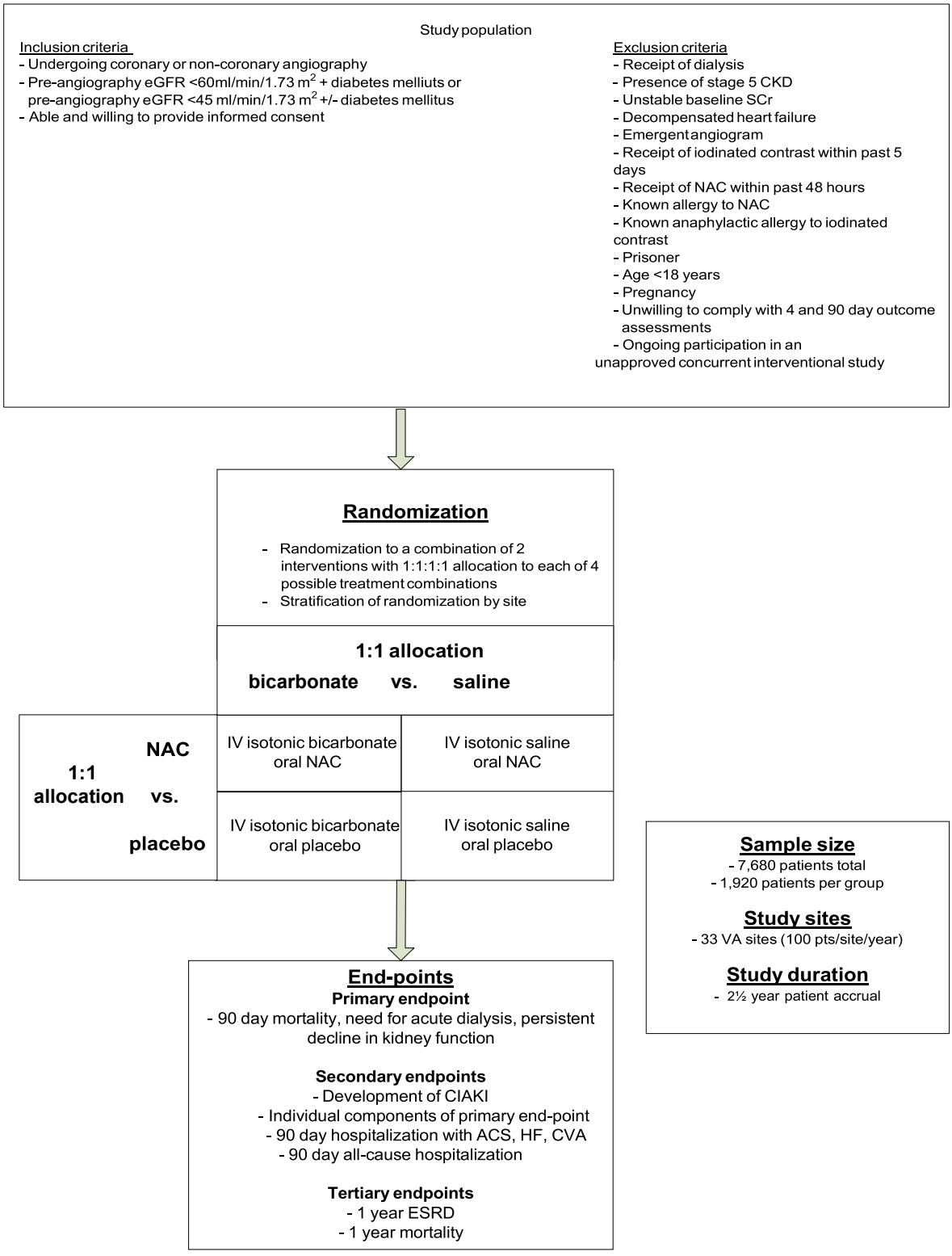
Intravenous (IV) isotonic fluid is the principal intervention with documented effectiveness for the prevention of CIAKI. Over the past half-decade, clinical trials have focused on the comparative effectiveness of IV sodium bicarbonate (bicarbonate) and IV sodium chloride (saline). While several trials demonstrated bicarbonate to be more effective than saline for the prevention of CIAKI, other trials reported no difference between these two IV fluids. Another preventive intervention for CIAKI that has received substantial attention over the past decade is peri-procedural administration of N-acetylcysteine (NAC), an anti-oxidant agent with vasodilatory properties. Published results regarding the efficacy of NAC are inconsistent. Multiple meta-analyses attempting to reconcile the conflicting studies on these interventions have themselves, been inconclusive. Consequently, there remains clinical equipoise regarding the superiority of bicarbonate (compared to saline) and role of NAC for the prevention of CIAKI.

We believe that there are three reasons that past trials and meta-analyses have not provided clear evidence to guide the use of bicarbonate and NAC for the prevention of CIAKI. First, all of the published clinical trials enrolled relatively small numbers of patients and most assumed unrealistically large effect sizes for the tested interventions. As a result, these studies were underpowered to detect biologically plausible, yet clinically important benefits of these interventions and were particularly susceptible to false positive and false negative results. Second, many trials included patients at low-risk for CIAKI, which resulted in relatively few primary study events and diminished the ability to discern the effects of these interventions in

higher-risk subjects, in whom they would theoretically have the greatest clinical utility. Third, and most importantly, nearly all prior trials used small absolute and/or relative increases in serum creatinine (SCr) as the primary study endpoint rather than serious, adverse patient-centered outcomes thought to represent downstream consequences of CIAKI (e.g., mortality, need for acute dialysis, or persistent decline in kidney function). While a multitude of studies have demonstrated that minor increases in SCr following angiography are associated with serious adverse events, it is unknown whether the prevention of small increases in SCr following contrast administration results in a reduction in clinically important patient-centered outcomes.

To assess the comparative effectiveness of bicarbonate and saline and the benefit of NAC, we propose to conduct a multicenter, randomized, clinical trial designed and adequately powered to evaluate these interventions for the prevention of clinically important, adverse, patient-centered outcomes in high-risk Veterans undergoing cardiac and non-cardiac angiography. In this trial, 7,680 patients scheduled to undergo coronary or non-coronary angiography who are at increased risk of developing CIAKI and experiencing serious downstream outcomes (i.e., diabetics with eGFR <60 ml/min/1.73 m^2 or any patient with eGFR <45 ml/min/1.73 m^2) will be enrolled. Using a 2 x 2 factorial design, patients will be randomized to receive: 1) either IV isotonic sodium bicarbonate or IV isotonic saline and 2) either oral NAC or oral placebo prior to and following the angiographic procedure. We will assess the effectiveness of bicarbonate compared to saline and NAC compared to placebo for the prevention of a composite primary endpoint consisting of clinically significant, patient-centered events including death, need for acute dialysis, or persistent decline in kidney function, all within 90 days following the index angiogram. As a secondary outcome, we will assess differences in the development of CIAKI, defined by an increase in SCr of at least 0.5 mg/dL and/or 25% at 4 days following angiography. By enrolling a large population of high-risk Veterans and comparing the effectiveness of these interventions for the prevention of clinically relevant outcomes, the findings of this trial will definitively establish the role of bicarbonate and of NAC for the prevention of serious, adverse patient-centered events following angiography and will help inform the care delivered to a very large and growing population of patients undergoing angiographic procedures within the VA Healthcare System and the broader medical community.

FIGURE 1 - OVERVIEW OF STUDY DESIGN



ABBREVIATIONS

AKI	acute kidney injury
ACS	acute coronary syndrome
BNP	brain natriuretic peptide
^{o}C	degrees centigrade
CI	confidence interval
CIAKI	contrast-induced acute kidney injury
CKD	chronic kidney disease
CSP	Cooperative Studies Program
CSPCC	Cooperative Studies Program Coordinating Center
CSPCRPCC	Cooperative Studies Program Clinical Research Pharmacy Coordinating Center
CVA	cerebrovascular accident
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
HF	heart failure
HR	hazard ratio
IV	intravenous
LOS	length of stay
MAVERIC	Massachusetts Veterans Epidemiology Research and Information Center
MI	myocardial infarction
NAC	n-acetylcysteine
NaCl	sodium chloride
$NaHCO_3$	sodium bicarbonate
NSTEMI	non-ST elevation myocardial infarction
OR	odds ratio
PCI	percutaneous coronary intervention
ROS	reactive oxygen species
RR	relative risk
RRT	renal replacement therapy
SCr	serum creatinine
STEMI	ST-elevation myocardial infarction

I. INTRODUCTION

Contrast-induced acute kidney injury (CIAKI) is defined by an abrupt loss of kidney function following the intravascular administration of iodinated contrast media. CIAKI occurs in a substantial proportion of high-risk patients following angiography and is associated with serious, adverse, short and long-term outcomes. CIAKI is one of the few preventable forms of acute kidney injury and substantial advancements in our understanding of its risk factors and pathogenesis have informed research efforts to identify safe and effective preventive interventions.

The cornerstone of preventive care for CIAKI is the administration of peri-procedure IV isotonic fluid. Recent clinical trials and meta-analyses suggest that IV isotonic sodium bicarbonate (bicarbonate) is more effective than IV isotonic sodium chloride (saline). However, these studies have significant limitations and definitive conclusions regarding the superiority of bicarbonate compared to saline have not been reached. Another promising preventive strategy is the provision of anti-oxidant therapy using N-acetylcysteine (NAC). Although some clinical trials and meta-analyses of NAC support its effectiveness, conclusive evidence is lacking due to limitations of the studies to date. Consequently, there continues to be clinical equipoise on the superiority of bicarbonate compared to saline and on the benefit of NAC for the prevention of CIAKI. Moreover, because the majority of past studies focused only on endpoints defined by short-term changes in kidney function, it is unknown whether the purported beneficial effects of these two interventions on the prevention of CIAKI translate into meaningful reductions in serious, adverse, patient-centered outcomes such as death, need for dialysis, or persistent decline in kidney function. Therefore, we propose to conduct a multicenter, randomized clinical trial to assess the effectiveness of IV isotonic bicarbonate compared with IV isotonic saline and oral NAC compared with oral placebo for the prevention of serious, adverse outcomes in high-risk Veterans undergoing coronary or non-coronary angiography.

II. STUDY HYPOTHESES AND OBJECTIVES

A. Study hypotheses

1. Compared to peri-procedural infusion of IV isotonic saline, peri-procedural infusion of IV isotonic sodium bicarbonate will decrease 90-day morbidity (i.e., need for acute dialysis, persistent decline in kidney function) and mortality in high-risk patients undergoing coronary or non-coronary angiography. The decrease in 90-day morbidity and mortality associated with sodium bicarbonate administration in high-risk patients will be mediated by a reduction in the incidence of contrast-induced acute kidney injury within 4 days of angiography.

2. Administration of NAC in the peri-procedural period will decrease 90-day morbidity (i.e., need for acute dialysis, persistent decline in kidney function) and mortality in high-risk patients undergoing coronary or non-coronary angiography. The decrease in 90-day morbidity and mortality associated with NAC administration in high-risk patients will be mediated by a reduction in the incidence of contrast-induced acute kidney injury within 4 days of angiography.

B. Study objectives

1. Primary Objectives
    a. To assess the effectiveness of IV isotonic sodium bicarbonate compared with IV isotonic saline for the prevention of 90-day adverse outcomes (i.e., death, need for acute dialysis, persistent decline in kidney function) in high-risk patients undergoing coronary or non-coronary angiography.
    b. To assess the effectiveness of NAC compared with placebo for the prevention of 90-day adverse outcomes (i.e., death, need for acute dialysis, persistent decline in kidney function) in high-risk patients undergoing coronary or non-coronary angiography.

2. Secondary Objectives
    a. Sodium bicarbonate versus saline
        i. To assess the effectiveness of IV isotonic sodium bicarbonate compared with IV isotonic saline for the prevention of CIAKI, defined by an increase in serum creatinine of ≥0.5 mg/dL and/or ≥25% at 4 days, in high-risk patients undergoing coronary or non-coronary angiography.

ii. To assess the effectiveness of IV isotonic sodium bicarbonate compared with IV isotonic saline for the prevention of the following outcomes within 90 days of coronary or non-coronary angiography in high-risk patients:
    a) death
    b) renal endpoints including need for acute dialysis or persistent decline in kidney function
    c) hospitalization with acute coronary syndrome, heart failure, or cerebrovascular accident
    d) all-cause hospitalization

b. NAC versus placebo
    i. To assess the effectiveness of NAC compared with placebo for the prevention of CIAKI, defined by an increase in serum creatinine of ≥0.5 mg/dL and/or ≥25% at 4 days, in high-risk patients undergoing coronary or non-coronary angiography.
    ii. To assess the effectiveness of NAC compared with placebo for the prevention of the following outcomes within 90 days of coronary or non-coronary angiography in high-risk patients:
        a) death
        b) renal endpoints including need for acute dialysis or persistent decline in kidney function
        c) hospitalization with acute coronary syndrome, heart failure, or cerebrovascular accident
        d) all-cause hospitalization

3. Tertiary Objective

To explore the comparative effectiveness of IV isotonic sodium bicarbonate versus IV isotonic saline and NAC versus placebo for the prevention of the following outcomes in high-risk patients within one year following coronary or non-coronary angiography:

a. end-stage renal disease
b. death

III. BACKGROUND

A. CIAKI: Definition, incidence, risk factors, and outcomes

1. Definition, incidence, and risk factors for CIAKI

Contrast-induced acute kidney injury (CIAKI) is defined as a sudden decline in kidney function following the intravascular administration of iodinated contrast media for diagnostic imaging.[1-3] While the threshold level of kidney injury used to define CIAKI varies across studies, the definition employed most commonly in research and clinical practice is an increase in the serum creatinine concentration (SCr) of at least 0.5 mg/dL and/or 25% within 3-4 days of contrast exposure.[4-6] Precise estimates of the incidence of CIAKI following angiography vary considerably based on patient characteristics, procedural factors, and the threshold change in SCr used to define this condition.[4, 7] We recently found that CIAKI occurred in 8.5% of clinically stable Veterans with eGFR <60 ml/min/1.73 m^2 undergoing non-urgent coronary angiography and 13.2% of clinically stable Veterans with eGFR <60 ml/min/1.73 m^2 undergoing non-urgent, non-coronary angiography.[8] Some studies demonstrate that up to 33% of very high-risk patients develop this condition following contrast-enhanced procedures.[9] This finding is particularly important given that more than 51,000 coronary and non-coronary angiograms are performed yearly within the VA Healthcare System involving patients at increased risk for CIAKI.

Past research has elucidated the principal patient and procedure-related risk factors for CIAKI (Table 1). Underlying kidney dysfunction is recognized as the most important risk factor for the development of CIAKI, with increasing levels of renal impairment associated with escalating levels of risk.[10] The presence of diabetes mellitus substantially amplifies the risk for CIAKI in patients with concomitant renal disease.[10-13] Patients with intravascular volume depletion are also susceptible to renal injury from iodinated contrast, as are patients with advanced heart failure.[10] In both clinical states, decreased effective circulating volume and reduced renal perfusion potentiate renal vasoconstriction following the administration of intravascular contrast. The risk of CIAKI increases with larger volumes of administered contrast.[14, 15] It is also believed that the risk for

Table 1 - Principal risk factors for CIAKI

- Underlying renal insufficiency
- Diabetes mellitus*
- Intravascular volume depletion
- Congestive heart failure
- Volume of contrast used
- Hyper-osmolal contrast media
- Intra-arterial contrast administration

*amplifies risk in the setting of renal insufficiency

CIAKI is greater following intra-arterial contrast administration than intravenous administration. Recognition of these major risk factors has helped providers more accurately identify which patients are most likely to develop CIAKI and has informed research efforts to assess the effectiveness of preventive interventions for this iatrogenic condition.

2. Association of CIAKI with clinically meaningful, patient-centered outcomes

a. Short-term mortality associated with CIAKI

Observational studies demonstrate an association between CIAKI (defined by small absolute and/or relative changes in SCr) and increased short-term mortality.[11, 16-22] In a retrospective study, Levy et al. found that the incidence of in-hospital death among 183 hospitalized patients who developed CIAKI (defined by an increase in SCr of ≥25% to at least 2.0 mg/dL) was 34% compared to 7% in 174 matched controls without CIAKI (unadjusted OR=6.5, p<0.001).[16] In analyses that accounted for underlying severity of illness, CIAKI remained a strong predictor of in-hospital death (OR=5.5, p<0.001). A subsequent study by McCullough et al. of 1,826 patients who underwent percutaneous coronary intervention (PCI) found an incidence of in-hospital mortality of 7.1% among patients who developed CIAKI (defined by an increase in SCr of >25%) compared to 1.1% in those without this change in SCr (p<0.0001).[11] In patients who developed CIAKI that required renal replacement therapy, in-hospital mortality was 35.7%. Six additional studies, including an analysis by our group of over 27,000 patients reported an independent association of CIAKI with short-term mortality (Table 2). [17-22]

Table 2 - Association of CIAKI with short-term mortality

Study authors	Number of patients	Definition of CIAKI	Adjusted OR[a]	95% CI
Bartholomew et al.[17]	20,479	↑ SCr ≥1.0 mg/dL	22	16 - 31
From et al.[18]	3,236	↑ SCr ≥25% or ≥0.5 mg/dL	3.4	2.6 - 4.4
Gruberg et al.[20]	439	↑ SCr >25%	3.9	2.0 - 7.6
Levy et al.[16]	357	↑ SCr ≥25% to ≥2.0 mg/dL	5.5	2.9 - 13.2
McCullough et al.[11]	1,826	↑ SCr >25%	6.6	3.3 - 12.9
Rihal et al.[21]	7,586	↑ SCr >0.5 mg/dL	10.8	6.9 - 17.0
Shema et al.[22]	1,111	↑ SCr ≥50% or ↓ eGFR ≥25%	3.9	1.2 - 12.0
Weisbord et al.[19]	27,608	↑ SCr 0.25-0.5 mg/dL	1.8	1.4 - 2.5

[a] OR denotes odds ratio for death

While consistent in demonstrating a strong relationship between small changes in SCr and short-term mortality, seven of these eight studies were retrospective analyses and hence, susceptible to ascertainment bias in the assessment of post-procedure SCr and to potential problems with missing data.[11, 16-19, 21, 22] However, prospective studies confirm these findings.[23, 24] A clinical trial by Marenzi et al. found that patients who developed CIAKI (defined by an increase in SCr of ≥25%) had a significantly increased incidence of in-hospital mortality compared to patients without this decline in renal function (26% v. 1.4%, $p<0.001$).[23] An even more recent trial of patients undergoing coronary angiography by Maioli et al. demonstrated that in-hospital mortality among patients who developed CIAKI (defined by an increase in SCr of ≥0.5 mg/dL) was markedly higher than among patients who did not develop this post-procedure complication (11.1% v. 0.2%, $p=0.001$).[24] Thus, data from observational studies and clinical trials support an association of small post-angiography decrements in renal function with short-term mortality.

b. Prolonged hospitalization and increased costs associated with CIAKI

A series of retrospective studies and clinical trials also document an association of CIAKI with other clinically-relevant short-term outcomes.[17, 19, 25-28] In our recent analysis of over 27,000 patients who underwent coronary angiography, a rise in SCr of 0.25 - 0.5 mg/dL was associated with a prolongation in hospital length of stay after adjusting for underlying severity of illness.[19] Progressively larger increases in SCr were associated with even longer lengths of stay. Bartholomew and colleagues found that patients who developed CIAKI after PCI were 15 times more likely to have their hospitalization prolonged more than four days.[17] In a clinical trial comparing IV fluids for the prevention of CIAKI, Adolph and colleagues found that patients with a post-angiography increase in SCr of ≥25% or ≥0.5 mg/dL remained in the hospital a mean of two days longer than patients without such an increase in SCr.[25] This extended length of hospital stay results in increased healthcare expenditures as documented in an observational study by our group.[27, 28] In our analysis of 598 diabetics with CKD undergoing coronary angiography, CIAKI (defined by a rise in SCr of ≥50%) was independently associated with a 2-fold increase in hospital costs.[27, 28] A study by Subramanian et al. that used a decision analytic model reported that CIAKI results in an average increase in hospital-related costs of more than $10,300 and 1-year costs in excess of $11,800.[26] Based on the number of angiograms performed across the United States, there may be 110,000 cases of angiography-associated CIAKI yearly

nationwide, with a cumulative cost of CIAKI of greater than $1.2 billion.[26, 29] Collectively, these data indicate that CIAKI is associated with prolonged hospitalization and substantial medical resource utilization, underscoring the significant economic implications of this iatrogenic condition.

c. Long-term adverse outcomes associated with CIAKI

In addition to increased short-term complications, CIAKI defined by small increases in SCr has also been linked with long-term mortality in recent studies (Table 3). [21, 30-34] Solomon et al. demonstrated that CIAKI following angiography (defined by an increase in SCr of ≥0.3 mg/dL) was associated with a greater than 3-fold increased risk of major adverse outcomes (death, stroke, myocardial infarction, end-stage renal disease requiring renal replacement therapy) at 1-year of follow up.[33] In an analysis by Harjai et al. of 985 patients who underwent PCI, CIAKI (defined by an increase in SCr of ≥0.5 mg/dL) was independently associated with increased mortality at 24 months of follow-up (HR=2.6; 95% CI: 1.5-4.4).[31] Four additional studies found an independent association of CIAKI with long-term mortality, although the study by Roghi et al. demonstrated a trend toward increased long-term mortality that did not reach statistical significance in multivariable analyses. [21, 30, 32, 34]

Table 3 - Association of CIAKI with long-term mortality

Study authors	Number of Patients	Definition of CIAKI	Follow-up (months)	Adjusted HR	95% CI
Brown et al.[34]	7,856	↑SCr ≥0.5 mg/dL	90	3.1	2.4 - 4.0
Goldenberg et al.[30]	78	↑SCr ≥0.5 mg/dL or ≥25%	60	2.7	1.7 - 4.5
Harjai et al.[31]	985	↑SCr ≥0.5 mg/dL	24	2.6	1.5 - 4.4
Rihal et al.[21]	7,075	↑ SCr >0.5 mg/dL	6	[a]	[a]
Roghi et al.[32]	2,860	↑SCr ≥0.5 mg/dL	24	1.8	1.0 - 3.4
Solomon et al.[33]	294	↑SCr ≥0.3 mg/dL	12	3.2 [b]	1.1 - 8.7

HR denotes hazard ratio for death

[a] HR not reported: 6-month mortality of 9.8% with CIAKI v. 2.3% without CIAKI (p<0.0001)

[b] reflects incident rate ratio of death, CVA, AMI, ESRD requiring renal replacement therapy

Past studies have also documented an association of CIAKI with more rapid progression of underlying CKD. Goldenberg and colleagues examined downstream outcomes among 78 patients with CKD and found that patients who manifested a transient post-procedure rise in SCr of ≥25% or ≥0.5 mg/dL following coronary angiography experienced a larger decrement in

eGFR two years following the procedure compared to patients without these small post-angiography increases in SCr (Δ eGFR = – 20 ± 11 ml/min/1.73 m^2 v. – 6 ± 16 ml/min/1.73 m^2, p=0.02).[30] In a study by Maioli et al., patients who developed CIAKI (defined by a rise in SCr of ≥0.5 mg/dL) had a 0.2 mg/dL higher mean SCr at one month post-angiography compared to patients who had not developed CIAKI (p=0.001).[24] Ribichini et al. demonstrated that patients who developed CIAKI following coronary angiography were more than five times as likely to manifest a ≥25% reduction in eGFR at 30 days compared to patients without CIAKI (OR=5.5, 95% CI: 2.2–13.3).[35] Finally, James et al. recently reported that patients who developed mild CIAKI following coronary angiography had a nearly 5-fold increased risk of experiencing a sustained reduction in kidney function at 90 days (adjusted OR=4.74, 95% CI: 3.92-5.74).[36] Patients who developed more severe CIAKI had a greater than 17-fold increased risk of persistent renal injury at 90 days following angiography (adjusted OR=17.3, 95% CI: 12.0-24.9), supporting a graded relationship between the severity of CIAKI and risk for sustained renal damage at 90 days. In this study, CIAKI was also associated with an increased risk of accelerated decline in kidney function, defined as a loss of eGFR >4 ml/min/1.73 m^2 per year over 2-3 years of follow up (OR=2.9, 95% CI: 2.2-3.7), as well as a markedly increased risk of ESRD over this same period of follow-up (OR=13.8, 95% CI: 7.4–25.9).[36] Collectively, these findings indicate that CIAKI, defined by small decrements in renal function, is associated with adverse long-term outcomes and more compromised renal function months to years following angiography.

d. Other data supporting a likely link between CIAKI and adverse outcomes

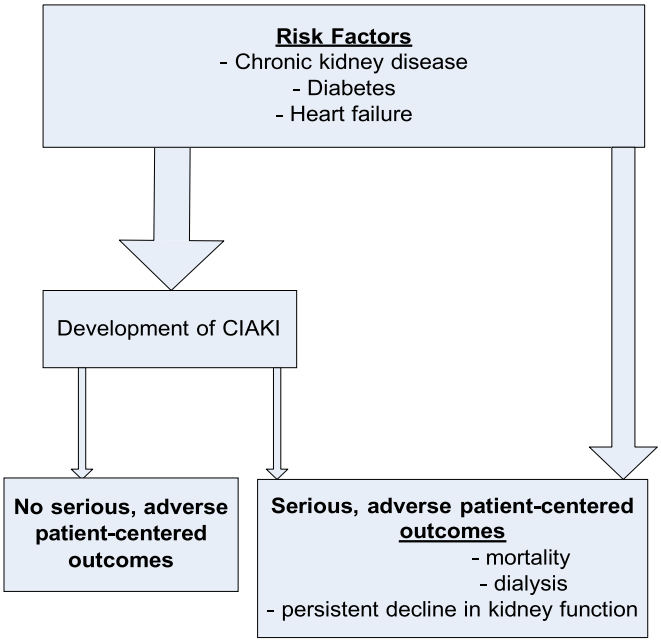
It is important to note that there are several lines of evidence that support the hypothesis that transient changes in SCr following angiography may mediate adverse renal and non-renal outcomes. First, mild AKI stemming from causes other than iodinated contrast (e.g., post-cardiac surgery, post-vascular surgery, following acute MI, medication-related) is independently associated with adverse outcomes including mortality and the development of ESRD.[37-40] Lassnig et al. demonstrated that increases in SCr of <0.6 mg/dL following cardiothoracic surgery were independently associated with a nearly 2-fold increase in 30-day mortality (HR=1.92, 95% CI: 1.34-2.77).[38] Similarly, in a study of over 87,000 patients, Newsome and colleagues demonstrated that increases in SCr of 0.3 to 0.5 mg/dL following acute MI were independently associated with an increased risk for ESRD (HR = 2.36, p<0.05) and long-term mortality (HR=

1.26, p<0.05).[40] Second, in animal models, there is persistent alteration in gene expression affecting the renal microvasculature and contributing to tissue calcification, inflammation, and fibrosis following recovery from ischemia-reperfusion injury.[41-46] Vascular dropout and renal fibrosis resulting from sustained injury to the renal microvasculature have been shown to be persistent sequelae of transient AKI and are believed to mediate a progressive and chronic decline in kidney function.[47] Moreover, immune up-regulation and T-cell infiltration of the kidney occur several weeks after ischemic renal injury and may be associated with long-term structural renal damage.[48] These downstream effects of transient AKI provide a biological basis for the link between mild decrements in SCr and progression of chronic kidney disease. Third, experimental models have demonstrated that transient ischemic renal injury is associated with the development of acute lung injury, cardiac apoptosis, and decreased heart function.[49, 50] Such extra-renal manifestations of transient AKI provide biological plausibility to the proposed link between AKI and adverse cardiovascular outcomes.

e. Importance of studying hard, patient-centered outcomes

Despite the abundance of epidemiological and experimental data associating small changes in SCr with adverse renal and extra-renal outcomes, the evidence remains inadequate to warrant the use of small changes in SCr as a surrogate primary endpoint in large transformative clinical trials. Although serious, downstream events following angiography occur as a consequence of CIAKI, they may also develop independent of this intermediate event, as many of the clinical conditions that predispose patients to the development of CIAKI (e.g., CKD, diabetes mellitus, heart failure) are also independently associated with mortality and other adverse outcomes (Figure 2). In

Figure 2 - Potential pathways to adverse patient-centered outcomes following angiography



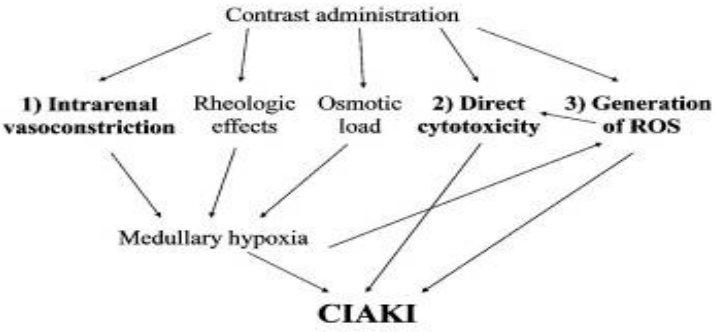
addition, not all episodes of CIAKI lead to clinically consequential sequelae. For this reason, we believe that it is most appropriate for a definitive trial of interventions for the prevention of CIAKI to demonstrate effectiveness in reducing serious, adverse, patient-centered outcomes rather than merely focusing on the amelioration of small changes in SCr. This view has been echoed by regulatory agencies including the United States Food and Drug Administration, which has indicated that small changes in SCr following contrast administration would not be an acceptable endpoint for trials seeking to register pharmaceutical agents for the indication of prevention of CIAKI.[51] While demonstrating the prevention of CIAKI is important for understanding the natural history of this condition, the prevention of more patient-centered outcomes is required for transformative clinical trials. Thus, our proposed primary endpoint is comprised of adverse, patient-centered events with the development of CIAKI serving as a key secondary endpoint.

B. Pathophysiology and prevention of CIAKI

1. Pathophysiology of CIAKI

Three principal mechanisms are thought to underlie the nephrotoxicity of iodinated contrast media (Figure 3).[52] First, the intravascular administration of iodinated contrast leads to transient systemic vasodilatation that is followed by intense constriction of intra-renal vascular beds. Vasoconstriction in the outer renal medulla, which has a particularly low baseline oxygen tension, leads to a mismatch of oxygen supply and demand resulting in ischemic tubular injury.[53-55] Second, iodinated contrast is directly toxic to renal tubular epithelial cells.[7, 56, 57] Third, the administration of iodinated contrast results in the generation of reactive oxygen species (ROS), which contribute to renal tubular cell injury.[58-60] Research elucidating these pathophysiologic processes has informed the development of interventions for the prevention of CIAKI.

Figure 3 – Pathophysiology of CIAKI



2. Prevention of CIAKI

Renal injury resulting from iodinated contrast is potentially preventable. Procedures that utilize intravascular contrast are usually scheduled in advance, providing sufficient time to implement preventive measures. Moreover, patients at increased risk for CIAKI are easily identifiable by the presence of known clinical risk factors. Past efforts to find effective preventive strategies for CIAKI have focused on four principal approaches: 1) use of less nephrotoxic contrast agents; 2) provision of pre-emptive renal replacement therapy to remove contrast from the circulation; 3) utilization of pharmacologic agents to counteract the nephrotoxic effects of contrast media; and 4) expansion of the intravascular space and enhanced diuresis with IV fluids.

Over the past 25 years, there has been considerable progress in developing less nephrotoxic contrast agents.[61] In the late 1980s, low-osmolal contrast replaced the considerably more nephrotoxic high-osmolal agents, resulting in a decreased incidence of CIAKI.[12, 62] Over the past decade, several trials have compared the renal effects of iso-osmolal and low-osmolal contrast media.[63-65] While these studies have yielded conflicting data regarding the relative risks of CIAKI with low versus iso-osmolal contrast media, it is clear that the incidence of CIAKI remains substantial in high-risk patients despite the use of these less nephrotoxic agents.[66-69]

Renal replacement therapies for the prevention of CIAKI have been largely ineffective, and in some instances, "prophylactic" hemodialysis has been associated with harm.[70-72] The interpretation of studies of hemofiltration for the prevention of CIAKI has been confounded by the use of change in SCr, a variable that is directly impacted by hemofiltration, as the primary study endpoint.[73, 74] As a result, use of dialysis or hemofiltration to prevent CIAKI is not currently recommended.[75]

Trials of pharmacologic agents, including furosemide, dopamine, fenoldopam, calcium channel blockers, and mannitol have failed to demonstrate benefit and in some cases have documented an increased risk of CIAKI.[9, 76-80] Studies on the benefit of natriuretic peptides, aminophylline, theophylline, statins, and ascorbic acid are mixed, yet the paucity of data on these interventions and potential safety concerns with natriuretic peptides, aminophylline, and theophylline has led experts to recommend against their routine use.[81] Based on a more complete understanding of the

pathophysiology of CIAKI, recent research has focused on assessing two specific preventive strategies: 1) the administration of IV fluids and 2) the use of antioxidant agents, most notably N-acetylcysteine (NAC).

3. Intravenous fluids for the prevention of CIAKI

Intravascular volume expansion with IV fluids is believed to have two actions that protect against the development of CIAKI. First, expansion of the intravascular space is thought to blunt the vasoconstrictive effect of contrast on the renal medulla due to the suppression of vasopressin, inhibition of the renin-angiotensin axis, and increased synthesis of vasodilatory renal prostaglandins.[82-86] Second, by decreasing the concentration and viscosity of contrast media in the tubular lumen, IV fluids are believed to attenuate the direct toxic effect of contrast agents on tubular epithelial cells.[87]

Several randomized clinical trials established the current evidence basis for the use of IV fluids to prevent CIAKI and provided preliminary data on the effect of IV fluid composition. In 1994, Solomon et al. tested the prophylactic effect of IV fluid alone or in combination with IV mannitol or furosemide.[79] Patients with CKD undergoing coronary angiography were randomized to receive IV 0.45% (half-isotonic) saline alone prior to and following angiography or in combination with either 25 gm of IV mannitol or 80 mg of IV furosemide prior to contrast administration. The incidence of CIAKI among patients who received IV fluids alone was 11% compared to 28% in the IV fluid plus mannitol group and 40% in subjects who received furosemide in addition to IV fluids (p=0.02 for comparison with IV fluid alone). While this trial did not include a control group of patients who did not receive IV fluid, Trivedi et al. subsequently confirmed the benefit of IV fluid in a small clinical trial of patients undergoing non-emergent coronary angiography.[88] Subjects in this study were randomized to receive either IV isotonic saline for 12 hours prior to and 12 hours following angiography or unrestricted oral fluids. The study was stopped at an interim analysis after 53 of 160 potential subjects had been enrolled when the rate of CIAKI was found to be nearly 10-fold higher in the oral fluid group compared to the IV saline group (34.6% v. 3.7%, p=0.005). The effect of tonicity of IV fluids on the development of CIAKI was assessed by Mueller and colleagues. Low-risk patients undergoing coronary angiography were randomized to receive peri-procedural IV volume

expansion with either 0.45% (half-isotonic) saline or 0.9% (isotonic) saline.[89] The overall rate of CIAKI was greater in patients who received half-isotonic saline compared to those who were administered isotonic saline (2% v 0.7%, P=0.04). On the basis of this study, it has generally been accepted that isotonic saline is superior to hypotonic saline for the prevention of CIAKI.

a. Clinical trials and meta-analyses of bicarbonate versus saline to prevent CIAKI

Recent research on IV fluids for the prevention of CIAKI has focused on identifying the optimal fluid composition; specifically, whether isotonic sodium bicarbonate (bicarbonate) is superior to isotonic sodium chloride (saline) for the prevention of CIAKI. One of the principal factors believed to be associated with the development of CIAKI is the generation of reactive oxygen species (ROS) in the kidney following contrast-induced ischemic injury to renal tubular cells (see Figure 3 above). Moreover, important clinical risk factors for CIAKI, including chronic kidney disease, diabetes, intravascular volume depletion, and heart failure are themselves associated with enhanced ROS formation.[60, 90-92] ROS are believed to contribute to a number of pathophysiologic processes that result in CIAKI-associated tubular damage. First, ROS are associated with the depletion of intracellular energy stores used for cellular reparative processes.[93, 94] Second, ROS may play an important role in potentiating intra-renal ischemia by generating and/or augmenting the effects of vasoconstrictors, including isoprostane, angiotensin II, and endothelin-I.[95-97] Third, ROS decrease the concentration and availability of the potent vasodilator nitric oxide, which leads to abnormal endothelial function, dysregulation of the renal microcirculation, and augmented renal hypoxia.[90, 98, 99] Fourth, ROS are hypothesized to impair cellular responses to ischemic injury.[100] Based on animal studies, the generation of ROS in the kidney is enhanced in acidic urine, and both ROS generation and tubular injury are attenuated by urinary alkalinization.[101] The theoretical underpinnings of the benefit of IV sodium bicarbonate for the prevention of CIAKI are based on the principal that urinary alkalinization with IV administration of bicarbonate will decrease the generation of ROS following contrast administration and mitigate these ROS-associated pathophysiologic processes that damage renal tubular cells. Over the past six years, ten clinical trials that compared IV isotonic bicarbonate with IV isotonic saline for the prevention of CIAKI have been published in the peer-reviewed literature. Six trials demonstrated a lower incidence of CIAKI with bicarbonate administration, whereas four showed no significant differences (Table 4).[24, 25, 102-109]

The disparate results of these ten clinical trials led to a proliferation of systematic reviews and meta-analyses comparing the effectiveness of bicarbonate and saline.[110-120] Of the eleven meta-analyses published to date, ten have reported a reduction in CIAKI with bicarbonate compared to saline.[111-120] However, these meta-analyses also describe substantial study heterogeneity and publication bias, which limited the ability of the investigators to draw definitive conclusions. Ten of these meta-analyses cite the need for large, adequately powered, multicenter, randomized trials comparing the effects of these two IV fluids on the prevention of CIAKI, and many suggest the need for such a study to be designed to detect differences in important patient-centered outcomes rather than merely focusing on the small changes in SCr used to define CIAKI.[111-120]

Table 4 - Clinical trials comparing IV isotonic bicarbonate and IV isotonic saline to prevent CIAKI

Authors	Number of patients	Diabetes	Baseline SCr (mg/dL)	Definition of 1^0 outcome	Frequency of CIAKI bicarbonate	Frequency of CIAKI saline	Dialysis	Death	PDKF[a]	Assumed effect size of bicarbonate
Positive studies										
Briguori et al.[103]	219	52%	2.0	↑ SCr ≥25%	1.9%	9.9%	1%	NA	NA	86%
Masuda et al.[104]	59	31%	1.3	↑ SCr ≥0.5mg/dL or ≥25%	6.6%	34.5%	7%	3%	NA	85%
Merten et al.[105]	119	48%	1.7-1.9	↑ SCr ≥25%	1.7%	13.6%	0%	NA	NA	66%
Ozcan et al.[106]	176	45%	1.4	↑ SCr ≥0.5mg/dL or ≥25%	4.2%	16.6%	1%	NA	NA	NR
Pakfetrat et al.[107]	192	30%	1.1	[c]	4.2%	12.5%	NA	NA	NA	NR
Recio-Mayoral et al.[108]	111	30%	1.0	↑ SCr ≥0.5mg/dL	1.8%	21.8%	4%	4.5%	NA	85%
Negative studies										
Adolph et al.[25]	145	34%	1.5-1.6	↑ SCr ≥0.5mg/dL or ≥25%	4.2%	2.7%	0%	NA	NA	87%
Brar et al.[102]	353	44%	1.5	↓ eGFR ≥25%	13.3%	14.6%	2% [b]	2% [b]	19% [b]	66%
Maioli et al.[24]	502	24%	1.2	↑ SCr ≥0.5mg/dL	10%	11.5%	<1%	1%	NA	50%
Vasheghani et al[d] [109]	265	22%	1.6-1.6	↑ SCr ≥0.5mg/dL or ≥25%	7.4%	5.9%	NA	NA	NA	71%

NA denotes not assessed; NR denotes not reported

[a] PDKF denotes persistent decline in kidney function

[b] outcomes assessed 2 weeks to 6 months following angiography

[c] three definitions of CIAKI assessed; differences between bicarbonate and saline based on ↑ SCr ≥0.3 mg/dL

[d] bicarbonate administered as 75 ml of 8.4% sodium bicarbonate added to 1 liter isotonic saline (i.e., hypertonic bicarbonate)

In an effort to reconcile the incongruent clinical trial findings, multiple systematic reviews and meta-analyses have been performed to analyze the collective results of these studies.[119, 121-137] In one of the more recent of these meta-analyses, Kelly and colleagues included 26 trials encompassing 3,393 patients.[138] Based on the pooled data, they calculated a 38% reduction in the risk of CIAKI associated with NAC (RR=0.62; 95% CI: 0.44-0.88). Although the investigators reported heterogeneity among the pooled studies, they found no evidence of publication bias. In another meta-analysis of 22 trials encompassing 2,746 patients published just 3 months earlier, Gonzalez et al. found significant heterogeneity among the trials.[127] In a cluster analysis, the investigators were able to divide the trials into two clusters that had minimal heterogeneity. One cluster that included trials in which NAC was found to be protective, was defined by an observed decline in SCr following contrast administration in the patients treated with NAC. In the studies included in the other cluster, there was no fall in SCr in the NAC-treated patients and no overall benefit for the prevention of CIAKI. The investigators concluded that NAC was not effective for the prevention of CIAKI. Thus, the conclusions of multiple meta-analyses of NAC are as disparate and inconclusive as the findings of the clinical trials that comprise these pooled analyses.

4. Clinical trials and meta-analyses of NAC for the prevention of CIAKI

The rationale for the use of NAC for the prevention of CIAKI relates to its capacity to scavenge ROS, reduce the depletion of glutathione, and stimulate the production of vasodilatory mediators including nitric oxide.[139, 140] Studies in animal models of AKI demonstrate that the administration of NAC reduces oxidative damage, attenuates outer renal medullary vasoconstriction, and decreases renal injury.[139, 141] These animal studies provided the scientific basis for clinical trials of NAC for the prevention of CIAKI.

Tepel et al. first described the efficacy of NAC for the prevention of CIAKI in humans a decade ago.[142] This trial randomized 83 patients undergoing computed tomography to receive 600 mg of NAC or placebo twice daily on the day prior to and the day of the procedure. Significantly fewer subjects treated with NAC developed CIAKI compared to patients in the placebo arm (2% v. 21%, p=0.01). A multitude of trials evaluating NAC for the prevention of CIAKI have since been published and have yielded highly conflicting results (Table 5). [23, 142-166]

Table 5 - Randomized clinical trials comparing NAC and placebo to prevent CIAKI

Authors	NAC dose	Number of patients	Definition 1^0 outcome	% CIAKI NAC	% CIAKI Control	Dialysis	Death	PDKF[a]	Assumed effect size NAC
Positive studies									
Baker et al[167]	[b]	80	↑ SCr ≥25%	5%	21%	0%	NR	NR	[c]
Balderramo et al[163]	1200 mg po x 2	61	↑ SCr ≥0.5 mg/dL	3%	7.1%	NR	NR	NR	90%
Diaz-Sandoval et al[160]	600 mg po x 4	54	↑ SCr ≥25%/0.5 mg/dL	8%	45%	NR	NR	NR	NR
Drager et al[159]	600 mg po x 4	24	mean Δ CrCl	NR	NR	NR	NR	NR	NR
Kay et al[146]	600 mg po x 4	200	↑ SCr ≥25%	4%	12%	0%	0%	NR	[c]
MacNeill et al[156]	600 mg po x 5	43	↑ SCr ≥25%	5%	32%	NR	NR	NR	NR
Marenzi et al[23]	[d]	352	↑ SCr ≥25%	11.6%	33%	2.6%	6%	NR	50%
Miner et al[166]	[e]	171	↑ SCr ≥25%	9.6%	22.2%	2%	5.5%	NR	50%
Ochoa et al[155]	1000 mg po x 2	80	↑ SCr ≥25%/0.5 mg/dL	8%	25%	NR	NR	NR	[c]
Shyu et al[151]	400 mg po x 4	121	↑ SCr ≥0.5 mg/dL	3.3%	24.6%	0.8%	NR	NR	[c]
Tepel et al[142]	600 mg po x 4	83	↑ SCr ≥0.5 mg/dL	2%	12%	0%	NR	NR	NR
Negative studies									
Allaqaband et al[150]	600 mg po x 4	80	↑ SCr ≥0.5 mg/dL	17.7%	15.3%	NR	NR	NR	NR
Amini et al[165]	600 mg po x 4	87	↑ SCr ≥25%/0.5 mg/dL	11.1%	14.3%	NR	NR	NR	90%
Azmus et al[161]	600 mg po x 4	399	↑ SCr ≥25%/↓eGFR 50%	7.1%	8.4%	0.5%	NR	NR	65%
Berwanger et al[168]	1200 mg po x 4	2,308	↑ SCr ≥25%	12.7%	12.7%	0.3%	2.0%	NR	30%
Briguori et al[144]	600 mg po x 4	183	↑ SCr ≥25%	6.5%	11%	0.5%	NR	NR	NR
Carbonnel et al[164]	600 mg IV x 4	216	↑ SCr ≥25%/0.5 mg/dL	10.3%	10.1%	0%	3.7%	NR	NR
Coyle et al[145]	600 mg po x 4	137	mean Δ SCr	NR	NR	NR	NR	NR	[c]
Durham et al[149]	1200 mg po x 2	79	↑ SCr ≥0.5 mg/dL	26.3%	22%	2.5%	NR	NR	NR
Fung et al[148]	400 mg po x 6	91	↑ SCr ≥25%/↓eGFR 50%	13.3%	17.4%	0%	NR	NR	90%
Goldenberg et al[158]	600 mg po x 6	80	↑ SCr ≥0.5 mg/dL	10%	8%	0%	0%	NR	90%
Gomes et al[147]	600 mg po x 4	156	↑ SCr ≥0.5 mg/dL	10.4%	10.1%	1.3%	4.5%	NR	50%
Kefer et al[157]	1200 mg IV x 2	104	↑ SCr ≥25%/0.5 mg/dL	3.8%	5.9%	0%	NR	NR	NR
Oldemeyer et al[154]	1500 mg po x 4	96	↑ SCr ≥25%/0.5 mg/dL	8.2%	6.4%	0%	NR	NR	NR
Rashid et al[153]	1000 mg IV x 1	94	↑ SCr ≥25%/0.5 mg/dL	6.5%	6.3%	NR	NR	NR	90%
Sandhu et al[152]	600 mg po x 4	106	↑ SCr ≥0.5 mg/dL	5.7%	0%	NR	NR	NR	NR
Webb et al[162]	500 mg IV x 1	487	↓ CrCl >5ml/min	23.3%	20.7%	0%	2.5%	NR	50%

NR denotes not reported

[a] PDKF denotes persistent decline in kidney function

[b] 150 mg/kg IV x 1 hr pre and 50 mg/kg IV x 4 hrs post-angiography

[c] effect size based on difference in mean change of SCr

[d] 2 NAC groups: standard dose = 600 mg IV and 600 mg po x 4; high dose = 1200 mg IV and 1200 mg po x 4

[e] 2000 mg po either x2 or x3

As with the trials comparing bicarbonate and saline for the prevention of CIAKI, the primary endpoints in all of the trials of NAC were based on small changes in SCr. This includes the most recently published ACT trial, which compared oral NAC to oral placebo in 2,308 patients undergoing angiography.[168] While this study did not demonstrate a benefit to NAC for the prevention of CIAKI, a small minority of patient-participants had underlying CKD (N=367) and hence, most were at minimal risk for renal injury. While approximately half of the trials of NAC tracked short-term need for dialysis, few assessed other clinically-relevant, adverse outcomes such as death or persistent decline in kidney function and none were powered to assess the effectiveness of NAC in preventing these patient-centered outcomes. One trial by Marenzi et al. demonstrated that in addition to preventing CIAKI, NAC was associated with a reduction in death and the need for dialysis.[23] Thus, there is a paucity of data on the effectiveness of NAC for the prevention of serious, adverse, patient-centered events following angiographic procedures.

5. Interaction between bicarbonate and NAC

There are limited data evaluating the interaction between bicarbonate and NAC in the prevention of CIAKI.[103, 108, 118, 119, 169] Using an experimental model, Romano et al. found no interaction between bicarbonate and NAC in the prevention of renal tubular cell apoptosis following exposure to iodinated contrast media.[169] In a recent systematic review and meta-analysis of IV sodium bicarbonate for the prevention of CIAKI, Zoungas et al. identified four studies which included data on 983 patients that evaluated combined treatment with sodium bicarbonate and NAC.[118] They observed no difference in the incidence of CIAKI following sodium bicarbonate administration with or without concomitant administration of NAC (p for heterogeneity = 0.73). Similar results were also seen in a meta-analysis by Brown et al.[119]

6. Summary of limitations of prior studies that evaluated bicarbonate and NAC for the prevention of CIAKI

We believe that there are common limitations of past trials comparing isotonic sodium bicarbonate to isotonic saline and prior trials evaluating NAC for the prevention of CIAKI. First, all of the published studies have been relatively small. The median number of patients enrolled in the trials comparing bicarbonate to saline was 184 (IQR 119, 265), while the median number of patients enrolled in the trials of NAC was 96 (IQR 80, 183). These small sample sizes mean that the individual studies only had adequate statistical power to detect clinical effects of such

magnitude that they are unlikely to be biologically plausible, while failing to detect benefits that were smaller and more plausible, yet still clinically meaningful. Second, all of the studies used small, short-term changes in SCr as their primary endpoint. While these changes in SCr have been used to define CIAKI, they have not been validated as a surrogate endpoint for patient-centered outcomes, including death, need for dialysis or persistent decline in kidney function. None of the trials to date has been designed with sufficient statistical power to detect differences in these clinically meaningful, patient-centered outcomes. Finally, many of the studies enrolled patients at relatively low-risk for the development of CIAKI, further diminishing the likelihood that a relatively small study could detect a meaningful clinical benefit. These limitations were well summarized by Bagshaw et al. in a 2006 review of the use of NAC in preventing CIAKI: "…given the clinical trial data published to date, meta-analyses cannot resolve the uncertainty engendered by 19 small [randomized clinical trials] with heterogeneous results for a surrogate outcome (change in serum creatinine level rather than "harder" end points, such as need for dialysis or mortality)…Ultimately, a much larger trial with high methodologic quality that involved multiple centers to achieve sufficient power to study clinically meaningful outcomes is needed……." [170] We believe these comments are equally applicable to the primary studies and meta-analyses comparing bicarbonate to saline.

C. Clinical implications of the equipoise on the effectiveness of bicarbonate and NAC

The lack of consensus on the role of bicarbonate and NAC for the prevention of CIAKI is evident from the inconsistent use of prophylactic regimens in clinical practice. We recently completed a prospective, observational study of 239 Veterans with CKD who underwent non-emergent coronary or non-coronary angiography.[171] Nearly 20% of patients did not receive any peri-procedural IV fluid. Of patients who received pre-procedure IV fluid, 66% received bicarbonate and 34% received hypotonic or isotonic saline. Of patients who received post-procedure IV fluid, 44% were administered bicarbonate and 56% received hypotonic or isotonic saline. One hundred and eighty-six (78%) of the 239 patients received NAC. However, 24 (12%) patients who received NAC did not receive any IV fluid, despite the absence of any studies conclusively and definitively demonstrating the effectiveness of NAC.

In this same study, we surveyed 87 VA providers on their knowledge of the effectiveness of different interventions for the prevention of CIAKI.[172] Nearly half of providers (48%) reported

that bicarbonate is ineffective for the prevention of CIAKI or were unsure of its effectiveness, while 54% reported NAC to be effective, 24% reported NAC to be ineffective, and 22% were unsure of its effectiveness. These observations reflect the clinical equipoise on the comparative effectiveness of bicarbonate and saline and benefit of NAC.

There are also data suggesting that that the failure to establish a solid evidence basis for the prevention of CIAKI and its adverse medical outcomes has contributed to the under-utilization of clinically indicated coronary angiograms in patients with CKD. Chertow and colleagues conducted an analysis of more than 55,000 patients to assess whether patients with CKD who were diagnosed with an acute MI underwent coronary angiography at a rate comparable to patients with intact kidney function.[173] While the provision of coronary angiography was associated with a significant reduction in mortality (OR=0.62; 95% CI: 0.54-0.70), those with CKD deemed to be appropriate candidates for this procedure were less than half as likely to undergo angiography compared to patients without CKD (OR=0.47; 95% CI: 0.40-0.52). Although the authors did not systematically examine the reasons for under-utilization of angiography in individuals with CKD, they posited that concern for the development of CIAKI may explain this finding. A subsequent study by Han et al., which included 45,343 patients with non-ST elevation MI, of whom 6,560 had moderate to advanced CKD, reported that the presence of CKD was independently associated with a nearly 50% decreased likelihood of undergoing coronary angiography with PCI (adjusted OR=0.52; 95% CI: 0.34-0.80). The investigators concluded that fear of CIAKI was a principal reason for this finding.[174] Finally, a recent study by Goldenberg et al. examined utilization of and outcomes after coronary angiography in over 13,000 patients with non-ST elevation ACS, more than one-third of whom had CKD. While the use of coronary angiography in patients with CKD was associated with a 36% lower risk of in-hospital mortality, considerably fewer patients with CKD underwent this procedure compared to patients without CKD (49.9% v. 67.8%, $p<0.001$).[175] One of the conclusions drawn by the investigators was that measures for the prevention of CIAKI should be implemented to facilitate the delivery of appropriate care to patients with CKD.

The clinical equipoise and absence of consensus on the comparative effectiveness of bicarbonate and saline and benefit of NAC is perhaps best exemplified by two recent clinical practice guidelines. The European Society of Intensive Care Medicine advocates the administration of IV

isotonic sodium bicarbonate rather than IV isotonic sodium chloride (grade 2B recommendation), yet recommends against the use of N-acetylcysteine (grade 2B recommendation) for the prevention of CIAKI.[176] In contrast, while guidelines from the Kidney Disease: Improving Global Outcomes (KDIGO) initiative recommend that providers administer isotonic IV crystalloid to prevent CIAKI, they specifically do not differentiate between use of sodium bicarbonate or sodium chloride (grade 1A recommendation).[177] Moreover, the KDIGO guidelines recommend the use of NAC (grade 2C recommendation) for the prevention of CIAKI. Thus, two clinical practice guidelines differ substantially in regard to their recommendations for the use of bicarbonate and NAC to prevent CIAKI.

D. Summary

CIAKI is a common complication of angiographic procedures in high-risk patients and is associated with serious adverse outcomes. Greater understanding of its risk factors and pathophysiology has informed research on preventive strategies. Although the two most promising preventive interventions are isotonic sodium bicarbonate and NAC, multiple clinical trials evaluating these interventions have yielded highly conflicting results. Past trials have been limited by the enrollment of inadequate numbers of patients based on implausibly large effect sizes; the inclusion of patients at relatively low risk for adverse outcomes; and the reliance on small and transient changes in SCr as a surrogate study endpoint, rather than clinically meaningful, patient-centered events. Finally and most importantly, past studies of preventive strategies were not designed or powered to determine the impact of bicarbonate or NAC on serious, adverse, patient-centered outcomes. The absence of a consensus on the benefit of these interventions has led to non-uniform implementation of these measures in clinical practice and may be a factor in the under-utilization of clinically indicated and potentially life-saving angiographic procedures in patients with CKD. Considered collectively, these observations underscore the need for a large, adequately powered, multicenter clinical trial to assess the effectiveness of bicarbonate compared to saline and NAC compared to placebo for the prevention of serious, adverse, patient-centered outcomes in high-risk patients undergoing angiographic procedures.

IV. SIGNIFICANCE OF THE PROPOSED RESEARCH TO THE VA

Approximately 3.6 million coronary and non-coronary angiograms are performed in the United States each year.[29] Using conservative estimates of the incidence of CIAKI in this broad patient population, which includes individuals with and without underlying risk factors for CIAKI, we estimate that there are at least 110,000 cases of angiography-associated CIAKI in the United States on an annual basis.[2, 12, 29] In addition to the serious medical outcomes associated with CIAKI reviewed above, the financial costs of this condition are substantial. A single episode of CIAKI is associated with an average one-year cost in excess of $11,800.[26] Applying this estimate to the calculated number of angiography-associated cases of CIAKI yields an annual cost estimate for this iatrogenic complication of approximately $1.3 billion. Given the associated morbidity, mortality, and financial costs, CIAKI has been identified as an important public health problem. The National Quality Forum, a national non-profit organization that aims to improve healthcare quality for Americans by setting national priorities and goals for quality improvement, has included prevention of CIAKI as one of 34 recommendations for safe clinical practice that should be universally implemented.[178]

Within the VA Healthcare System, there are more than 51,000 coronary and non-coronary angiograms performed each year involving Veterans with chronic kidney disease (CKD). As a result, there are likely many thousands of Veterans who develop angiography-associated CIAKI each year. Several epidemiological and clinical observations suggest that the incidence of CIAKI following angiography is likely to increase substantially within the VA Healthcare System. First, CKD, which is a principal risk factor for CIAKI and other adverse events following angiography, affects more than 550,000 Veterans nationwide and due to an aging Veteran population, is likely to substantially increase in prevalence over the next decade. Second, diabetes mellitus, which amplifies the risk for CIAKI in patients with underlying CKD and is an independent predictor of adverse outcomes following angiography, affects over 1,000,000 patients within the VA and is increasing in prevalence. Third, patients with CKD who undergo magnetic resonance angiography with gadolinium-based contrast agents have been shown to be at risk for nephrogenic systemic fibrosis, a debilitating and potentially fatal disorder.[179] As a result, many patients who in years past would have undergone magnetic resonance angiography will now likely undergo conventional angiography with iodinated contrast, increasing the number of patients at risk for CIAKI and angiography-related adverse events. In fact, a recent study by Kim

et al. confirmed that following the initial public health advisory in 2006 regarding the association of gadolinium-based contrast agents with nephrogenic systemic fibrosis, there was a 71% decrease in the number of gadolinium contrast-enhanced MRI procedures performed within the VA Healthcare System among Veterans with eGFR <30 ml/min/1.73 m^2.[180] Thus, a large and growing number of high-risk Veterans will be undergoing angiographic procedures that will place them at risk for CIAKI and its serious, adverse sequelae. The findings of this proposed comparative effectiveness trial to prevent serious, adverse patient-centered outcomes will be directly applicable to this large and growing population of Veterans.

The proposed clinical trial is focused on angiographic procedures because the risk for CIAKI and its associated serious, adverse downstream outcomes is believed to be greater following intra-arterial compared to intravenous injection of iodinated contrast. However, intravenous administration of iodinated contrast also poses a risk for adverse events in Veterans with advanced CKD. There are many more contrast-enhanced computed tomography scans performed each year within the VA than angiographic procedures. While many thousands of Veterans likely develop CIAKI annually following angiography, a considerably larger number of patients likely develop this condition following contrast-enhanced computed tomography. Findings from the proposed trial will be applicable to the tens of thousands of Veterans with advanced CKD who undergo contrast-enhanced computed tomography scans each year and will inform the delivery of preventive care to this additional large and growing patient population.

We previously demonstrated that the use of bicarbonate and NAC in high-risk Veterans undergoing angiography is highly variable.[8] This prior study found that providers administer NAC in lieu of IV fluids in a substantial proportion of patients at risk for CIAKI. This sub-optimal care can be explained by the documented uncertainty of VA providers on the effectiveness of bicarbonate and NAC.[172] The proposed comparative effectiveness trial will resolve the clinical equipoise regarding these interventions and facilitate the uniform implementation of evidence-based preventive care to Veterans undergoing angiographic procedures.

By determining the effectiveness of bicarbonate compared to saline and of NAC compared to placebo, the findings of this clinical trial will provide a solid evidence basis that VA providers

will be able to use to decrease the incidence of serious, adverse, patient-centered outcomes in the large and growing population of Veterans who are at-risk for preventable complications of contrast administration.

V. OVERVIEW OF STUDY DESIGN

The proposed comparative effectiveness study is a multicenter, randomized, double-blind clinical trial that will use a 2 x 2 factorial design to assess the effectiveness of IV isotonic sodium bicarbonate compared to IV isotonic saline and NAC compared to placebo for the prevention of serious, adverse, patient-centered outcomes in high-risk patients undergoing coronary or non-coronary angiography. The primary hypotheses to be tested are that isotonic bicarbonate is more effective than saline and that NAC is more effective than placebo for the prevention of serious morbidity and mortality following coronary and non-coronary angiography in high-risk Veterans. Each of these two hypotheses are of equal importance as there is clinical equipoise on both the comparative effectiveness of bicarbonate and saline and the benefit of NAC. Moreover, despite the lack of any data establishing the efficacy of NAC in the absence of concomitant IV fluids, our data indicate that as many as 12% of high-risk Veterans receive this anti-oxidant in lieu of any IV fluids (*vide supra*).[8] We believe that the beneficial effects of these interventions on adverse outcomes will be mediated through a reduction in the development of CIAKI.

Patients will be enrolled if, at the time of angiography, they have underlying CKD with an eGFR <60 ml/min/1.73 m^2 and a diagnosis of diabetes mellitus, or an eGFR <45 ml/min/1.73 m^2 regardless of whether or not they have diabetes mellitus. Eligible patients who consent to participate will be randomized prior to angiography to receive: 1) IV isotonic bicarbonate or IV isotonic saline and 2) oral NAC or oral placebo. Randomization will be stratified by site. At least 3 ml/kg of the IV isotonic study crystalloid solution (sodium bicarbonate or saline) will be infused over a minimum of 1 hour at an infusion rate of not less than 1 mL/kg per hour and not more than 3 mL/kg per hour immediately prior to the angiographic procedure; 1-1.5ml/kg per hour will be infused during angiography; and at least 6 ml/kg will be administered during over at least 2 hours at an infusion rate of not less than 1 mL/kg per hour and not more than 3 mL/kg per hour following the procedure. This approach will ensure the provision of a minimum necessary volume of IV fluid, yet permit providers to administer additional study IV fluid as they deem clinically appropriate based on their assessment of individual patients. In patients who are obese (BMI >30 kg/m^2) and weigh more than 125 kg, calculated rates of fluid administration should be capped based on a weight of 125 kg. NAC or placebo will be administered in an oral dose of 1200 mg twice daily beginning on the day of angiography and continuing for a total of 5 days.

The primary study outcome will be a 90-day composite end-point comprised of death, need for acute dialysis, or persistent decline in kidney function, defined based on an increase in SCr at 90 days of ≥50% relative to baseline. The development of CIAKI, defined by an increase in SCr of ≥0.5 mg/dL and/or ≥25% at 4 days following contrast administration will be assessed as a secondary outcome. As additional secondary outcomes, we will evaluate death, the renal components of the primary composite endpoint (i.e., need for acute dialysis, persistent decline in kidney function), hospitalization with major adverse cardiac events (i.e., ACS, HF, CVA), and all-cause hospitalization. We will assess the development of ESRD and mortality at 1 year as a tertiary (exploratory) outcome.

Based on analyses of over 25,000 Veterans with CKD who underwent angiography within the VA Healthcare System, we estimate that the baseline incidence of our primary study endpoint among eligible patients is 8.7%. Using this rate in the control arms of our study allows us to more conservatively estimate the overall event rate to be 7.6%. Considering these estimates, an intervention effect size of 25%, the absence of an interaction between our two interventions, a two-sided alpha of 0.025, and anticipated loss to follow-up of 3%, 7,680 patients (1,920 patients per treatment cell) will be required to test the primary hypothesis with 90% power. Thirty-three VA sites will be expected to enroll an average of 100 patients per year during the 2½ year recruitment period.

Table 6 - Overview of data collection

	Screening and Eligibility	Pre-angiography	Post-angiography (prior to discharge)	12 hours – 4 days post-angiography	4 days post-angiography	5-8 days post-angiography	35-49 days post-angiography	90 days post angiography	1-Year post angiography
Informed consent obtained	X								
Clinical care SCr	X [a]				X				
Eligibility criteria	X [b]								
Study Scr		X [d]			X [d]			X [d]	
Subject contact info, military history		X							
Medications		X	X	X [e]					
Weight, blood pressure		X [c]							
Urine protein, albumin, Cr		X [i]							
Hemoglobin, glucose, electrolytes, BUN, HCO_3 [a]		X [a, h]							
Hemoglobin A1C (if diabetic)		X [g, h]							
Demographics		X [h]							
Medical comorbidities		X [h]							
Non-study IV fluid administration		X	X						
Urine pH			X						
Procedural data/complications			X						
Post-angiography events			X	X [e]					
NAC pill count						X			
Assessment of adverse events		X	X	X	X	X	X	X	
Assessment of 1^0 outcome								X	
Assessment of 2^0 outcomes					X [f]			X	
Assessment of ESRD									X
Assessment of long-term mortality									X

[a] denotes labs or procedures performed as part of routine clinical care by providers within 30 days prior to angiography

[b] eligibility based on eGFR calculated from SCr performed as part of routine clinical care within 30 days prior to angiography. If no Scr measurement was taken within 30 days prior to angiography, the patient's consent will be sought and if obtained, a blood sample will be drawn for Scr measurement at the site's VA laboratory to determine eligibility.

[c] blood pressure denotes measurement taken as part of routine clinical care within 3 days prior to angiography; weight is most recent weight in medical record or by patient report or coordinator measurement

[d] denotes SCr sent to central study laboratory for endpoint ascertainment

[e] denotes information collected on subjects who remain hospitalized following angiography or who return to the hospital within 4 days of angiography

[f] denotes assessment of CIAKI based on 4-day study SCr

[g] denotes labs performed as part of routine clinical care by providers within 1 year prior to angiography

[h] depending on the time constraints prior to angiography, this data may be collected immediately following the angiography procedure.

[i] denotes urine sample collected prior to contrast administration and tested in the site's VA laboratory

VI. STUDY POPULATION AND PATIENT RECRUITMENT

A. Study population

The study population will consist of outpatients and inpatients undergoing coronary or non-coronary angiography at any of the study sites who are at high risk for the development of CIAKI and its serious, adverse medical outcomes. Since a major risk factor for CIAKI and subsequent adverse clinical events following angiography is the presence of decreased kidney function, and at any given level of kidney function the risk is increased in patients with diabetes mellitus, we will enroll patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 who have diabetes mellitus, as well as patients who have an eGFR <45 mL/min/1.73 m^2 regardless of whether or not they have diabetes mellitus.[11-13, 181] To optimize the recruitment of patients at particularly high risk for adverse events following angiography, we will include patients undergoing urgent procedures and those with non-decompensated heart failure (i.e., heart failure that is not being treated with inamrinone, milrinone, dobutamine or nesiritide, isolated ultrafiltration therapy, and/or an intra-aortic balloon pump) at the time of their procedure.

1. Inclusion criteria

- Planned elective or urgent coronary or non-coronary angiography with iodinated contrast media in which it is anticipated that there will be an interval of ≥3 hours between the identification of the indication for angiography and the time of the planned procedure. (Procedures in which this interval is anticipated to be <3 hours will be considered emergent and these patients will be excluded – see exclusion criteria below)
- Pre-angiography eGFR <60 ml/min/1.73 m^2 with diabetes mellitus or
  pre-angiography eGFR <45 ml/min/1.73 m^2 with or without diabetes mellitus
  - eGFR will be calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) formula. The specific 4-variable MDRD formula used will depend on whether the screening SCr value was measured using an IDMS-traceable or non-IDMS traceable laboratory methodology. This screening SCr will be measured as part of routine clinical care within 30 days prior to angiography.[182] For patients with multiple pre-procedure SCr values in this 30-day time frame, we will base eligibility on the SCr measured as part of routine

clinical care most proximate to the index angiogram that was obtained prior to the initiation of study IV fluids. Our past research and recent queries of VA clinical sites nationwide indicates that 91-95% of Veterans undergoing angiography have a SCr measured within 30 days prior to angiography.

- Diabetes mellitus will be defined as current use of oral hypoglycemic medications and/or insulin and/or :
  - Hgb A1C value of ≥ 6.5% within the previous 12 months or:
  - Medical record documentation of end-organ diabetic disease (e.g., diabetic retinopathy, diabetic nephropathy and/or diabetic neuropathy).

- Ability to provide informed consent

2. Exclusion criteria

- Currently receiving hemodialysis, peritoneal dialysis, continuous renal replacement therapy, or sustained low efficiency dialysis (SLED)
- Stage 5 CKD (eGFR <15 mL/min/1.73 m^2)
- Unstable baseline SCr (if known) at the time of angiography defined by a change in SCr of ≥25% over the 3 days prior to angiography
- Decompensated heart failure requiring any of the following therapies at the time of angiography (we are excluding these patients because IV fluid administration may be contraindicated):
  - IV milrinone, inamrinone, dobutamine, or nesiritide
  - Isolated ultrafiltration therapy
  - Intra-aortic balloon pump
- Emergent angiography procedures defined as an anticipated duration of <3 hours between the identification of the indication for angiography and the time of the planned procedure. We are excluding these patients due to the limited time to collect necessary research data and to ensure that research procedures do not interfere with time-sensitive clinical care.
- Receipt of intravascular iodinated contrast within the 5 days preceding angiography
- Receipt of oral or IV NAC within the 48 hours preceding angiography
- Known allergy to NAC
- Known anaphylactic allergy to iodinated contrast media

- Age <18 years
- Pregnancy
- Prisoner
- Ongoing participation in an unapproved concurrent interventional study

Eligible patients who indicate at the time of recruitment an unwillingness to comply with the 96-hour and 90-day outcome assessments will also be excluded.

B. Screening and patient recruitment

Requisite waivers of HIPAA authorization and informed consent for screening will be obtained in order to allow study coordinators to review angiography logs/schedules in advance to identify patients scheduled for coronary or non-coronary angiography and assess their electronic medical records for eligibility. After the study is introduced to the patient by an individual participating in their care, research personnel will contact potentially eligible subjects to describe the study and complete the screening process.

Based on our past study of Veterans undergoing angiography and recent queries of VA clinical sites nationwide, more than 90% of patients will have had a SCr measured as part of routine care within 30 days prior to angiography. For the small number of patients who have not had a SCr measured within 30 days, research personnel will contact them as stated above and, if they are agreeable, administer informed consent and then obtain a screening SCr prior to angiography to assess eligibility based on their underlying level of kidney function.

We will require that potentially eligible female subjects who are able to have children (not considered post-menopausal [had a menstrual period within previous 12 months], not had tubal ligation, a hysterectomy or bilateral oophorectomy) and are sexually active, have a negative pregnancy test before being enrolled in the study.

We believe that even for urgent angiograms for indications such as non-ST elevation MI or peripheral vascular occlusion, there will be sufficient time (>3 hours) prior to the procedure to determine eligibility, obtain consent, perform randomization, and implement the study interventions. Including these subjects will help ensure the recruitment of a high-risk patient

population. No adult patient (age ≥18 years) will be excluded from participating based on age, gender, race, ethnicity, or sexual preference.

VII. STUDY PROCEDURES

A. Assessment of pre-procedure renal function

Based on the structure of healthcare delivery within the VA Healthcare System in which patients frequently travel long distances to large VA Medical Centers for procedures such as angiograms, the SCr measured by the treating provider as part of routine clinical care prior to the procedure may be performed at a different VA laboratory than the SCr measured by the treating provider after the procedure. While an increasing majority of VA laboratories are using a standardized, IDMS-traceable method of measuring SCr, not all VA laboratories are using this calibrated methodology. Therefore, there may be inter-laboratory variation in SCr values due to differences in laboratory instrumentation and the lack of use of standardized methods of calibration. To reliably and accurately assess the development of persistent decline in kidney function (component of the primary endpoint) and CIAKI (secondary endpoint), it is essential that pre- and post-procedure SCr measurements for this purpose be standardized. We will therefore utilize a central laboratory to measure the pre-procedure study SCr and follow-up SCr values for endpoint ascertainment.

The timing of the pre-procedure study SCr (reference SCr) measurement used to assess these outcomes is also critical as the administration of IV fluids may lead to hemodilution and artifactual lowering of SCr. In addition, variation in intravascular volume status affects renal function, particularly in patients with underlying CKD. Therefore, we will standardize the timing of assessment of the reference SCr for endpoint ascertainment. This sample will be obtained following patient enrollment and immediately prior to the initiation of study IV fluids and study drug capsules to avoid any potential effects of study interventions on the baseline SCr level. This reference SCr sample will be distinct from the baseline pre-procedure SCr measured by the treating provider as part of routine clinical care that we will use to determine study eligibility. It is possible that due to expected variation in SCr levels and measurements, the baseline SCr used to determine eligibility will differ from the reference SCr such that patients who meet inclusion criteria based on the screening SCr would not have been eligible based on the reference SCr. Such patients will <u>not</u> subsequently be excluded or withdrawn from the study.

B. Randomization procedures

All patients meeting eligibility criteria and providing informed consent will be randomized to each of the two study interventions (IV isotonic bicarbonate versus IV isotonic saline and NAC versus placebo). The 2 x 2 factorial design will result in four discrete treatment combinations (bicarbonate/NAC, bicarbonate/placebo, saline/NAC and saline/placebo). Patients will be allocated in a 1:1:1:1 manner to each of these four treatment combinations. Randomization will be accomplished using a permuted block scheme with block size set to provide equal distribution into these four possible treatment combinations. Some offset or variability will be inserted to prevent anticipation of the next treatment. Randomization will be stratified by study site. Stratification by site is necessary to account for local variation in processes of care including the type and volume of iodinated contrast media administered during angiography and site-specific differences in peri-procedural provider practices such as discontinuation of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and diuretics.

Study coordinators at each site will be responsible for obtaining a randomized treatment assignment for each eligible patient. A web-based randomization program will be provided to study sites for this purpose. This web-based program will be tested at each site prior to the start of the trial and will be reviewed, as per Center guidelines, by the CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) and the MAVERIC CSPCC. At the time of subject enrollment, study coordinators will enter the Subject ID number and study site into the randomization program. The program will check that all eligibility criteria are met. If met, the program will select the first unused entry from the pre-specified list of random treatment assignments for the particular site. The lists are stored on a secure server at the CSPCRPCC. If the electronic system fails, the same process will be carried out by telephone and fax. In such instances, research personnel at the site will contact the CSPCRPCC for instructions on completing a manual randomization. The eligibility criteria will be verified by the CSPCRPCC. If eligible, the random treatment assignment will be provided to research personnel.

C. Blinding

Providers performing angiography, participating patients, personnel at the study chairmen's office, and research personnel at each site will be blinded to treatment assignment. Study IV

fluids will be provided in coded bags without specific labeling on the bag regarding the composition of the fluid. The appearance of the sodium bicarbonate solutions and sodium chloride solutions will be identical. NAC will be provided as 300 mg capsules or matching placebo capsules prepared by the VA CSP Clinical Research Pharmacy Coordinating Center in Albuquerque, NM. The use of NAC powder as a capsule avoids the difficulty of masking the strong odor and unpleasant taste associated with the liquid formulation of NAC.

D. Study interventions

In each of the four study arms, patients will receive a combination of the two interventions:

- IV isotonic sodium bicarbonate or IV isotonic saline
- Oral NAC or oral placebo

1. IV fluids

We will administer ≥3 ml/kg of study IV fluid over ≥1 hour at an infusion rate of not less than 1 mL/kg per hour and not more than 3 mL/kg per hour immediately prior to the angiographic procedure, 1-1.5ml/kg of study IV fluid per hour during angiography, and ≥6 ml/kg of study IV fluid over ≥ 2 hours following the procedure at an infusion rate of not less than 1 mL/kg per hour and not more than 3 mL/kg per hour. Providers will retain discretion to administer larger volumes of the randomly allocated study IV fluid (up to a maximum of 12 mL/kg) over durations of up to 12 hours pre and 12 hours post-procedure. The protocol will prohibit the delivery of smaller volumes of study IV fluid over shorter durations than the pre-specified minimums described above. In patients who are obese (BMI >30 kg/m^2) and weigh more than 125 kg, calculated rates of fluid administration should be capped based on a weight of 125 kg.

We chose this individualized approach rather than a strict protocol for IV fluid administration for two reasons. First, the optimal rate, duration, and volume of IV fluid for the prevention of CIAKI and other adverse outcomes have not been conclusively determined. Although there is a general belief that "more fluid" is superior to "less fluid," this premise has not been rigorously tested. This uncertainty is underscored by published expert recommendations for the use of IV fluids that acknowledge the lack of evidence to support a specific IV fluid regimen.[183] Second, requiring that IV fluids be administered at a specific rate for a precise period of time would likely be perceived as non-evidence based, could significantly limit provider willingness to have

their patients participate, and would reduce the generalizability of study findings. In clinical practice, the volume and duration of pre and post-procedure IV fluid often vary based on the clinical setting and individual patient circumstances.

We do not believe that using this approach will compromise our ability to determine differences in study outcomes between the two isotonic IV fluids. The theoretical underpinning for the effect of bicarbonate relates to alkalinization of renal tubular fluid. Based on prior studies, which have used variable rates of fluid administration ranging from 3 mL/kg for 1 hour pre-procedure and 1.5 mL/kg/hr for 4 hours post procedure to 1 mL/kg/hr for 12 hours pre and post-procedure, the rates of fluid administration that we propose to use should be more than sufficient to achieve urinary alkalinization among patients randomized to receive bicarbonate.[103, 105] In addition, we anticipate that randomization will result in the delivery of equivalent volumes of study IV fluid across treatment groups.

2. NAC and placebo

NAC or placebo will be administered at a dose of 1200 mg orally to all patients approximately 1 hour prior to angiography, approximately 1 hour following the procedure, and then twice daily for the next 4 days. Although initial studies using NAC utilized a dose of 600 mg per dose, subsequent studies have suggested greater benefit with higher doses of this agent.[184] Therefore, we will provide 1200 mg per dose of oral NAC. Nearly all prior studies administered NAC for a total of 2 days. However, iodinated contrast may persist in the kidney tubules for a prolonged period of time, particularly in patients with decreased kidney function.[185, 186] Although it is not known whether this residual contrast results in persistent renal damage, there may be benefit to more sustained therapy with NAC with little added cost or risk. Therefore, we will administer NAC capsules twice daily for 5 days.

Although several prior trials investigated the benefit of NAC administered intravenously for the prevention of CIAKI, we chose to use oral administration for three reasons.[23, 157, 162, 167] First, oral NAC is associated with minimal risk, while up to 15% of patients who receive IV NAC experience an adverse reaction, which rarely, includes anaphylaxis.[187, 188] Second, IV NAC is considerably more expensive than the oral preparation.[189] Finally, there is no clear evidence that

IV NAC offers greater protection against CIAKI or serious adverse outcomes compared to oral NAC.

E. Additional peri-procedural management issues

While all contrast agents may be a source of potential clinical complications, the osmolality of the contrast agent is believed to potentially impact the risk for CIAKI. Data conclusively demonstrate that high osmolality (>1200 mOsm/kg) agents pose a greater risk for CIAKI than low osmolality (500-860 mOsm/kg) agents in high-risk patients.[12, 62] However, data on the comparative incidence of CIAKI with iso-osmolal and low-osmolal contrast are conflicting and inconclusive. To provide care that is consistent with prior guidelines issued by the American College of Cardiology/American Heart Association for the use of iodinated contrast in patients with CKD, all patients in this trial will receive either iso-osmolal contrast media (i.e., iodixanol) or non-ionic, low-osmolal contrast media with a recommendation to avoid using ioxaglate and iohexol.[190] Selection of the specific contrast agent and the volume of contrast administered will be at the discretion of the treating provider as there is no current consensus on the least nephrotoxic contrast agent. Given the very large number of patients targeted for enrollment, we believe that the process of randomization will result in comparable distributions of patients who receive different contrast agents across study groups.

We will recommend to the treating provider that selective and non-selective non-steroidal anti-inflammatory medications other than once daily aspirin be stopped at the time of the procedure and held for 4days following angiography, as the use of these medications is believed to increase the risk for CIAKI.[183, 191] We will defer decisions on the discontinuation of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and diuretics to the treating provider(s) because there are no conclusive data on the optimal approach to the management of these medications in patients with CKD undergoing angiography.

Finally, should the patient require bolus administration of IV fluid in excess of 250 ml during the angiogram, we will instruct providers performing the procedure that IV saline should be administered rather than study IV fluid since the bolus administration of large volumes of bicarbonate poses potential safety concerns due to abrupt systemic alkalemia. We do not believe

that such emergency boluses of saline are likely to affect our outcomes because only a minority of patients is likely to require such additional fluid boluses and the benefit of bicarbonate relates to its ability to alkalinize the urine. To assess urinary alkalinization in patients randomized to receive bicarbonate and evaluate differences in urine pH between IV fluid arms, we will obtain a urine specimen within approximately 4 hours following angiography for analysis of pH using a digital pH analyzer.

F. Post- procedure management issues

Following angiography and prior to discharge from the hospital, study coordinators will provide the participant with instructions on how to take their study medication (i.e., NAC or placebo capsules) while at home. Participants will be given a study medication diary to record the dates and number of capsules taken. Participants will be instructed to notify study staff and bring their study medication with them in the event they require hospitalization. Prior to discharge, study coordinators will also arrange the participant's blood specimen collection 4 days following their angiography. Options for this blood draw may include, but not be limited to: 1) returning to the study VA; 2) having a mobile phlebotomy service draw the blood; or 3) having the blood drawn at a non-study VA site such as a Community-Based Outpatient Clinic (CBOC) or another VA facility closer to the participant's home.

G. Study Outcomes

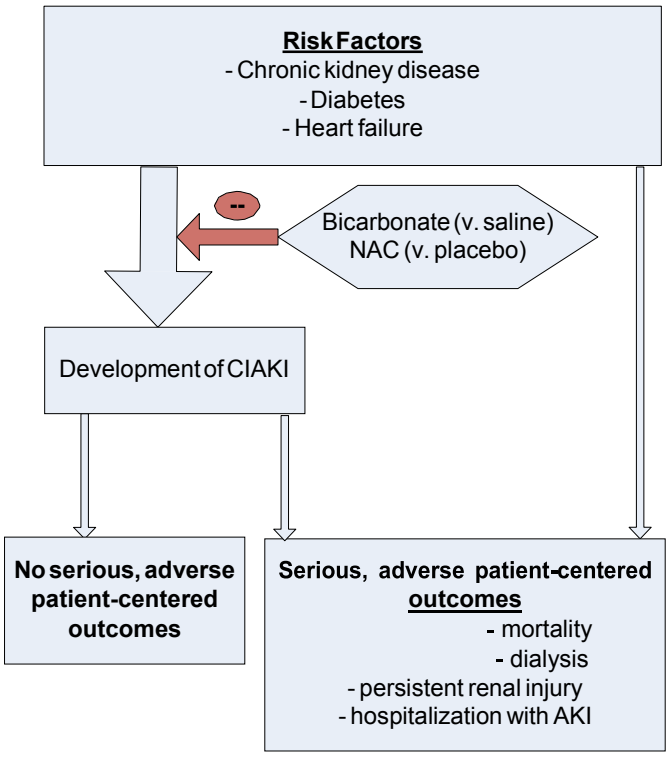
1. Conceptual basis for study outcomes

Nearly all clinical trials of IV fluid and NAC for the prevention of CIAKI utilized the surrogate endpoint of change in SCr within 2 to 5 days of contrast administration and were not designed or powered to test the hypothesis that these interventions prevent serious, adverse downstream outcomes. While there is a strong association between small changes in SCr within days of angiography and adverse downstream outcomes, not all episodes of CIAKI lead to serious downstream events (Figure 4). For this reason, the primary objective of this trial is to evaluate whether bicarbonate (as compared to saline) and NAC (as compared to placebo) reduce the incidence of serious, adverse patient-centered outcomes. We postulate that the beneficial effects of bicarbonate and NAC on adverse downstream outcomes will be mediated specifically by means of a reduction in the incidence of CIAKI.

2. Primary study outcome

The primary outcome will be a composite of serious, adverse, patient-centered events, including death, need for acute dialysis, or persistent decline in kidney function within 90 days following angiography. These outcomes, which we refer to as major adverse kidney events and death (MAKE-D) will be defined as follows:

Figure 4 - Conceptual basis for primary outcomes



- **Death** based on medical record and/or vital status registry documentation.
- **Need for acute dialysis** defined as the initiation of any modality of renal replacement therapy (intermittent hemodialysis, peritoneal dialysis, continuous renal replacement therapy, or sustained low-efficiency dialysis) within 90 days of the index angiographic procedure.
- **Persistent decline in kidney function** defined by an increase in SCr from the baseline value of at least 50% at 90 days following the index angiographic procedure. This outcome will be based on a comparison of the pre-angiography and 90-day SCr values analyzed at the central laboratory.

3. Justification for components of the primary endpoint

We selected the individual components of the primary endpoint based on the biologically and clinically plausible link between the development of CIAKI and these clinically-relevant downstream events. Each of the components of the primary outcome is a recognized complication of CIAKI and analyses of our database of over 25,000 Veterans with CKD who underwent coronary angiography demonstrate that patients who developed CIAKI following angiography were four times more likely than patients without CIAKI to experience one or more

of the events that comprise our primary endpoint. Prevention of CIAKI will likely decrease the incidence of each of these downstream outcomes.

a. Justification for inclusion of death in primary endpoint

Multiple prior studies (*vide supra*) have demonstrated an association of CIAKI with death.[11, 16, 19, 21, 192] While we anticipate that fewer patients will experience death compared to the other components of the primary endpoint, death is the most serious outcome and a competing event, and is therefore important to include in our composite endpoint.

b. Justification for inclusion of acute dialysis in primary endpoint

The need for dialysis as a component of our primary composite outcome refers to acute dialysis that may or may not lead to the chronic long-term requirement for renal replacement therapy. Given that we are proposing to enroll patients with Stage 3 and Stage 4 CKD (baseline eGFR 15-60 ml/min/1.73 m^2), it would be unexpected for these patients to progress to ESRD and need chronic dialysis within the 90-day follow-up period without an acute change in the trajectory of their chronic kidney disease. For patients who require acute dialysis in the setting of AKI, failure to recover kidney function within 90 days is the conventionally accepted transition from acute dialysis to end-stage renal disease and "chronic" dialysis.[193, 194] Thus, the need for dialysis within 90 days of contrast administration as a component of the primary outcome in this study is, by definition, acute dialysis. Patients who require acute dialysis following an episode of CIAKI may: i) experience a full or partial recovery of kidney function obviating the need for continued dialysis therapy; ii) develop ESRD necessitating chronic renal replacement therapy; or iii) die within 90 days before meeting the definition of ESRD/chronic dialysis. While CIAKI resulting in death or the need for chronic dialysis (i.e., ESRD) is relatively uncommon, the clinical significance of such outcomes is unequivocal. Less well recognized are the important adverse short and long-term implications of AKI that requires acute transient dialysis. Acute temporary dialysis, either with intermittent hemodialysis or continuous renal replacement therapy, is associated with important short-term adverse outcomes, including bleeding and blood-borne infection related to dialysis catheter placement, hemodynamic instability due to fluid and solute shifts during the dialysis procedure, and financial costs that may exceed $500 to $1,000 per treatment. Two recently published large studies demonstrated the longer-term implications of

acute temporary dialysis following an episode of AKI. Wald et al. conducted a population-based cohort study comparing long-term outcomes of 3,769 patients who developed AKI that required temporary dialysis with 13,598 matched controls who were hospitalized, but did not develop AKI.[195] At a median of 3 years of follow-up, the risk for ESRD was more than 3-fold higher among patients who required acute transient dialysis compared to severity of illness matched controls (adjusted HR 3.23; 95% CI: 2.70-3.86). Another study by Lo and colleagues examined the association of AKI that required transient dialysis with progression of CKD and mortality.[196] Among 562,799 hospitalized patients who had a baseline eGFR ≥45 ml/min/1.73 m^2, 703 sustained dialysis-requiring AKI, of whom 295 (42%) died, 65 (9%) remained chronically dialysis dependent, and 343 (49%) recovered sufficient kidney function to be able to discontinue dialysis by the time of hospital discharge. In multivariate analyses, AKI requiring transient dialysis was associated with a 28-fold increased risk of developing progressive CKD, defined as a decline in kidney function to an eGFR ≤30 ml/min/1.73m^2, and a 2-fold increase risk of death over 6 years of follow up.[196] Thus, the need for acute transient dialysis following an episode of AKI has substantial short and long-term clinical implications and represents a clinically important component of our primary composite endpoint.

c. Justification for inclusion of persistent decline in kidney function in primary endpoint

A series of recent studies demonstrated robust associations of CIAKI with persistent renal injury and with an acceleration in the long-term rate of decline in kidney function.[24, 30, 197] We propose to include persistent renal injury at 90 days following angiography, defined by an increase in SCr from baseline of ≥50%, in our primary composite endpoint. In preliminary analyses, we found that the development of CIAKI following angiography was associated with a prognostically meaningful, greater than 2-fold increase in the risk of developing a ≥50% increase in SCr at 90 days (OR = 2.4, 95% CI 1.9-3.0) confirming the strong link between CIAKI and persistent renal injury at 90 days. However, in order to confirm the clinical

Table 7. Associations of Changes in SCr at 90 days with adverse 1 year outcomes

	25-50% ↑ SCr		**≥ 25% ↑ SCr**		**≥ 50% ↑ SCr**	
1-yr Outcome	OR	95% CI	OR	95% CI	OR	95% CI
Death	1.7	1.3-2.3	2.7	2.2-3.3	4.9	3.7-6.3
Need for dialysis	1.8	1.5-2.2	2.8	2.4-3.2	5.2	4.3-6.2
Doubling in SCr	4.8	3.1-7.1	6.5	4.7-9.1	7.9	5.3-11.8
Composite	2.0	1.7-2.3	3.0	2.7-3.4	5.9	4.9-7.0

significance of this level of persistent decline in kidney function at 90 days following angiography and justify its inclusion in our primary endpoint, we performed more long-term follow-up of over 25,000 Veterans with CKD who underwent coronary or non-coronary angiography within the VA Healthcare System. Using this VA database, we examined the associations of variable threshold increases in SCr at 90 days with adverse 1-year outcomes (i.e., death, need for dialysis, or doubling in SCr) (Table 7). While increases in SCr at 90 days of 25% to 50% and >25% were associated with increased risk for each of these adverse 1-year outcomes, the risk of these long-term events increased markedly among patients with a >50% increase in SCr at 90 days. Compared to patients who did not experience a ≥50% increase in SCr at 90 days following angiography, patients who developed a ≥50% increase in SCr at 90 days were nearly 6 times more likely to die, develop the need for dialysis, and/or experience a doubling in SCr within one year (Table 7). Collectively, these data confirm the strong association between CIAKI and a ≥50% increase in SCr at 90 days following angiography, demonstrate the clinical importance and downstream implications of this threshold level of persistent renal injury at 90 days, and provide robust evidence supporting the inclusion of this outcome as a component of our primary composite endpoint.

d. Justification for 90-day time frame to assess the primary endpoint

We chose to assess our primary endpoint at 90 days following angiography for two reasons. First, this represents a period of time during which adverse outcomes are more likely than not to be associated with the index angiographic procedure. Second, 90 days is commonly used in clinical practice and is proposed by the Kidney Disease: Improving Global Outcomes Foundation and the National Kidney Foundation to define the transition between acute and chronic impairment in kidney function. Therefore, persistent decline in kidney function measured at 90-days after the index angiographic procedure likely represents irreversible renal damage.

4. Secondary study outcomes

The secondary outcomes consist of:

- CIAKI defined by an increase in SCr of ≥0.5 mg/dL and/or ≥25% from the pre-procedure value at 4 days following angiography.
- Death within 90 days of the index angiographic procedure.

- The renal components of the primary endpoint:
  - Need for acute dialysis within 90 days of the index angiographic procedure
  - Persistent decline in kidney function at 90 days following the index angiographic procedure
- Hospitalization with acute coronary syndrome, heart failure, or cerebrovascular accident within 90 days following the index angiographic procedure. These outcomes will be defined as a primary or secondary discharge diagnosis of acute coronary syndrome (i.e., STEMI, NSTEMI, unstable angina), heart failure, or cerebrovascular accident documented in the VA electronic medical record or the hospital discharge summary obtained for non-VA hospitalizations. (This will include the occurrence of any of these events during the index hospitalization).
- All-cause re-hospitalization within 90 days of the index angiographic procedure assessed as episodes of re-hospitalization, days of hospitalization (inclusive of the index hospitalization), and hospital free days (alive and not in the hospital) through day 90.

Because AKI can occur following angiography for reasons unrelated to the administration of iodinated contrast, in a sensitivity analyses, we will also evaluate the development of CIAKI using the same threshold change in SCr, but excluding patients who experienced hypotension and/or who underwent cardiac surgery or non-cardiac vascular surgery within the 4 days following angiography.

5. Tertiary (exploratory) outcomes

- Development of end-stage renal disease within one year following angiography defined by the requirement for chronic dialysis for ≥3 months based on documentation in the United States Renal Data System database.
- Death within one year following angiography based on documentation in the VA Beneficiary Identification and Records Locator System, the National Center for Health Statistics National Death Index database, the Social Security Administration's Death Master File and/or other similar databases.

H. Data collection

1. Assessment of baseline demographic and clinical characteristics

Following patient enrollment, research personnel will interview the subject and/or conduct a comprehensive review of the electronic medical record to abstract the following data elements:

- Whether the subject was an inpatient or outpatient immediately prior to the angiography procedure
- Demographic characteristics including date of birth, gender, race, and ethnicity
- Contact information including home, work, and cell phone numbers; address; email; preferred contact times; as well as the same information for an alternate contact
- Social security number
- Military history
- Pre-procedure laboratory parameters obtained as part of routine clinical care including date of test:
    - Hemoglobin level, serum glucose, serum bicarbonate, sodium, potassium and blood urea nitrogen most proximate to and within the 30 days preceding the index angiogram
    - If diabetic, most recent Hgb A1C within the past year
- Comorbid medical conditions including a history of :
    - Myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, and chronic pulmonary disease. Standard procedures and definitions will be developed to systematically evaluate patients' records for each of these conditions.
- History of hypertension or being prescribed blood pressure medication
- Smoking history
- Administration of any non-study IV fluid including the type within the 12 hours prior to the initiation of study IV fluids
- Weight in kilograms. The preferred method of obtaining the patient's weight will be for research personnel to weigh them. In the event this is not possible, the most recent measurement found in the patient's medical record will be recorded. Though not preferred, if there is no measurement in the medical record, this information will be collected via subject report.

- Blood pressure most proximate to and within 72 hours prior to the index angiogram including date of assessment
- Names of all pre-procedure medications, including those prescribed by physicians outside the VA, regularly taken by the subject
- Whether the subject was instructed by their physician to discontinue any medications before their angiography procedure and if so, the name of the medication.

2. Collection of baseline blood and urine specimens

Prior to the initiation of study IV fluids, the subject will be asked to provide a blood sample for Scr testing at the designated Central Laboratory. We will collect the date of this blood draw and whether it was collected prior to the initiation of study IV fluids.

In addition to the blood draw, subjects will be asked to provide a urine sample to measure urine albumin and creatinine. In the event the patient cannot provide urine prior to the angiogram, they will be asked to provide a urine specimen after the angiogram.

3. Evaluation of procedure-related data

Subsequent to the angiogram, research personnel will review the electronic medical record and angiogram procedure report to determine:

- Date of index angiogram
- Type of angiography
- Indication for coronary angiography
- Type and total volume of contrast administered. If ioxaglate (Hexabrix) or iohexol (Omnipaque) are noted, a reason must be given as to why that particular agent was used.
- Site of the arterial puncture for the angiogram
- Performance of percutaneous intervention
- Left ventricular end-diastolic pressure if measured
- Complications during the procedure including:
    - hypotension necessitating the administration of additional non-study IV fluid including the type of non-study IV fluid administered
    - hypotension necessitating the insertion of an intra-aortic balloon pump and/or the administration of vasopressor therapy
    - acute pulmonary edema necessitating the administration of IV diuretics

Assessment of procedure-related complications will ensure that we capture all events that could impact the development of our primary and secondary outcomes. To clarify and confirm all of these procedure-related data, research personnel may also conduct a brief structured interview with the angiography nurse/technician.

4. Evaluation of study IV fluid and NAC/placebo administration

Research personnel will track and record from the electronic medical record the total volume and total duration of study IV fluid administered pre-procedure, intra-procedure, and post-procedure, and the administration of NAC or placebo capsules while the patient is in the hospital. NAC or placebo capsule administration outside the hospital will be captured during a follow up assessment 5-8 days following the angiography procedure (See Section VII.H.8.).

5. Evaluation of post-procedure course (within 12 hours post procedure)

Research personnel will review the electronic record and collect the following data elements:

- Use of any IV fluids other than those specified as study IV fluids within the 12 hours following angiography including the type
- Use of IV inotropes, vasodilators, and/or vasopressors
- Episodes of hypotension defined as systolic blood pressure <90 mmHg and/or MAP <55 mmHg
- Performance of additional radiology procedures including coronary or non-coronary angiography or computed tomography with intravascular iodinated contrast including whether the procedure was planned and the type and volume of contrast administered

Within approximately four hours of the angiography, research personnel will obtain a urine sample from the patient and record the date of collection, whether study IV fluids were being administered at the time of collection and the urine pH value. The collection of this urine sample outside the range of 12 hours pre- and 12 hours post-angiography will constitute a reportable protocol deviation.

6. Evaluation of post-procedure hospitalization course (12 hours – 4 days post procedure)

Research personnel will review the electronic record on a daily basis for patients who remain in the hospital following their angiography procedure or for patients who are readmitted to the

hospital within 4 days of their angiography procedure to assess a series of events/procedures that could impact the risk for our primary and secondary outcomes. These include:

- Episodes of hypotension defined as systolic blood pressure <90 mmHg and/or MAP <55 mmHg
- Use of IV inotropes, vasodilators, and/or vasopressors
- Performance of additional radiology procedures including coronary or non-coronary angiography or computed tomography with intravascular iodinated contrast including the date of procedure, whether the procedure was planned and the type and volume of contrast administered. If ioxaglate (Hexabrix) or iohexol (Omnipaque) are noted, a reason must be given as to why that particular agent was used.
- Performance of surgical procedures requiring general or epidural anesthesia including the date and type
- Use of renal replacement therapy
- Occurrence of MI including the date and if it was an ST elevation MI
- Duration of hospital stay beginning at the time of angiography
- In-hospital death
- Date of hospital discharge

To capture these data in patients discharged from the hospital within the first 4 days following the index angiogram, we will provide patients with a study card at the time of their discharge with instructions to call research personnel if they visit an emergency room and/or are hospitalized within the 96-hour time frame following the index angiogram. For patients who visit a VA emergency room and/or are hospitalized within the VA, research personnel will review the electronic medical record to abstract the aforementioned data elements. For patients who visit a non-VA emergency room and/or are hospitalized outside the VA, research personnel will obtain the requisite release of information form(s) from the patient. Once the completed form(s) are received, research personnel will request the emergency room and/or hospital records to assess the aforementioned data elements.

7. <u>4 day blood collection</u>

Participants discharged from the hospital within four days following angiography will be asked

to provide a blood sample 4 (±1) days following the angiogram. Options for this blood draw may include, but not be limited to: 1) returning to the study VA; 2) having a mobile phlebotomy service draw the blood; or 3) having the blood drawn at a non-study VA site such as a Community-Based Outpatient Clinic (CBOC) or another VA facility closer to the participant's home.

We chose this time frame to assess post-procedure renal function as almost all patients who develop CIAKI have an elevated SCr within 4 days. One aliquot of this sample will be sent to the central study laboratory to assess the development of CIAKI. A second aliquot from this sample will be delivered to the nearest VA laboratory in order for the practitioner who performed the angiogram to ascertain whether the patient experienced a rise in SCr. This approach will obviate the need for the patient to have more than one blood draw to assess for the development of CIAKI for study and clinical purposes. For patients who remain hospitalized for at least 4 (±1) days following angiography, a blood sample will be drawn at 4 (±1) days post-procedure. One aliquot of this sample will be sent to the central study laboratory for subsequent analysis for the development of CIAKI, while a second aliquot will be delivered to the hospital laboratory for the primary provider to review whether the patient experienced a post-procedure rise in SCr.

To ensure patient safety and assist providers, research personnel will notify the provider who performed the angiography that a 4 (±1) days SCr will be processed in the VA laboratory as part of the study and will send an encrypted email to the patients' primary provider describing the results of this 4 (±1) days post-procedure SCr within 2 days of the completion of this test.

Since this creatinine determination is part of the secondary end-point, it is very important that the blood collection be done at 4 (±1) days after angiography. We recognize that unforeseen circumstances may preclude collection within this window. Under such circumstances the blood should be collected as soon as possible and most proximate to 5 calendar days after the date of angiography. In the event the blood is obtained before 3 or after 5 days following angiography, a protocol deviation should be completed.

8. Day 5 post procedure assessment

(5 days post angiography, allowable range 5-8 days post angiography)

Five days post-angiography, research personnel will review the electronic medical record and perform a structured telephone interview with the patient. For patients who remain hospitalized at this time point, research personnel will speak with them in-person. Beginning on the day of the patient's angiography, the date and number of NAC/placebo capsules taken will be documented. Reasons for non-compliance will be collected. Research personnel will also review the EMR to verify that NAC/placebo was administered appropriately (at least one hour prior to the procedure and then again at least one hour following the procedure) on the day of the angiography procedure.

During the EMR review and follow-up call (or visit to the patient in the hospital), research personnel will inquire about any adverse events the patient experienced, including any hospitalizations or the need to begin dialysis. To assess the adequacy of patient blinding to the interventions, research personnel will also ask participants to guess which IV fluid arm of the study they were assigned to and whether they received NAC or placebo capsules.

Finally, research personnel will verify that the patient had their 4-day blood sample collected.

We recommend that this contact should be made 5 days after angiography, with an allowable range of 5-8 days post angiography. We recognize that sometimes it may be difficult to contact a patient within this window. However, it is important to collect the required data, which should be done even if done after the recommended time frame has elapsed. It will not be considered a protocol deviation as long as the required data are collected and there is progress note documenting the attempt to schedule the data collection during the recommended time frame.

9. Day 35 post procedure assessment

(35 days post angiography, allowable range 35-49 days post angiography)

Thirty five days following the angiography, research personnel will review the electronic medical record and perform a structured telephone interview with the patient to inquire about any adverse events they experienced related to study participation.

We recommend that this contact should be made at 35 days after angiography, with an allowable range of 35-49 days. We recognize that sometimes it may be difficult to schedule a patient within this window. However, it is important to collect the required data, which should be done even if done after the recommended time frame has elapsed. It will not be considered a protocol deviation as long as the required data are collected and there is progress note documenting the attempt to schedule the data collection during the recommended time frame.

10. Day 90 post procedure assessment

(90 days post angiography, allowable range 90-104 days post angiography)

a. 90 day blood collection

In advance of the patient's 90 day assessment, they will be contacted by research personnel regarding their 90 day blood collection. The blood sample obtained will be sent to the Central Laboratory for Scr measurement. Patients who are willing and able will return to the study VA at which their angiogram took place 90 days (allowable range of 90-104 days) following their index angiogram to provide this blood sample. Other options for this blood draw may include, but not be limited to: 1) having a mobile phlebotomy service draw the blood; or 2) having the blood drawn at a non-study VA site such as a Community-Based Outpatient Clinic (CBOC) or another VA facility closer to the participant's home.

If a participant initiates renal replacement therapy (intermittent hemodialysis, peritoneal dialysis, continuous renal replacement therapy [CRRT], or prolonged intermittent renal replacement therapy [PIRRT]) within 90 days of the index procedure , the study coordinator will collect the 90-day blood draw based on the following criteria:

- If the participant initiates renal replacement therapy within 90 days of the index angiography procedure and continues to require renal replacement therapy on or after day 90, the 90-day blood draw will not need to be collected
- If the participant initiates renal replacement therapy within 90 days of the index angiography procedure but recovers kidney function and renal replacement therapy is discontinued prior to day 90, the participant should have his/her 90-day blood drawn

Since this creatinine determination is part of the primary end-point, it is very important that the blood collection be done 90 days after angiography, with a target range of 90-104 days, and with an allowable range of 90-180 days. We recognize that unforeseen circumstances, such as patient hospitalization outside the VA system, may preclude collection within the 90-104 day range. Under such circumstances the blood should be collected as soon as possible and most proximate to 90 days within 180 days and a protocol deviation should be noted if outside the target range of 90-104 days.

This 90-day SCr value will be used to assess for evidence of persistent decline in kidney function. In subjects with a ≥50% increase in SCr between their baseline and 90 day measurements, a confirmatory SCr measurement will be obtained. Options for this blood draw may include, but not be limited to: 1) returning to the study VA; 2) having a mobile phlebotomy service draw the blood; or 3) having the blood drawn at a non-study VA site such as a Community-Based Outpatient Clinic (CBOC) or another VA facility closer to the participant's home. For purposes of determining whether the endpoint of a ≥50% increase in SCr at 90 days (persistent decline in kidney function) has been met, both SCr values will need to be ≥50% higher than baseline and mean of these two SCr will be used. If the 50% increase is confirmed, research personnel will notify the patient's primary care provider using an institutionally approved notification method.

Reimbursement will be provided for travel expenses to have study-related blood draws if these are not done by the mobile specimen collection agency. This payment will be dispersed by the local site according to their procedures. Other than travel reimbursement, patients will not receive any payment for their participation in this study.

b. 90 day assessment

Ninety days following the index angiogram, research personnel will review the electronic medical record and perform a structured telephone interview with the patient. The electronic medical record review will specifically focus on assessing the development of any of the following primary and/or secondary end-points within the VA Healthcare System:

- death including date based on medical record documentation
- need for renal replacement therapy including date of initiation and duration of therapy
- hospitalization including date and primary and secondary hospital discharge diagnoses (to assess for ACS, HF, and/or CVA)

The 90-day structured telephone interview with the patient will complement the electronic medical record review. This telephone interview will verify data that was abstracted from the electronic medical record and enable research personnel to inquire about hospitalizations at non-VA facilities that would not have been captured in the VA electronic medical record. For any patients who were hospitalized outside the VA, the research personnel will obtain the requisite release of information form(s) from the patient. Once the completed form(s) is received, research personnel will acquire the pertinent medical records to assess for the development of any of these outcomes. In addition, death within this 90-day time period will be ascertained by linking our study database with the VA Beneficiary Identification and Records Locator System, National Center for Health Statistics National Death Index database, Social Security Administration's Death Master File, and/or other similar databases.

We recommend that the telephone contact be performed 90 days after the initial angiography, with an allowable range of 90-104 days. We recognize that sometimes it may be difficult to schedule a patient within this window. However, it is important to collect the required data, which should be done even if done after the recommended time frame has elapsed. It will not be considered a protocol deviation as long as the required data are collected and there is progress note documenting the attempt to schedule the data collection during the recommended time frame.

11. 1-year assessment

We will link our database with the United States Renal Data System to ascertain the development of ESRD and the date of initiation of renal replacement therapy within one year of the index angiographic procedure. Finally, death within this 1-year period will be ascertained by linking our database with the VA Beneficiary Identification and Records Locator System, National Center for Health Statistics National Death Index database, Social Security Administration's Death Master File and/or other similar databases. Timing the performance of these linkages will depend upon the availability of data from the USRDS and the vital status registries, which may lag by 12-18 months after the end of each calendar year.

VIII. POTENTIAL PITFALLS OF THE PROPOSED STUDY DESIGN AND ALTERNATIVE STUDY DESIGN CONSIDERATIONS

A. Study Hypotheses

1. Relationship between CIAKI and patient-centered outcomes

Our study design is based on a conceptual model in which CIAKI is not only associated with, but is the proximate event in a direct causal pathway leading to serious, adverse downstream outcomes. While we postulate that CIAKI mediates serious, adverse downstream events, we recognize that it is possible that the small changes in kidney function that define CIAKI may simply represent a marker of underlying cardiac and/or vascular disease and reflect pre-procedure risk for morbidity and mortality. Thus, it is possible that the proposed interventions may reduce the incidence of CIAKI, defined by change in SCr, but not affect the incidence of serious, adverse, patient-centered outcomes. While this outcome might be viewed as disappointing, we believe that such a finding would be extremely significant and would have a substantial impact on clinical care and resource allocation.

Similarly, we recognize that post-angiography AKI has etiologies other than iodinated contrast, most notably hypotension and atheroembolic disease. Our interventions are unlikely to impact the development of AKI in such cases. To address this possibility, we will conduct sensitivity analyses in which we will evaluate the development of CIAKI using the same threshold change in SCr, but exclude patients who experienced hypotension, underwent cardiac or non-cardiac vascular surgery within the 4 days following angiography, and/or had a documented cause for acute kidney injury in the primary or secondary discharge diagnoses, other than contrast associated AKI.

2. Effectiveness of Bicarbonate and NAC

Our hypotheses that bicarbonate (compared to saline) and NAC (compared to placebo) will decrease the incidence of serious, adverse 90-day outcomes are based on the purported effectiveness of these interventions in preventing the short-term changes in SCr that define CIAKI. We recognize that if bicarbonate (compared to saline) and NAC (compared to placebo) are not effective for the prevention of CIAKI, we are unlikely to observe an effect of these

interventions on the events that comprise our primary study endpoint. For this reason, we have included prevention of CIAKI as a key secondary outcome.

B. Study Population

1. Inclusion of patient undergoing coronary or non-coronary angiography

Most past studies of CIAKI have focused on patients undergoing coronary angiography. We propose enrolling patients undergoing either coronary or non-coronary angiography. While including patients undergoing non-coronary angiography will increase the heterogeneity of the study population, data from our prospective cohort study suggest that CIAKI and serious adverse events are even more common following non-coronary angiography than coronary angiography.[198] Moreover, non-coronary angiograms make up approximately one-third of angiographic procedures performed within the VA. Therefore, we believe that despite the effect on patient heterogeneity, inclusion of patients undergoing non-coronary angiography will enrich the study population with high-risk patients, significantly increase the number of patients available for recruitment, and broaden the generalizability of the study findings.

2. Exclusion of patients undergoing contrast-enhance computed tomography

There are past trials of interventions for the prevention of CIAKI that included and/or were focused exclusively on patients undergoing contrast-enhanced computed tomography.[142, 199] Although inclusion of patients undergoing contrast-enhanced computed tomography in our proposed trial would substantially increase the pool of eligible patients, our prior observational cohort study of Veterans undergoing contrast-enhanced procedures found that CIAKI was less common following computed tomography than after angiography.[8, 198] Inclusion of these lower risk patients would decrease the anticipated event rate and result in the need for a considerably larger study than we have proposed. Nevertheless, interventions to decrease the risk of CIAKI and serious, adverse, patient-centered outcomes following angiographic procedures will likely be applicable to high-risk patients undergoing contrast-enhanced computed tomography.

3. Criteria for selection of high-risk patients

Our study targets patients who are at high risk for CIAKI and serious, adverse events following angiography. While the inclusion of lower risk patients would broaden the study population, it

would result in the need to recruit a considerably larger number of participants and would likely add complexity to and decrease the feasibility of the study. We chose to define our patient population as being at high-risk based on the presence of underlying chronic kidney disease, with diabetes serving as an amplifier of risk in the setting of impaired renal function. We chose this approach because chronic kidney disease is commonly cited as the primary risk factor for CIAKI, is easily assessed, and is present in a large proportion of patients undergoing angiographic procedures.[21, 183] We recognize that other clinical conditions (e.g., heart failure, intravascular volume depletion) are also associated with an increased risk for CIAKI and adverse, downstream outcomes and could be used to define a study population as high-risk. However, assessment of the presence and severity of heart failure and intravascular volume depletion is somewhat subjective and therefore more difficult to protocolize.

C. Study interventions

1. Fluid administration

There is no consensus among experts on the optimal rate and duration of IV fluid administration for the prevention of CIAKI or single protocol for the administration of IV fluid that has been shown to be the most effective. Individual patient circumstances and provider preferences commonly dictate the volume and duration of IV fluids administered. We anticipate that some providers might be unwilling to have their patients participate in this trial if they have no control over the rate or duration of IV fluid administration in their patients. For these reasons, rather than adopting one of the multitude of fluid administration protocols employed in prior clinical trials for the prevention of CIAKI, the planning committee decided that a more flexible approach that specified a minimum volume and duration of administration of IV fluids would be more acceptable to providers without deviating from what would be considered appropriate preventive care. While we believe that this approach will provide a volume of IV fluid that is comparable to that used in most recent trials comparing bicarbonate and saline, it is possible that this strategy could result in systematic differences in the rate and duration of fluid administration in patients randomized to bicarbonate and saline. While this is very unlikely given the large trial size and blinding of fluid composition, we will closely monitor duration and volumes of fluid administration across groups.

2. Complications of fluid administration

We anticipate that some patients will develop volume overload/pulmonary edema and/or elevated left ventricular end-diastolic pressure during angiography. In such instances, providers performing angiography may discontinue post-procedure IV fluids resulting in patients failing to receive study IV fluid following the angiogram. It is likely that this event will occur in a small proportion of patients and be equally distributed across treatment arms. While the volume of study IV fluid administered pre, during and post-procedure will be carefully recorded for all patients, given the importance of patient safety, we believe it would be inappropriate to require the administration of post-procedure study IV fluid in such instances. Since all analyses will be based on the intent-to-treat principle, these patients will not be excluded from the study analyses.

3. Route and dose of NAC administration

There is currently no universally accepted protocol for the route of administration of NAC for the prevention of CIAKI. While most prior studies used oral NAC, a small number of studies administered NAC intravenously.[23, 153, 157, 162, 164, 167] The primary putative advantage of IV administration is a reduction in first-pass inactivation of NAC by the liver after enteric absorption, thereby increasing delivery to the kidneys. Notwithstanding this theoretical benefit of IV NAC, we selected the oral route of administration for three reasons. First, there are inadequate clinical data to demonstrate that the theoretical benefits of IV NAC translate into greater clinical effectiveness than oral NAC. Second, IV administration of NAC is associated with a considerably higher risk for adverse reactions, including anaphylaxis, than the oral formulation. Finally, the IV preparation of NAC is considerably more expensive than the oral preparation.

Although the optimal dose of NAC for the prevention of CIAKI has not been clearly established, we have chosen to administer 1200 mg twice daily for four reasons. First, clinical trials that assessed the impact of dose on the incidence of CIAKI and serious, adverse outcomes demonstrated a benefit to higher dose NAC.[23, 184] Second, data from experimental models suggests a dose-dependent effect of NAC with higher doses associated with less renal tubular damage.[169] Third, there is little safety risk with higher doses of NAC compared to lower doses of

NAC. Finally, current opinion-based recommendations for the prevention of CIAKI advocate the use of 1200 mg of NAC twice daily.[183, 200]

4. Duration of study interventions

The optimal duration of strategies for prevention of CIAKI is not known. As discussed in section VII.D.2, there are preliminary data indicating that iodinated contrast may persist in the kidney for several days following contrast-enhanced procedures. While it is not known whether this persistent contrast contributes to, or is a marker of renal injury, the planning committee felt that extending the administration of oral NAC to 5 days could be beneficial with little to no safety risk. Unlike the safety of longer duration NAC, extending the duration of IV fluids poses a risk for volume overload/pulmonary edema, would require prolonged hospitalization, and could be viewed unfavorably by both patients and providers. There was consideration given to providing oral sodium bicarbonate and oral sodium chloride tablets for 5 days. However, to match the amount of bicarbonate or saline given intravenously, nearly 7 grams of oral sodium bicarbonate and 5 grams of oral sodium chloride would have to be given daily, which would pose safety concerns regarding exacerbation of heart failure and/or worsening of hypertension. While lower doses of oral sodium bicarbonate and sodium chloride could be used, there are no preliminary clinical data to support this approach for the prevention of CIAKI or serious, adverse downstream outcomes. Therefore, although we extended the use of NAC to 5 days, our bicarbonate/saline intervention will be limited to IV fluid administration in the immediate peri-procedural period.

5. Potential for interaction between bicarbonate and NAC

Implicit in our use of a 2 x 2 factorial design is the *a priori* assumption that there is minimal to no interaction between the two study interventions. That is to say, the relative effect of bicarbonate in patients receiving NAC is the same as in patients receiving placebo, and the benefit of NAC is the same in patients receiving bicarbonate or saline. We acknowledge, however, that there are only limited data evaluating this interaction, and that these data are restricted to the prevention of CIAKI rather than prevention of serious, adverse outcomes. For example, in a recent systematic review and meta-analysis of IV sodium bicarbonate for the prevention of CIAKI, Zoungas et al. observed no difference in the incidence of CIAKI following

sodium bicarbonate administration with or without concomitant administration of NAC (p for heterogeneity = 0.73) in four studies which included data on 983 patients.[118] Similarly, Brown and colleagues found that combination treatment of NAC with IV sodium bicarbonate reduced CIAKI by 35% compared to NAC with saline in a meta-analysis of 10 randomized controlled trials.[119] In an experimental model, Romano et al. found no interaction between bicarbonate and NAC in the prevention of renal tubular cell apoptosis following exposure to iodinated contrast media.[169] Nonetheless, these data are insufficient to definitively exclude the possibility of an attenuation of benefit associated with combined therapy. We have taken this into consideration in our statistical analysis (*vide infra*); as designed, the study will retain greater than 80% statistical power even in the presence of a 50% attenuation in effect with combined therapy.

D. Selection of the primary study outcome

We recognize that there are potential pitfalls to the use of composite endpoints in clinical trials generally, and drawbacks to the specific components of our proposed primary composite outcome.[201] First, we selected the renal components of the endpoint as being representative of accepted, clinically meaningful decrements in kidney function, and included death as it represents a competing risk for the renal outcomes. However, we acknowledge that no prior studies have specifically examined the impact of interventions to prevent CIAKI on one component of this outcome: persistent decline in kidney function. Second, there may be disproportionate event rates for the individual components of the primary endpoint, although our preliminary analyses of existing data suggest that the incidence of each of the three components of the primary composite outcome occur with reasonably similar frequency. Third, we do not include major adverse cardiovascular events (e.g., acute coronary syndrome, heart failure, cerebrovascular accident) in the primary endpoint. Although these outcomes are of great clinical importance, they may primarily occur independent of the development of CIAKI in our study population. Moreover, we were concerned that any reduction in these events as a result of our study interventions would be masked by a high rate of these events that occurred independent of the interventions. Thus, we decided not to include these cardiovascular events in the primary study endpoint, but will assess them as a secondary outcome.

E. Ascertainment of baseline kidney function

In order to ascertain a change in kidney function, it is critical to standardize the definition of baseline kidney function. SCr often fluctuates over time because of variations in volume status, protein and salt intake, and drift in the calibration of laboratory instruments. The specific timing of the SCr used to screen patients is less critical than the value used to define the baseline SCr for endpoint ascertainment. For practical purposes, we propose to screen patients based on a SCr obtained as part of routine clinical care performed by the patient's provider within the 30 days prior to angiography. This will not be the same pre-angiography study SCr (reference SCr) that will be used to assess the development of persistent decline in kidney function (component of the primary endpoint) or to assess the development of CIAKI (a secondary endpoint). As a result, some patients who are found to be eligible and enrolled in the study based on the eGFR calculated from the SCr performed as part of routine clinical care will subsequently have an eGFR calculated from the pre-angiography study (reference) SCr measured at the central laboratory that is >60 mL/min/1.73 m^2 (diabetic patients) or >45 mL/min/1.73 m^2 (non-diabetic patients). While we do not anticipate that there will be many cases in which this discrepancy occurs, patients with such differences between the screening and pre-angiography study eGFR will not be excluded as the risk of CIAKI with progressive CKD is continuous and does not increase in a step-wise fashion as transitions between CKD stages occur. For example, the risk of CIAKI for a diabetic patient with an eGFR of 61 ml/min/1.73 m^2 (i.e., stage 2 CKD) is comparable to that of a diabetic patient with an eGFR of 59 ml/min/1.73 m^2 (i.e., stage 3 CKD). Thus, we anticipate that including the small number of study patients who are deemed eligible based on their screening eGFR but whose baseline study SCr corresponds to an eGFR greater than the inclusion criteria will have minimal impact on our event rate estimates. We believe that it is critical to use a central laboratory to ascertain the reference and endpoint SCr values to minimize variation related to drift in instrument calibration. Samples for reference and endpoint ascertainment on a single patient will be run sequentially on the same analyzer to minimize issues related to drift in calibration. While this introduces issues related to sample storage, SCr is known to be stable over time in samples stored at -20 ^oC.[202]

F. Assessment of secondary outcomes

1. Assessment of CIAKI

Most patients who develop CIAKI manifest an initial increase in SCr within 2 to 4 days following contrast administration. However, past studies demonstrate that some patients who develop CIAKI may not be identified by a single SCr assessment at 48 hours.[68] The optimal timing of assessment of SCr following the index angiogram to assess for the development of CIAKI in our trial was carefully considered by the planning committee. While it was agreed that multiple SCr assessments (e.g., at 2 days and 4 days) would ensure the identification of all patients who developed CIAKI, we ultimately determined that a single assessment at 4 days following angiography was optimal for several reasons. First, almost all patients who develop CIAKI will manifest an increase in SCr at 4 days following angiography. Second, an increase in SCr at 4 days following angiography is more likely to represent clinically significant CIAKI than an increase in SCr at 48 hours, as early changes in SCr are more likely to reflect transient hemodynamically-mediated perturbations in SCr rather than clinically consequential renal injury. Finally, the planning committee did not feel that measuring SCr at multiple time points in order to identify a small number of additional patients who meet criteria for this secondary outcome justified the added cost of more than $350,000 for each additional SCr assessment.

1. Assessment of cardiovascular outcomes

We acknowledge the potential limitations of using administrative data/medical records for the assessment of cardiovascular outcomes, including heart failure, acute MI and stroke. We will assess these outcomes by reviewing the hospital discharge summary for documentation of any of the events that comprise the secondary cardiovascular outcomes. We considered the possibility of adjudicating the secondary outcomes using more comprehensive medical record review. However, we believe that while this would be a more robust approach, the additional time, effort and cost required to adjudicate these secondary outcomes using a comprehensive review of the medical record was not justified.

G. Inclusion of a cost-effectiveness analysis and return on the investment to the VA

While the inclusion of an economic analysis as part of this trial was strongly considered, we ultimately decided that the addition of economic data collection would detract from the primary

conduct of the study. Given the reasonably low expense of our interventions and the considerable effort and cost of tracking patients' health resource utilization both within and outside the VA for an extended period of time (90 days), it was felt that including an economic analysis as part of this proposal was not advisable. If bicarbonate and/or NAC reduce the incidence of serious downstream outcomes following angiography as we hypothesize, there will likely be little reason to question their cost-effectiveness considering their low cost. That is, the effectiveness of the interventions will dominate the associated costs.

While the cost of this trial is substantial, there will be a clear return on the investment to the VA whether the trial results are positive or negative. After consulting with a series of pharmacists, we conservatively assume an incremental cost of preparing bicarbonate and NAC of $20 compared to the use of saline and non-use of NAC. Using conservative estimates of the number of angiograms performed in patients at high-risk for CIAKI, published costs of a single episode of CIAKI, and the incidence of this condition, demonstrating an absolute reduction in the incidence of CIAKI by 3% with bicarbonate or NAC will result in the study paying for itself within 1.3 years considering the costs to the VA and within 1 month considering the costs for all US health care (Table 8).

Table 8 – Return on the investment to VA Healthcare System and across all US health care

	VA Healthcare System	US Health care
Assumptions		
# high risk patients undergoing angiography yearly	50,000	750,000
Incremental cost of NAC and bicarbonate, per patient	$20	$20
Cost per episode of CIAKI [26]	$11,800	$11,800
Cost of study	$23,400,000	$23,400,000
If either NAC or bicarbonate decreases CIAKI by 3%		
# patients at risk	50,000	750,000
# patients/ year in whom CIAKI is averted by intervention	1,500	22,500
Projected cost benefit if study is positive, per year	$17,700,000	$265,500,000
Time to pay off cost of study	1.3 years	1 month
If both interventions are ineffective		
# patients/ year not treated with NAC and bicarbonate	50,000	750,000
Savings per patient	$20	$20
Annual savings of not implementing interventions	$1,000,000	$15,000,000
Time to pay off cost of study	23.4 years	1.6 years

While the return on the investment to the VA will take considerably longer in the event that bicarbonate and NAC are ineffective, a negative study also has important clinical as well as cost implications. First, it will prevent the widespread use of ineffective measures (i.e., bicarbonate and NAC) in perpetuity without an evidence basis to support their use. Second, it will prevent needless delays in the performance of angiographic procedures in urgent and emergent cases while awaiting bicarbonate and NAC preparation and administration. It is also important to note that these estimates of the return on the investment do not take into account the impact our findings are likely to have on preventive care provided to the large number of high-risk patients undergoing contrast-enhanced computed tomography both within and outside the VA Healthcare System. As our findings are highly likely to be translated to this large population of patients, the return on the investment to the VA and US health care overall is surely to be even greater than projected in Table 8.

H. Secular trends in the prevention and incidence of CIAKI

We acknowledge that it is possible that there will be new knowledge gained and changes in practice patterns related to the prevention of CIAKI and serious adverse outcomes following angiography during the conduct of the proposed trial. A comparison of the incidence of CIAKI reported in studies conducted in the 1980s to the incidence described in recent studies reveals a trend toward fewer patients experiencing this iatrogenic complication. However, much of this trend is likely related to the transition from the more nephrotoxic high-osmolal contrast agents to low and iso-osmolal contrast agents. Over the past decade, there is no evidence of a continued decline in the incidence of CKAKI or attenuation in the relationship between CIAKI and serious, adverse outcomes. This is best illustrated by a recent study of over 1,100 hospitalized subjects who underwent contrast-enhanced procedures that demonstrated that CIAKI developed in over 40% of patients and was associated with a 2-fold increase in hospital duration and a 10-fold increase in mortality.[22]

I. Alternative study design considerations

We acknowledge that the proposed study, which uses a 2 x 2 factorial design, does not include a comparison of NAC to placebo in the absence of IV fluids. While assessing the benefit of NAC in the absence of IV fluids would be an interesting question, there are two reasons we did not

consider this approach. First, it is widely viewed that the primary intervention with documented effectiveness for the prevention of CIAKI is IV administration of isotonic crystalloid. A randomized clinical trial by Trivedi et al. demonstrated that high-risk patients who received IV isotonic saline at the time of angiography were at markedly lower risk of developing CIAKI than patients who received unrestricted oral fluids only (RR=0.11, 95% CI: 0.02-0.8).[88] As a result, IV isotonic fluid is currently considered the standard of care for the prevention of CIAKI and withholding such treatment in a clinical trial is unlikely to be approved by existing Institutional Review Boards (IRB). Second, all but one of the published trials investigating NAC for the prevention of CIAKI were performed in conjunction with the administration of IV fluids.[23, 142, 144, 146-151, 153-158, 160-167] The single trial that did not use concomitant IV fluids enrolled a low risk patient population and failed to demonstrate a benefit of NAC.[152] Therefore, evidence of the efficacy of NAC in the absence of IV fluids is lacking. Thus, we believe that including a study arm that received NAC or placebo without any concomitant IV fluids would be inconsistent with the current standard of care, would lead to refusal of practitioners to allow their patients to participate in the study, and would likely be viewed as unethical by IRBs.

IX. FEASIBILITY OF RECRUITMENT

While our projected sample size is substantial, there are multiple important factors that support the feasibility of recruiting this large number of patients. First, the proportion of potentially eligible patients we will need to recruit in order to meet enrollment targets is relatively small. Approximately 47,000 Veterans who would meet eligibility criteria for our study undergo coronary or non-coronary angiography each year within the VA Healthcare System, of whom 27,000 (57%) undergo these procedures at the 33 busiest VA Medical Centers. The number of angiographic procedures performed on an annual basis in potentially eligible patients at these 33 centers ranges from a minimum of 519 to a maximum of 1,504. Assuming the need to enroll an average of 2 patients per week (100/year), successful recruitment of 6.7% of patients from the busiest center and 19% of patients from the 33rd busiest center would ensure the attainment of our target recruitment goal. Even if our estimate of the number of potentially eligible subjects was 25% lower than projected, we would need to recruit no more than 26% of subjects from the 33rd busiest hospital. In the event that not all of these 33 centers were able to participate in the study and certain of the 14 VA Medical Centers (sites 34-47) with the next highest volume of angiographic procedures were selected as sites, we would need to recruit no more than 25% of potentially eligible patients from the 47th busiest VA Medical Center to meet the target of 100 participants yearly. Second, patients undergoing coronary and non-coronary angiography are easily identifiable. Nearly all of these procedures are non-emergent and scheduled in advance, which greatly facilitates identification and screening of potential study subjects. Third, unlike trials that recruit from a diverse array of patient settings (e.g., primary care offices, hospital wards, specialty clinics), our trial will recruit patients from just two hospital venues: cardiac catheterization laboratories and interventional radiology suites. This greatly simplifies the process of identifying and locating potentials participants. Fourth, at most VA Medical Centers, coronary and non-coronary angiograms are performed by a small number of medical practitioners. Unlike trials that require the assistance of many providers to identify potential patients, our study staff will only need to engage a small number of interventional cardiologists and radiologists at each study site. Fifth, many patients undergoing angiograms would be receiving one or both of our interventions (IV fluids and NAC) independent of study participation. Therefore, few patients or providers are likely to view the interventions as experimental or unsafe. Sixth, patient burden in this study is quite limited since there is no need

to return to the hospital for study visits. Follow up data collection will be performed using telephone calls, while multiple options are provided for the required blood draws including use of a mobile phlebotomy service if the patient is unable to return to the VA or the option of having the blood drawn at non-study VA site such as a Community-Based Outpatient Clinic (CBOC) or another VA facility closer to the participant's home. Therefore, patients are unlikely to view participation as unduly burdensome.

It is also essential to note that the VA cohort study that we conducted in 2005-2006 provided us with highly valuable experience recruiting patients undergoing coronary and non-coronary angiography and demonstrates our past success in enrolling Veterans undergoing angiographic procedures. In that prospective study that required patients to return to the VA following angiography for a follow-up blood draw, we successfully recruited 63% of eligible patients. This recruitment rate is more than 3-fold higher than the most conservatively estimated recruitment rate that will be required for the successful attainment of the target population in the proposed clinical trial. We are highly confident in our capacity to successfully recruit the number of patients needed to meet our enrollment targets.

X. ANTICIPATED BARRIERS TO RECRUITMENT AND STRATEGIES TO ADDRESS POTENTIAL UNDER-ENROLLMENT

A. Development of multi-disciplinary study teams

Despite the feasibility of recruitment as outlined above, successful enrollment of the large number of patients we hope to enroll will depend in large part on the interest and willingness of interventional cardiologists and radiologists to have their patients enrolled. We recognize that these practitioners may not be focused on or necessarily prioritize the prevention of CIAKI and its associated outcomes, especially since they are often not involved in the longitudinal care of patients and may not be notified of delayed complications of angiography. We believe that establishing multi-disciplinary study teams at each site, including nephrologists, interventional cardiologists, and interventional radiologists will optimize the potential for successful subject enrollment. Just as we had a multi-disciplinary planning committee, we will include interventional cardiologists and interventional radiologists as site Principal Investigators. We will have a pre-study meeting with providers who perform angiograms at each study site to discuss the protocol and address questions and concerns they have regarding the study. We believe that the flexibility built into the protocol for study IV fluid administration rates, volumes, and durations will be attractive to providers performing angiography and will increase their interest in and willingness to have their patients participate in the study.

B. Exclusion of patients enrolled in other clinical trials

Given the significant number of large, clinical trials targeting patients undergoing coronary angiography, it is possible that patients who are eligible for inclusion in our study could be enrolled in or eligible for other interventional trials. Current CSP policy, while discouraging dual enrollment, does allow it if certain conditions are met. We will follow CSP policy, as per the following paragraph, in this regard:

> It is CSP policy that a participant be enrolled in only one drug or device intervention, randomized clinical study at any one time. It is permissible for participants to be in other non-interventional studies while participating in a CSP study (e.g., surveys, long-term follow-up cohort studies). Exemptions to this CSP policy will be allowed for individual participants on a case-by-case. Exemptions on the basis of an entire study are

rare. Exemption requests will require the agreement in writing of all of the following individuals or groups: (1) the Site Investigators of both studies; (2) the Study Chair of the involved studies; and (3) the appropriate CSP Center Director(s). Exemptions sought on a per study basis are obtained using a similar process with the exception that letters from individual SIs would not be required. The Director, CSR&D makes the final decision. Only after the Director, CSR&D has given final approval, will the participant be allowed to participate in both studies. Approvals for exemption are primarily based on what is best for the participant and to protect the integrity of the involved studies.

C. Strategies to address under-recruitment of study subjects

Given the large size of our study and the critical importance of adequate patient recruitment, we anticipate using a number of strategies to address under-recruitment should it occur. First, in addition to the 33 VA study sites that we will include at the outset of the study, we will identify at least five additional VA centers as alternative study sites. We will closely monitor screening and enrollment at each site on an ongoing basis. Sites that fail to meet pre-specified milestones for recruitment may be placed on probationary status (See Section XIV.E.). If a participating site continues to fail to meet enrollment targets at pre-specified time points, we will exercise the option of replacing the site with one of the pre-identified alternative VA centers. Alternatively, we may choose to reduce funding to underenrolling sites (e.g., eliminating payment for the Research Associate or reducing funding for the Study Coordinator to less than full-time status) and utilize those funds to increase support to high enrolling sites, or within budgetary constraints, to activate one or more additional study sites. One advantage of the short follow-up (90 days) is that it will allow us to re-allocate resources in a relatively short period of time.

Second, based on current eligibility criteria, we will exclude patients with baseline eGFR values of 45-60 ml/min/1.73 m^2 who do not have diabetes because they are at slightly lower risk for CIAKI and serious, adverse, downstream outcomes. However, if we encounter difficulty meeting recruitment targets, we will reconsider the option of broadening our eligibility criteria to include patients with baseline eGFR 45-60 ml/min/1.73 m^2 without diabetes,

but who have a documented history of heart failure in their medical record, which is another known risk factor for CIAKI. This approach, which would require us to operationalize a definition of non-decompensated CHF (e.g., NY Heart Association Functional class III-IV and/or a history of pulmonary edema due to cardiac disease), would only be utilized if all other efforts to boost enrollment were unsuccessful.[203] We believe that having these two strategies to address potential under-enrollment will help ensure the attainment of the target sample size without compromising the scientific integrity of the study.

D. Inclusion of non-VA study sites in Australia, New Zealand, and Malaysia

As part of the planning process for this trial, we engaged with investigators from The George Institute for Global Health (TGI) in Sydney, Australia. The George Institute has an impressive track record in the conduct of large clinical trials and has collaborated with the Australia/New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) in prior trials of acute kidney injury. While collaboration with The George Institute is not necessary to execute the trial based on our estimates of the numbers of procedures performed within the VA, collaboration will allow for the inclusion of non-VA study sites, increase the number of potential participants, and enhance the generalizability of the study to non-Veterans and women. The investigators from TGI are being sponsored by the National Health and Research Council of Australia for funding of approximately 10 sites and will enroll a total of 1,000 patients.

XI. FUTURE ANCILLARY STUDIES

In addition to the primary study, we may in the future perform additional ancillary studies related to the primary study, including following patients for a longer time to track renal and cardiovascular outcomes and mortality. In addition we may collect blood and urine specimens for biomarker testing to develop diagnostic and prognostic tests. These future ancillary studies will have separate protocols, consent documents and funding but will enroll participants from the parent study.

XII. HUMAN SUBJECTS

A. Informed consent

Potentially eligible patients will be identified by research personnel at each site. After the study is introduced to the patient by an individual participating in their care, research personnel will contact potentially eligible subjects to describe the study and present him/her with the detailed informed consent form and supplementary material to read and review.

The general purpose of the study will be delineated and the treatment comparisons will be clearly described. The process of randomization will be discussed and a clear explanation of what will be expected of the patient will also be described. The risks associated with treatments and procedures will also be addressed. The importance of patient confidentiality will be stressed, including a description of the process for maintaining patient confidentiality. Research personnel will ensure that the patient understands every aspect of the trial, including its risks and benefits, prior to signing the informed consent.

If the patient agrees, his/her consent to participate in the study will be documented on the Agreement to Participate in Research form (VA form 10-1086). The original will be placed in the patient's medical record. Copies of the consent form will be provided to the patient, placed in the patient's study file, and faxed to the MAVERIC CSPCC at the time of enrollment in the study. A copy of the consent will also be posted in the patient's electronic medical record. If the site is unable to scan the consent into the patient's electronic medical record, a CPRS template or Word document that contains the currently approved consent language can be included in the enrollment note in CPRS. The note should contain information that indicates that the Veteran signed a paper copy of the consent and should list the ICF version number and date of signature. The note should also state that the copy is located in the investigators study file.

Informed consent requires that the patient understand the details of the study and agree, without coercion, to participate in the study. To obtain informed consent, the following information shall be provided to each subject:

- Name of the study
- Name of the Principal or Site Investigator(s)
- Explanation that the study involves research
- Explanation of the purpose of the study
- Explanation of the treatment procedures
- Description of randomization
- Description of the risks and benefits of participation in the study
- Description of alternatives to participation in the study
- Explanation that all records will be kept confidential, but that records may be examined by representatives of the VA and/or the FDA
- Whom to contact for questions about the research and about subjects' rights
- Whom to contact in the event of a research-related injury
- A statement that participation in the study is voluntary and that a decision not to participate or to withdraw from the study after initially agreeing involves no penalty, loss of benefits, or reduction in access to medical care
- A statement that the treatments provided as part of this study are free

Merely obtaining signed consent from the patient does not constitute informed consent. However, the use of a standardized consent form aids in assuring that subjects receive adequate and consistent information about the trial and that they have consented to participate.

In conjunction with the informed consent procedure, patients will review and be asked to sign the Authorization for Release of Protected Health Information Form as required by HIPAA.

B. Risks and benefits

Any procedure/intervention has potential risks. The interventions used in this study may cause all, some, or none of the risks and side effects listed. There is also the potential for rare or unknown risks to occur. Active study participants will be informed of any information that becomes known during the course of the study regarding risks of the interventions that might affect their willingness to continue to participate.

1. Side effects associated with infusion of intravenous fluids

Reactions due to solution or technique of administration: febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, and extravasation of fluids

2. Side effects associated with infusion of sodium chloride

Cardiovascular: heart failure (aggravated), edema

Endocrine and metabolic: hypernatremia, hyperosmolarity, hypokalemia, metabolic acidosis

Respiratory: pulmonary edema

3. Side effects associated with infusion of sodium bicarbonate

Cardiovascular: heart failure (aggravated), edema

Central nervous system: hyper-irritability or tetany may occur due to rapid shifts of free ionized calcium or serum protein alterations arising from changes in pH

Endocrine and metabolic: hypernatremia, hyperosmolarity, hypocalcemia, hypokalemia, increased affinity of hemoglobin for oxygen, reduced pH in myocardial tissue, necrosis when extravasated, intracranial acidosis, metabolic alkalosis

Respiratory: pulmonary edema

4. Side effects of NAC

Cardiovascular: flushing, tachycardia, edema

Dermatologic: urticaria, rash, pruritus

Gastrointestinal: diarrhea, nausea, vomiting

Respiratory: pharyngitis, rhinorrhea, rhonchi, throat tightness

Central nervous system: dizziness

<1%, postmarketing, and/or case reports (limited to important or life-threatening):
anaphylaxis, bronchospasm, chest tightness, cough, dyspnea, hypotension, respiratory distress, stridor, wheezing

Possible benefits of this study include a reduced risk of serious adverse outcomes, including death, need for acute dialysis, and persistent decline in kidney function among subjects receiving bicarbonate and/or NAC.

XIII. DATA MANAGEMENT

Source documents may include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Paper source document worksheets will be provided to study coordinators to facilitate data collection. If a paper source document worksheet is used as a primary means of collecting data (the data elements are newly created and not transcribed from other sources) then it will be considered a source document and must be maintained. The MAVERIC CSPCC will manage the trial data using a web-based Electronic Data Capture (EDC) system. The EDC system will allow study coordinators to enter the source data into a web-based study database and manage their patients, handle data clarifications, and correct patient data. Accordingly, the electronic system will be used to create, modify, maintain and retrieve clinical data for CSP#578 during each step of the data collection process.

After the study is approved, the Study Chairmen and Study Director will prepare an Operations Manual for site staff to guide them through the operation and management of the study and data collection tools. A training session will occur at the study kick-off meeting for all investigators and coordinators to assure uniformity in patient management, data collection, and study procedures. At this training, coordinators will be provided with reference materials on the software tool and tasks. Once formal training is completed, user accounts utilizing a URL specific to the study to access and use the system and enter patient data will be activated. Accounts will be password protected and unique to the users' functional study group (i.e., those for a study coordinator would differ from those of the coordinating center or site monitors). Formal training on the use of the EDC system for clinical study management will also be provided. Systems training may also be held at annual meetings and on an as-needed basis for new research personnel.

The MAVERIC CSPCC will utilize an EDC tool that is fully compliant with U.S. Federal regulations regarding electronic web-based data capture systems established by the FDA under

21 CFR 11. This system is designed to make the process of patient data management easier, timelier, and more efficient. Accessing the system requires a VA intranet connection and a web-browser. The paper source documents from which data will be entered into the electronic data capture tool's case report forms provide the official clinical record for data collection. All paper-based study records will be kept under lock and key. The EDC system will be validated by the MAVERIC CSPCC Validation Team to ensure the integrity of the data capture software. Validation documentation and all system dependability documentation (i.e., software and hardware versions, etc.) will be maintained as study documentation, but will not be detailed in this protocol.

For this trial, EDC designers will create a study-specific database that includes case report forms, interview schedules, and data queries using customized code imbedded directly into electronic case report forms. Data clarifications forms (DCFs) or data queries will be managed in two ways. Certain queries will be programmed into the forms that are designed to activate upon data entry. Additional DCFs will be programmed using other data analysis tools such as SQL and will be uploaded into the system for study coordinators to address. Furthermore, the system will allow manual DCFs to be entered into the EDC system by the coordinating center as needed. Updates to the electronic forms and database can be generated during the study without impacting collected data. Study reports can be generated from exported data in order to track the study progress and to monitor adverse events, in particular Serious Adverse Events. Study reports will be circulated to appropriate members, including the site investigators, the study chairmen, and the Data Monitoring Committee (DMC).

The servers housing the study databases will be located at secure VA facilities that support round-the-clock web services and monitoring within a secure VA environment in order to provide an optimal infrastructure for the protection of sensitive information. The clinical database with all research data will be housed behind the VA firewall on VA owned and maintained servers. Accordingly, the information housed within the EDC system will be afforded the same level of security as all forms of VA protected and/or highly sensitive information. Additionally, the system will be monitored by the MAVERIC CSPCC Quality Assurance and Information Technology teams to ensure that all applicable VA regulations and directives are strictly followed.

Backup copies of the database will be transferred behind the VA firewall to the MAVERIC CSPCC on a frequent basis depending on the study need (at least once per day). These backup copies will be transferred and stored across secure connections according to VA regulations and MAVERIC CSPCC operating procedures. Periodic off-site back-ups will be made as part of a comprehensive disaster recovery plan. The Director of Information Technology will ensure that backup media are stored in compliance with all federal and VA regulations on the storage of potentially sensitive information. The Director of Information Technology will also ensure that all backup media are encrypted in compliance with the current best practices established and approved by the Center Director(s). Encrypted backup media will be stored in a physically secure location with access restricted to essential personnel. Access to back-ups may be at the discretion of the Center Director(s) and/or the Director of Information Technology.

Access to the study data is heavily restricted to individuals with CSP approval. Individuals must be properly credentialed research staff and must be compliant with VA security trainings (i.e., Research Data Security, HIPAA and VA Privacy Training, Information Security Awareness, and Good Clinical Practices). In addition, research data will be stored on VA secure servers with restricted permissions for copying and exporting data. Only properly approved Coordinating Center personnel will have the ability to copy and export data. These individuals have received training on the local SOP governing their permissions and will not access or export data without written approval from the MAVERIC CSPCC Center Director. Furthermore, the permissions of the electronic systems are structured such that individual sites can only see the data for their study participants. They cannot see or access the data for another clinical site or for another participant.

Access to protected health information (PHI) will be restricted to individuals approved by CSP to have access to the data. Once an individual is no longer an active member of the research team, their access to research data will be removed.

At the Local Clinical Sites, individuals in these positions will be able to access PHI:

- Site Investigator
- Co-Site Investigator
- Study Coordinator
- Project Support Staff

At the MAVERIC CSPCC, individuals in these positions will be able to access PHI:

- Center Director
- Study Director
- Project Manager
- Project Coordinator
- Research Assistant
- Data Manager
- Database Coordinator
- Biostatistician
- Junior Biostatistician
- Quality Assurance Officer
- SAS Programmer

At the CSPCRPCC, individuals in these positions will be able to access de-identified forms of PHI:

- Clinical Monitors
- Study Pharmacist
- Adverse Event Specialist (Regulatory Affairs and Safety Officer)
- Pharmacy Project Manager

Research data will only be stored on secure VA servers within the VA firewall. Data will not be stored on desktops or on University affiliate servers. Study data will be coded with a unique study identifier for each participant and stored in a de-identified manner. Identifiable information will be collected for patient tracking and safety purposes. All private information will be kept on an encrypted, password protected server to which a small number of people will have access. Access to the cross-walk file linking the participant's identifiers and their study data will be

restricted to the clinical site and to the approved personnel at the coordinating center. This file will be destroyed according to CSP policy.

When the study is on-going, the electronic data capture systems will utilize state-of-the-art technologies in order to protect the data during transmission. All of these technologies exceed the current VA standards for transport. In brief, electronic systems will employ secure socket layer technology and FIPS 140-2 compliant encryption algorithms to ensure that data is not vulnerable during transport. In addition, all data will be stored within the VA firewall and will be password protected at all times. Hard copy data will be sent via a traceable mail system (i.e., UPS), via a courier, or via secure fax. Faxes are electronically routed to document management systems housed on VA protected servers located at the Regional Data Center in Philadelphia, PA. Access to these secure fax servers is restricted to the Coordinating Center personnel with approved access to the system. All secure fax servers are compliant with VA directive 1605.1 and 6500. All data security incidents will be reported in accordance with VA policy within one hour of discovering the incident to the District (local) Information Security Officer (ISO) and the MAVERIC CSPCC Data Security Officer. Data security incidents will be reported to the VA Central IRB within 5 days of becoming aware of the event.

Quality control checks and clinical monitoring will enable the Coordinating Center to survey the study database and the clinical sites to ensure that the data have not been improperly used or accessed. 21 CFR part 11 compliant audit trails and access logs will be checked routinely. In addition, the clinical monitors (SMART) will provide continuing education on good clinical practices and will check clinical site operations for compliance with data security policies and best practices.

The clinical data for CSP 578 are considered property of the Cooperative Studies Program and shall not be sent off-site (i.e., outside of the VA) without the expressed, written permission from the MAVERIC CSPCC Center Director and CSP Central Office. All data transfer and data security policies of the VA, the Cooperative Studies Program, the MAVERIC CSPCC, and the local healthcare system will be closely followed. The MAVERIC CSPCC Quality Assurance team will work closely with the local research compliance officer, the information security

officer, and the VA privacy officer as needed to ensure that data security and data transfers are handled appropriately.

Retention and destruction of data will be conducted according to CSP operating procedures and federal and local VA regulations. This will include paper and electronic data stored at the local sites, the MAVERIC CSPCC, and at the VA facility housing our servers. Identifiable data will be kept according to CSP policy as outlined in the "CSP Guidelines for the Planning and Conduct of Cooperative Studies."

At the completion of the study, a data set from the study will be banked at the MAVERIC CSP Coordinating Center in a data repository that will be established for research purposes under the oversight of the VA Boston Institutional Review Board. The Data Repository will be established and used in accordance with the Repository Protocol, relevant Standard Operating Procedures, and existing regulations. Data will be made available to appropriately credentialed researchers conducting studies related to the topics explored in this protocol or other health questions in accordance with the Standard Operating Procedures of the Data Repository.

Regarding our collaboration with The George Institute in Australia, as described in Section X.D., study data from the VA and The George Institute will be submitted to MAVERIC CSPCC and analyzed as one combined dataset.

XIV. QUALITY CONTROL PROCEDURES

A. Standardization/validation of measurements

Prior to the initiation of the study, all investigators from the clinical sites as well as study coordinators will meet to review study procedures and receive training on collecting data for the study. Much of this training will take place during the study kickoff meeting. The protocol and source document worksheets will be sent to site investigators and coordinators to review prior to the meeting. During the meeting, study coordinators will receive training on obtaining and maintaining source documents and completing study assessments and electronic case report forms. Verbal feedback and discussion will follow to ensure that each coordinator comprehends the proper methodology for assessment. The meeting will also cover an in-depth review of the study operations manual. Such a review will serve to reinforce the training described above and will orient the research personnel to the reference guides for the study.

Prior to the start of any study using the MAVERIC CSPCC electronic data capture tool, extensive study specific validation will be performed. This process will be documented and placed on file at the MAVERIC CSPCC.

B. Patient management

For CSP 578, the site investigator at each site will be responsible for the management of his/her patients. If the patient is unable to return to the VA facility at which their angiogram was performed for specimen required blood collection other o ptions for this blood draw may include, but not be limited to: 1) having a mobile phlebotomy service draw the blood; or 2) having the blood drawn at a non-study VA site such as a Community-Based Outpatient Clinic (CBOC) or another VA facility closer to the participant's home. Every effort will be made to accommodate the patient's schedule and safety concerns.

C. Protocol deviations

Documentation of any protocol deviations will be required. A Protocol Deviation form has been created by the MAVERIC CSPCC to ensure the proper tracking of events. Protocol deviations will be evaluated by the Study Chair's office and the MAVERIC CSPCC, and a determination made regarding the validity of any justification for the deviation. Any medical center or subject

with repeated protocol deviations in the absence of valid justification, and after remedial protocol training, will be recommended for termination to the DMC. If any member of the DMC or the monitoring bodies for CSP 578 feel that adherence to the protocol will be detrimental to a participant's health or well-being, the interest of the participant will take precedence and the subject will be withdrawn after consultation with the Executive Committee. Protocol deviations will be reported to the VA Central IRB as required.

D. Unblinding the study treatment

This CSP clinical trial is a double-blinded study in which neither the patient nor the site investigator knows to which of the four study arms the patient has been assigned. The CSPCRPCC will not provide Emergency Code Envelopes to the sites' Pharmacy Service. Emergency unblindings will be managed through the 24-hour emergency call service (505-248-3203). This number is also listed on the patient ID cards given to each patient participating in CSP #578. The system managed by the CSPCRPCC will electronically capture up-to-date study drug assignment information gathered from the PRESERVE IWRS.

Under unusual circumstances, chiefly related to participant safety, unblinding may be necessary. This is usually done after consultation with the Study Chair, Steven Weisbord MD, MSc or Study Co-Chair, Paul Palevsky MD. If Dr. Weisbord and Dr. Palevsky are unavailable, the CSPCRPCC Clinical Research Pharmacist (Todd Conner, PharmD) or the Study Director (James Kaufman, MD) should be contacted. Current telephone numbers are listed in the study personnel directory on the CSP578 Main SharePoint Site.

If unblinding is required in an emergency, the Local Site Investigator (LSI) or Study Coordinator (SC) must contact the CSPCRPCC through the 24-hour emergency call service to obtain study drug assignment information. The CSPCRPCC will notify the Study Chair's Office and the MAVERIC CSPCC by telephone as soon as possible after an unblinding has occurred. If the CSPCRPCC receives a request for unblinding information from anyone other than the LSI or SC, the CSPCRPCC will refer the requester to the LSI or SC or, in his or her absence, the CSPCRPCC will confer with the parties above.

E. Probation/termination of participating centers

The recruitment rate and operational aspects of this study will be monitored continuously by the Study Chairmen and MAVERIC CSPCC. Medical centers may only continue participation if the performance measures described below are met. Termination of a center will only be taken in accordance with Cooperative Studies policies and procedures.

The following performance measures will be used to determine whether sites are at risk for or should be placed on probation. Other reasons for probation include, but are not limited to, noncompliance with the protocol, ICH, or applicable federal regulations.

1. Recruitment rate. Recruitment rate will be calculated by dividing the number of randomized patients by the number of expected patients. This measure will be continuously monitored and sites between 75% and 90% of expected recruitment will be subject to remediation such as action plans or mentoring. Sites under 75% cumulative recruitment after a 3-month ramp-up period may be placed on probation. Assessment for probation will occur on a monthly basis.

2. Follow-up rate. Follow-up rate will be calculated by dividing the number of patients with any 90-day follow-up forms completed by the expected number of patients with 90-day visits due. Both the numerator and denominator will be subject to a 4-week delay in order to allow for scheduling of the 90 day visit and completion of forms. Sites with cumulative follow-up rates below 90% may be placed on probation. Assessment for probation will occur on a monthly basis.

3. Forms Completion rate. Forms completion rate will be calculated by dividing the number of completed forms by the number of expected forms, where the number of expected will exclude forms marked not collected. Forms completion rates will be calculated both by patient and by form. Sites with cumulative forms completion rates under 90% may be placed on probation. Assessment for probation will occur on a monthly basis.

Once a site is placed on probation, failure to meet the requirements specified by the end of the probation period will result in a recommendation for termination. Additionally, sites that fail to meet two or more of the above performance measures, and sites that habitually under-perform by any of these measures, will be at risk of termination. After careful monitoring of site performance by study leadership, a site may be terminated without being put on formal probation if deemed appropriate.

XV. GOOD CLINICAL PRACTICES

1. Role of GCP

This trial will be conducted in compliance with Good Clinical Practice (GCP) regulations. The intent of these regulations is to safeguard subjects' welfare and assure the validity of data resulting from the clinical research. The VA Cooperative Studies Program will assist Local Site Investigators (LSIs) in complying with GCP requirements through its Site Monitoring, Auditing and Resource Team (SMART) based in Albuquerque, NM. SMART serves as the Quality Assurance arm of CSP for GCP compliance. Study site personnel will receive a GCP overview at the study organizational meeting.

.SMART will provide training, manuals and materials to assist study personnel in organizing study files and will be available throughout the trial to advise and assist LSIs regarding GCP issues.

2. Summary of Monitoring and Auditing Plans
   a. Monitoring Visits –
      (1) Initiation visits at each site soon after study start-up
      (2) Subsequent monitoring will be conducted yearly thereafter
      (3) Final monitoring visit to each site during last year of study
      (4) Additional monitoring visits may be conducted as deemed necessary by study leadership or SMART.
   b. Audits
      (1) Routine audits – independent site visits to one or more sites per year as determined by SMART.
      (2) For-Cause audits –independent audit of a site as requested by study leadership or CSP Central Office.
      (3) Audits may be scheduled or unannounced.

XVI. STUDY MONITORING AND AUDITING PLANS

Protection of the rights and welfare of patients is a primary concern of CSP. In addition to the International Conference on Harmonisation (ICH) Good Clinical Practice Guidelines, this trial will be conducted in compliance with VA guidelines, the Declaration of Helsinki, and the applicable parts of the United States Code of Federal Regulations or local laws governing the conduct of good clinical studies.

A. Monitoring bodies

Four external bodies will oversee the ongoing scientific and ethical conduct of the study including the Data Monitoring Committee, the CSPCC Human Rights Committee (HRC), the VA Central IRB and Clinical Monitors (SMART). In addition, at the mid-point of the study, the Cooperative Studies Scientific Evaluation Committee (CSSEC) will review the study.

By agreeing to participate in the study, the medical center delegates responsibility for global monitoring of the ongoing study to these four bodies. However, the Research and Development (R&D) and the Human Studies Committee of the local medical center may require the investigators to submit additional reports concerning the status of the study. Internal operational oversight (described in Section XVIII) will be conducted by the MAVERIC CSPCC, the CSPCRPCC and the Study Chairmen's Office.

1. Data Monitoring Committee

The Data Monitoring Committee (DMC) will review the progress of the study and monitor adherence to the protocol, participant intake, outcomes, complications, and other issues related to participant safety. They will also monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate. The DMC will be composed of experts in nephrology, cardiology, and clinical trials. The Study Chairmen will make nominations to the Director, Cooperative Studies Program, who will make the final selection for the Committee. The DMC will make recommendations to the Director of the Cooperative Studies Program as to whether the study should continue or be terminated. The DMC can consider participant safety or other circumstances as grounds for early termination, including either compelling internal or external

evidence of treatment differences or feasibility of addressing the study hypotheses (e.g. poor participant enrollment, poor adherence). The DMC will conduct an in depth assessment of safety and efficacy data every six months at which time the study biostatistician will provide the DMC with an interim summary report on the study status and on safety data for monitoring purposes.

2. Human Rights Committee

The Human Rights Committee (HRC) at the Coordinating Center may review the study at the request of the Coordinating Center Director in order to provide suggestions regarding study participants' protection.

3. VA Central IRB

The VA Central IRB provides expert ethical and scientific review of multi-site projects while ensuring local issues are addressed. The VA Central IRB performs full, expedited, exempt, and continuing review and provides waivers of HIPAA authorization as necessary and appropriate. The VA Central IRB meets monthly in person and/or by video or teleconference. The Study Chairmen will initially submit a principal investigator (PI) application which will include model documents such as the informed consent form and any waiver requests. Once approved, this application package will be sent to all potential participating sites who will be responsible for submitting their own local site investigator (LSI) applications. Once both the PI and LSI applications have been approved, the study is reviewed in accordance with local R&D Committee policies and the VA Central IRB is provided a copy of the site approval document for the study to begin at that site. Continuing reviews are done annually.

4. CSP Site Monitoring, Auditing and Resource Team (SMART)

The CSP Site Monitoring, Auditing and Resource Team (SMART), located in the CSPCRPCC in Albuquerque, will monitor the trial for compliance with Good Clinical Practices. GCP monitors from SMART will visit participating sites shortly after enrollment is initiated and subsequent monitoring will be conducted yearly thereafter to monitor investigator regulatory and protocol compliance and to evaluate research practices. SMART will provide an orientation to GCP at the study kick-off meeting and provide GCP tools to enhance compliance. Additionally, SMART will

conduct periodic routine audits throughout the course of the study and for-cause audits as requested by study leadership or CSP VACO

B. Monitoring adverse events (AEs) and serious adverse events (SAEs)

Timely and complete reporting of safety information assists study management in identifying any untoward medical occurrence, thereby allowing: 1) protection of study patients' safety; 2) a greater understanding of the overall safety profile of the study interventions and therapeutic modalities; 3) appropriate modification of the study protocol; 4) improvements in study design or procedures; and 5) compliance with regulatory requirements.

The local Site Investigator will be responsible for the AE and SAE reporting requirements as described in this protocol and outlined below:

- Closely monitoring research subjects during the study for the development of new AEs and SAEs.
- Reviewing the accuracy and completeness of all AEs and SAEs reported.
- Reporting all SAEs to the CSPCRPCC and MAVERIC CSPCC within 72 hours of becoming aware of the event.
- Complying with VA Central IRB policies for reporting adverse events
- Implementing plans the Study Group and Executive Committee may develop in response to safety concerns.

1. Adverse events

Adverse events (AEs) are defined by the VHA Handbook 1058.01, paragraph 4 (a) as "An AE is any untoward physical or psychological occurrence in a human subject participating in research. An AE can be an unfavorable and unintended event, including an abnormal laboratory finding, symptom, or disease associated with the research or the use of a medical investigational test article. An AE does not necessarily have to have a causal relationship with the research. "

For the purpose of CSP 578, the study interventions are study IV fluids and oral NAC/placebo. Related events involve an assessment of the degree of causality (attribution) between the study interventions and the event. Site investigators will be asked to provide an assessment of

relatedness. All AEs with a reasonable causal relationship to the investigative treatment will be considered "related." A definite relationship does not need to be established.

Local site investigators, with assistance from their study coordinator, are responsible for collecting AE information regarding the subjects at their sites. During the study, data on adverse events will be collected spontaneously through patient reports, actively elicited during the angiography visit through open-ended questioning and examination, and gathered at the time of telephone contact and medical record reviews during the follow-up period. Related adverse event data will be collected from the time of consent to 35 days post angiography. If a patient receives care at a non-VA facility for an adverse event they experience, research personnel will obtain the requisite release of information form(s) from the patient and once received, acquire the pertinent medical records from the facility.

AEs related to the study intervention that are reported to research personnel will be recorded on an adverse event form and documented in source records (e.g., the electronic VA medical record and/or the subject's study record). In this way, the site creates a permanent record that provides information on the subject's clinical course while in the study.

Adverse events which develop into Serious Adverse Events, as defined below, will be reported as such and followed to resolution or stabilization.

2. Serious adverse events

Serious adverse events (SAEs) are a subset of adverse events defined in VHA Handbook 1058.01, paragraph 4(r) and 21 CFR 312.32(a), as follows:

Definition of SAE from CFR 312.32 (a): Serious adverse event. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening,

or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Definition of SAE according to VA Handbook 1058.01: An SAE is an untoward occurrence in human research that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth defect, or that requires medical, surgical, behavioral, social, or other intervention to prevent such an outcome.

All SAEs, as defined in VHA Handbook 1058.01, paragraph 4(r) and 21 CFR 312.32(a), will be collected, regardless of whether or not they are considered related to the study interventions. SAEs with a reasonable causal relationship to the study interventions and associated medications will be reported as "related." A definite causal relationship does not need to be established.

Local site investigators, with assistance from their study coordinator, are responsible for collecting SAE information regarding the subjects at their sites. SAEs will be collected from the time of consent through day 90 following the patient's index angiography procedure or the time of patient termination if before day 90. During the study, data on SAEs will be collected spontaneously through patient reports, actively elicited during the angiography visit through open-ended questioning and examination, and gathered at the time of telephone contact and medical record reviews during the follow-up period. If a patient receives care at a non-VA facility for a serious adverse event they experience, research personnel will obtain the requisite release of information form(s) from the patient and once received, acquire the pertinent medical records from the facility.

SAEs that are reported to research personnel will be documented in source records (e.g., the electronic VA medical record and/or the subject's study record). In this way, the site creates a permanent record that provides information on the subject's clinical course while in the study. Research personnel at the site will ask follow-up questions to determine the exact nature of the SAE and obtain appropriate medical records, if needed. Each SAE will be followed to resolution or stabilization or until the end of study participation.

a. Expedited reporting of serious adverse events

All SAEs must be reported to CSPCRPCC and MAVERIC CSPCC and entered into the EDC system within 72 hours of the local site staff becoming aware of the event. The site must notify MAVERIC CSPCC, Chair's Office, and CSPCRPCC of the event by email upon entering the SAE into the EDC system. The SAE will also be documented in source records (e.g., the electronic VA medical record and/or the subject's study record).

SAEs that are BOTH unanticipated AND related to the study interventions (administration study fluids or NAC/Placebo) will be reported, in writing, to the VA Central IRB within 5 business days of the local staff becoming aware of the event. In addition, any research deaths that are BOTH unanticipated AND related to the study interventions will be reported by telephone to the VA Central IRB immediately upon the local staff becoming aware of the death. Written notification to the VA Central IRB must follow within 5 business days of becoming aware of the death.

All other SAEs (i.e., SAEs that are either anticipated or unrelated to the study interventions), including deaths that are either anticipated or unrelated to the study interventions, will only be reported to the VA Central IRB at the time of Continuing Review (CR). Sites should maintain the individual participant CSP #578 AE Tracking Logs provided by SMART to facilitate this reporting.

If an event meets FDA reporting criteria, meaning it is serious, unexpected and deemed possibly related to the study drug it will be reported by the CSPCRPCC to the CRADO after review by the Study Pharmacist, Study Chairs, MAVERIC CSPCC Director, and CSPCRPCC Director.

If needed, as required under the Food and Drug Administration Investigational New Drug (IND) protocol, CSPCRPCC will report SAEs that are both related to study intervention and unexpected to the FDA no later than 15 days from when they are notified. If the SAE is a death or a life-threatening event, this notification will happen within 7 days.

b. Monitoring of serious adverse events

SAEs will be monitored throughout the study by the Data Monitoring Committee. The study pharmacist and study biostatistician will generate tabulations of AEs and SAEs and present a summary of all AEs and SAEs to the DMC on a schedule set by the DMC. The DMC will also determine when they should be unblinded to treatment assignment for the reviewing of adverse event data. The DMC will recommend to the CSRD Director whether the study should continue or be stopped for safety reasons. The DMC will also monitor the primary endpoint at pre-determined intervals and recommend to the CSRD Director whether the trial should be stopped for efficacy or futility. Summary reports from the DMC will be provided to the VA Central IRB. We believe that the independent DMC can effectively monitor the trial for safety, since it will regularly review all outcomes according to treatment assignment, and will also have access to statistical support to determine the significance of any observed differences.

XVII. BIOSTATISTICAL CONSIDERATIONS

A. Overview of design

1. The analytic model

There are two primary hypotheses that will be tested: 1) peri-procedure infusion of sodium bicarbonate is superior to infusion of sodium chloride for the prevention of serious, adverse clinical events within 90 day of angiography and; 2) peri-procedure administration of oral N-acetylcysteine (NAC) is superior to placebo for the prevention of serious, adverse clinical events within 90 day of angiography. The study will enroll 7,680 subjects over 2.5 years and evaluate each subject 90 days after the intervention. Within each site, subjects will be randomly assigned to one of four combinations of study interventions: 1) bicarbonate and NAC placebo, 2) saline and NAC placebo, 3) bicarbonate and NAC and 4) saline and NAC.

The study design for the primary hypothesis is a 2 x 2 factorial design with a binary outcome - any of a selected list of important clinical events occurring within 90 days of study treatment including death, need for acute dialysis, and persistent change in SCr at 90 days of at least 50% from the baseline SCr. We denote the 90-day binary outcome as 'MAKE-D' (major adverse kidney events and death). The binary predictors are the interventions bicarbonate and NAC. The interaction term, bicarbonate*NAC, represents the combination of these two interventions. The primary analysis is a logistic regression analysis with three binary predictors.

For the primary hypothesis, the model equation for the analysis is:

$$\text{MAKE-D} = \beta_1 * \text{Bicarbonate} + \beta_2 * \text{NAC} + \beta_{12} * \text{Bicarbonate*NAC} \qquad \textbf{Model Equation}$$

where, β_1 , β_2, and β_{12} are the logistic regression beta coefficients.

The two main questions of interest that we will test for the primary hypothesis are:

1) Does bicarbonate reduce the incidence of MAKE-D?
2) Does NAC reduce the incidence of MAKE-D?

The power calculation for determining the total sample size depends only on these two main effect hypotheses. This means that the exploratory analyses do not have any associated power analyses. The primary analysis will not test the significance of the interaction term, but the interaction term remains in the model as a potential confounder. We will test the two main hypotheses in the primary analysis by means of logistic regression without adjustment for any additional covariates.

2. Incidence of the 90-day endpoint and effects of our interventions

The events included in MAKE-D are death, need for acute dialysis, and persistent decline in kidney function. These events overlap. As previously discussed and summarized in Tables 4 and 5, most published randomized trials that investigated the proposed interventions did not report on these outcomes. However, for those that did track these events, acute dialysis was necessary in 0-7%, death occurred in 0-6%, and persistent decline in kidney function occurred in up to 19% of patients. Using the VA Austin database, we identified 25,909 Veterans who recently underwent coronary or non-coronary angiography who met our study entry criteria. Examining event rates at 90 days following angiography, we found that 1% died, 5% initiated dialysis, and 4% had a persistent increase in SCr of at least 50% (only about one-half of the patients had a measurement of SCr at 90 days). Overall, 8.7% had at least one of these events within 90 days. We therefore believe that the baseline incidence of MAKE-D in this patient population is 8.7%. Assuming an equal distribution of use of NAC versus no use of NAC and saline versus bicarbonate in this population with an overall event rate of 8.7%, a 25% reduction in the incidence of the composite primary outcome with bicarbonate (vs. saline) and with NAC (vs. placebo) would lead to the distribution of events with each treatment combination shown in Model 1. Using this approach, the overall sample size estimate, assuming a type 1 error of 0.025, 90% power, and 3% loss to follow-up, would be 6,500 subjects.

Model 1

	Bicarbonate	Saline	
NAC	6.4%	8.5%	7.5%
Placebo	8.5%	11.3%	9.9%
	7.5%	9.9%	

Overall event rate 8.7%

Our proposed sample size of 7,680 patients, based on the rates summarized in Model 2 (see below), arises from more conservative assumptions. The 8.7% overall event rate derived from the VA Austin database represents the incidence of this composite outcome in a patient population in which the specific use of preventive care for CIAKI is unknown. Recognizing that these patients may or may not have received the interventions we propose to study, we have taken a more conservative approach to estimating the necessary sample size by assuming that this 8.7% event rate represents the rate in each of the control arms (i.e., placebo with saline or bicarbonate and saline with or without NAC) as shown in Model 2. In this proposed model, the overall event rate in the entire population is 7.6%, which is 13% lower than the event rate (8.7%) which is suggested by our analyses of the VA Austin database. Using this more conservative estimate of the overall event rate resulted in our proposed sample size of 7,680 patients. We believe that this approach will help ensure that our study is not underpowered and is grounded on conservative, yet clinically reasonable event rate estimates.

Model 2

	Bicarbonate	Saline	
NAC	5.59%	7.46%	6.52%
Placebo	7.46%	9.95%	8.70%
	6.52%	8.70%	

Overall event rate 7.6%

Most trials have reported effect sizes for the outcome of CIAKI rather than for our defined 90 day primary composite outcome. For CIAKI, a recent meta-analysis reported a pooled relative risk of 0.62 (95% CI: 0.45-0.86) favoring bicarbonate when compared to saline, with the individual study effect sizes ranging from 2% to 92%. There were too few studies that systematically tracked other clinical outcomes to reliably analyze the risks for dialysis (RR=0.51, 95% CI: 0.17-1.51) or death (RR=0.83, 95% CI: 0.32-2.19). Similar results have been reported for NAC. The Planning Committee felt that a 25% effect size would be clinically meaningful and within the range of what might be expected from previous studies, since the reduction in 90 day clinical outcomes is likely mediated by a reduction in CIAKI, which available literature suggests is reduced by as much as 92%.

Therefore, considering Model 2, we postulate that:

- Under control conditions, the 90-day event rate for our primary outcome (MAKE-D) is 8.7%
- Each of the two interventions will prevent 25% of these events
- Under each intervention condition, the 90-day event rate is 6.52%
- The absolute effect of each intervention will be a 2.18% reduction in 90-day events

We have two primary hypotheses, one for each main effect in the model. We will therefore allocate the type I error of 5% equally across the two interventions, assigning a type I error of 2.5% to each. Including a third test for the interaction term from the set of primary hypotheses would slightly decrease the statistical power. We discuss the potential impact of the interaction on the power of the study later in this section. One interim analysis using an O'Brien-Fleming rule will be carried out when half the expected number of MAKE-D events have occurred.

B. Primary end-points

The two main interventions will be analyzed in the same way. Hence, we fully describe the bicarbonate versus saline intervention and the MAKE-D outcome. The analyses for the other intervention, NAC versus placebo, are analogous.

The null hypothesis is that the two treatment groups (bicarbonate and saline) do not differ in terms of the proportion of subjects who experience MAKE-D events. The alternative hypothesis is that the absolute difference in the incidence of MAKE-D between the bicarbonate intervention group and the saline group is 2.18% or more.

Formal statement of the null hypothesis

Under the null hypothesis:

- The proportion of 90-day MAKE-D events for patients administered bicarbonate is 8.70%
- Under the alternative hypothesis, the proportion of 90-day MAKE-D events for patients administered saline is 8.70%

The formal hypothesis test is two-sided allowing for bicarbonate to be either more or less effective than saline. However, the study of bicarbonate will only be viewed as more successful if subjects treated with bicarbonate have a significantly lower proportion of 90-day MAKE-D events than patients who receive saline. We will test this hypothesis with one model that contains both main factors and an interaction term as specified by the Model Equation.

C. Secondary end-points

Our secondary objectives, as previously outlined, will be tested using a logistic regression analysis similar to the primary objective. These objectives are:

1. To assess the effectiveness of the interventions to prevent CIAKI, defined by an increase in SCr of $\geq$ 0.5 mg/dL and/or $\geq$ 25% at 96 hrs following angiography compared to baseline values.
2. To assess the effectiveness of the interventions for the prevention of the following outcomes within 90 days of coronary or non-coronary angiography:
    a) death
    b) major adverse kidney endpoints (MAKE) including need for acute dialysis or persistent decline in kidney function defined by an increase in SCr of at least 50% at 90 days
    c) hospitalization with acute coronary syndrome, heart failure, or cerebrovascular accident defined by primary or secondary ICD-9 discharge diagnosis codes of acute coronary syndrome (i.e., STEMI, NSTEMI, unstable angina), heart failure, or cerebrovascular accident and/or by documentation of any of these three events in the hospital discharge summary.
    d) all-cause hospitalization

D. Tertiary (exploratory) end-points

We also wish to explore whether the interventions prevent adverse outcomes occurring within the first year after angiography. To that end, using logistic regression analysis, we will determine whether the interventions prevent:

1. Development of end-stage renal disease within one year following angiography defined by the requirement for chronic dialysis for ≥ 3 months based on documentation in the United States Renal Data System
2. Death within one year following angiography based on documentation in the VA Beneficiary Identification and Records Locator System, the National Center for Health Statistics National Death Index database, or the Social Security Administration's Death Master File

E. Additional exploratory analyses

We will explore several other hypotheses related to the binary 90 day MAKE-D outcome:

1. The combination of bicarbonate and NAC (interaction term) is more effective than bicarbonate or NAC alone.
2. (Per Protocol analysis) Bicarbonate, NAC, and their combination reduce the incidence of the primary outcome, MAKE-D, among subjects who received the full dose of bicarbonate.
3. (Per Protocol analysis) Bicarbonate, NAC, and their combination reduce the incidence of the primary outcome, MAKE-D, among subjects who received the full course of NAC.
4. Bicarbonate, NAC, and their combination reduce the incidence of the individual components of MAKE-D, each treated as a separate outcome: death, need for acute dialysis, and persistent decline in kidney function.
5. Bicarbonate, NAC, and their combination reduce the incidence of each of the individual cardiovascular components of the secondary outcome; namely acute coronary syndrome, heart failure, and cerebrovascular accident.
6. Bicarbonate, NAC, and their combination result in a greater reduction in the incidence of MAKE-D outcomes in subjects who develop CIAKI compared to those who do not develop CIAKI.
7. Bicarbonate, NAC, and their combination increase the mean number of days that participants are alive and hospitalization free (hospital free days) in the 90 days after angiography.

8. The benefits of bicarbonate, NAC, and their combination on MAKE-D outcomes are independent of the volume and rate of fluid administration above the minimum values prescribed in the protocol.

This brief list entails a large number of analyses. However, the sample size is large and the implicit hypotheses are highly inter-correlated. Thus, we anticipate that we can use a significance level of 1% ($p = 0.01$) to detect associations of potential clinical importance in these exploratory analyses.

Analyses of the association of CIAKI with MAKE-D events

Most previous studies of outcomes following procedures that utilized iodinated contrast have focused on acute increases in SCr within days of contrast administration (CIAKI). Compared to the events that comprise our 90-day primary outcome (MAKE-D), CIAKI occurs more frequently. While some episodes of CIAKI foreshadow MAKE-D events, some do not. Our analysis of data from the VA Austin databases demonstrated that compared to patients who do not develop CIAKI following angiography, patients who develop CIAKI have a nearly four-fold increased risk of experiencing a MAKE-D event. We propose to explore this relationship by stratifying the study participants into two groups: those who do and those who do not develop CIAKI. We will then run the logistic regression model for each stratum. This analysis may reveal different levels of effectiveness of the interventions based on whether CIAKI developed. We will carry out a more global analysis using log-linear models to address the same question by adding many interaction terms without explicit stratification. We chose a sensitive definition of CIAKI based on an increase in SCr of ≥0.5 mg/dL and/or ≥25%. This definition has been used in most prior trials and will permit us to compare our findings with prior studies on CIAKI. Nonetheless, we will also examine the incidence of CIAKI defined by more stringent criteria (AKIN definition), evaluate the effectiveness of our interventions on the prevention of larger changes in SCr, and assess the association of CIAKI defined by greater increases in SCr with MAKE-D outcomes.

Our protocol involves administering treatment before we assess the occurrence of CIAKI. Hence, the occurrence of CIAKI cannot be viewed as a simple treatment confounder. In fact, we

hypothesize that CIAKI lies on a causal pathway leading to MAKE-D events. Therefore, the exploratory analysis based on strata defined by the development of CIAKI is the first step in confirming the presence of such a causal pathway.

F. Sample size and statistical power considerations for the primary hypotheses

The results for the primary outcome measure, occurrence of a 90-day MAKE-D event, will be analyzed by means of the two-sided logistic regression model analysis specified by the Model Equation above. Removing all independent terms from the model equation except the bicarbonate term, the analysis is equivalent to a comparison of two proportions by means of the Chi-square test of association for a 2 x 2 contingency table.

The following table shows the sample size that would be needed for a range of powers, event rates, and effect sizes. The calculations are based on the assumptions of a type I error of 2.5% and equal allocation to each treatment arm.

Table 10 - Sample size for selected response rates

Rate in control (C) group	Rate in treatment (T) group	% reduction (C -T)/C	Total sample size 80% power [b]	Total sample size 90% power [b]
7.0	4.90	30%	5,030	6,562
7.0	5.25	25%	7,432	9,688
7.0	5.6	20%	11,924	15,546
8.7	6.1	30%	3,995	5,196
8.7[a]	6.52[a]	25%[a]	5,900 [a]	7,680 [a]
8.7	7.0	20%	9,440	12,317
10.4	7.3	30%	3,271	4,285
10.4	7.8	25%	4,844	6,314
10.4	8.3	20%	7,763	10,123

[a] rates and sample size for proposed model (with adjustment for losses to follow-up)

[b] adjusted for an O'Brien-Fleming stopping rule with one interim and one final test of hypothesis and considering a two-sided type I error = 0.025.

Thus, based on a 90 day event rate of 8.70% in the control group (i.e., saline or placebo) and 6.52% in the treatment group (i.e., bicarbonate or NAC), an absolute difference of 2.18% and a relative difference of 25%, we would need 7,450 patients to test the primary hypotheses with 90% power, assuming a type I error of 2.5% (splitting the alpha equally between the two primary hypotheses) without accounting for loss to follow up. Accounting for 3% lost to follow up, we

would need 7,680 patients. For the NAC intervention, the description above is entirely analogous.

Adjustment for Lost to Follow-Up

Because follow-up does not require a return to the VA medical center after the index angiogram and can be accomplished through electronic medical record review, telephone contact of patients, and mobile blood draws, we expect losses to follow-up to be uncommon and have estimated them to be 3%. Accounting for this estimated loss to follow up rate, our adjusted sample size will be 7,680. The study will permit secondary analysis of any SCr values assayed at a local laboratory that fit specimen collection timeframes for those blood specimens that were unable to be collected for analysis by the central laboratory.

Impact of Potential Interaction between Treatments on Sample Size and Statistical Power

The prior discussion of sample size and statistical power is predicated on the assumption that the effects of bicarbonate and NAC are independent. Stated in other terms, we have assumed that the relative reduction in the rate of MAKE-D events in patients assigned to bicarbonate/NAC compared to saline/NAC will be the same as that in patients assigned to bicarbonate/placebo compared to saline/placebo. Similarly, we have assumed that the relative reduction in the rate of MAKE-D events in patients assigned to bicarbonate/NAC compared to bicarbonate/placebo will be the same as that in patients assigned to saline/NAC compared to saline/placebo. The event rates under these assumptions are summarized in the following model.

Model 2 in the Absence of Interaction

	Bicarbonate	Saline	
NAC	5.59%	7.46%	6.52%
Placebo	7.46%	9.95%	8.70%
	6.52%	8.70%	

The rate of 5.59% for the combination of bicarbonate and NAC is lower than the rate of 7.46% for NAC with saline because, some patients who do not respond to NAC will, at random, respond to bicarbonate. This is what is meant by 'the absence of interaction.' In contrast, an interaction between NAC and bicarbonate could result in an absence of further benefit from combined treatment as compared to treatment with either agent alone.

Model 2 with Interaction Resulting in Complete Attenuation

	Bicarbonate	Saline	
NAC	7.45%	7.45%	7.45%
Placebo	7.45%	9.95%	8.7%
	7.45%	8.7%	

In this scenario, the overall effect at the margins would be reduced from a 25% reduction in MAKE-D events with each treatment to slightly more than a 14% relative reduction in events as demonstrated in the model above. This decrease in effect size would result in a reduction in the statistical power of the study to 40% with the proposed sample size of 7,680 patients; the total sample size would need to be increased to over 18,900 subjects to restore statistical power to 80% under these conditions. Fortunately, such an attenuation of effect of our interventions has not been observed in trials that have utilized both agents for the prevention of CIAKI. [103, 108, 118, 119] However, the possibility of a smaller attenuation of benefit cannot be excluded as the result of an interaction between bicarbonate and NAC. The impact of lesser degrees of interaction between the two interventions is illustrated in Table 11 below. These calculations are based on assumptions of a 25% reduction in MAKE-D events with bicarbonate (compared to saline) and NAC (compared to placebo); a baseline rate of events in the patients treated with both bicarbonate and NAC of 5.6% assuming no interaction/attenuation of effect; an overall sample size of 7,680 individuals equally allocated to each treatment arm; an estimated loss to follow-up rate of 3%; and a type I error of 2.5%.

Table 11 - Impact of Interaction between Bicarbonate and NAC on Statistical Power

% attenuation from interaction between Bicarbonate & NAC	Rate in subjects assigned to Bicarbonate/NAC	Rate in treatment (T) group	Rate in control (C) group	% reduction (C-T)/C	Power
No interaction	5.60 %	6.52%	8.7%	25%	90%
10% attenuation	5.78%	6.62%	8.7%	23.9%	87.5%
20% attenuation	5.97%	6.71%	8.7%	22.9%	84%
30% attenuation	6.15%	6.81%	8.7%	21.7%	79.3%
50% attenuation	6.53%	6.99%	8.7%	19.7%	69.4%

Thus, the study will retain nearly 80% statistical power with the proposed sample size of 7,680 patients even if an interaction between bicarbonate and NAC leads to a 30% attenuation of their combined effect.

G. Interim analysis

Using the O'Brien-Fleming procedure, we will carry out an interim analysis after half the expected number of events (292 events) has occurred, roughly after 18 months, to determine if either intervention shows a substantial beneficial effect. We will compare the proportion of subjects with a MAKE-D event with and without the use of bicarbonate and will compare the proportion of subjects with a MAKE-D event with and without the use of NAC. The respective absolute differences are dBicarbonate and dNAC. At the interim analysis, a z-value of 3.18 will be needed to reject the null hypothesis with Type I error of 2.5%. At the final analysis a z-value of 2.25 will be needed to reject the null hypothesis with Type I error of 2.5%.

H. Data analysis plan

The primary analysis will be based on intention to treat principles. Since treatment is given for a very short duration (five days), we expect very few drop outs or crossovers.

Analytic reports

Analytic reports will provide the proportions, the differences among proportions, the odds ratios, and the 95% confidence intervals for each of the summary statistics. This will be followed by a report of the results of confirmatory analyses. The confirmatory exploratory analyses will add to the basic model, factors related to disease severity, demographic and anthropomorphic measures, and structural factors such as medical site. The regression modeling we shall employ will include a model with treatment by covariate terms to explore the possibility of treatment by covariate effects (that is, exploration of potential subgroup effects). We will test that results vary or do not vary significantly by medical site. Finally we will explore the effect of including site as a random effect by extending logistic regression to generalized linear models that treat site as a random effect.

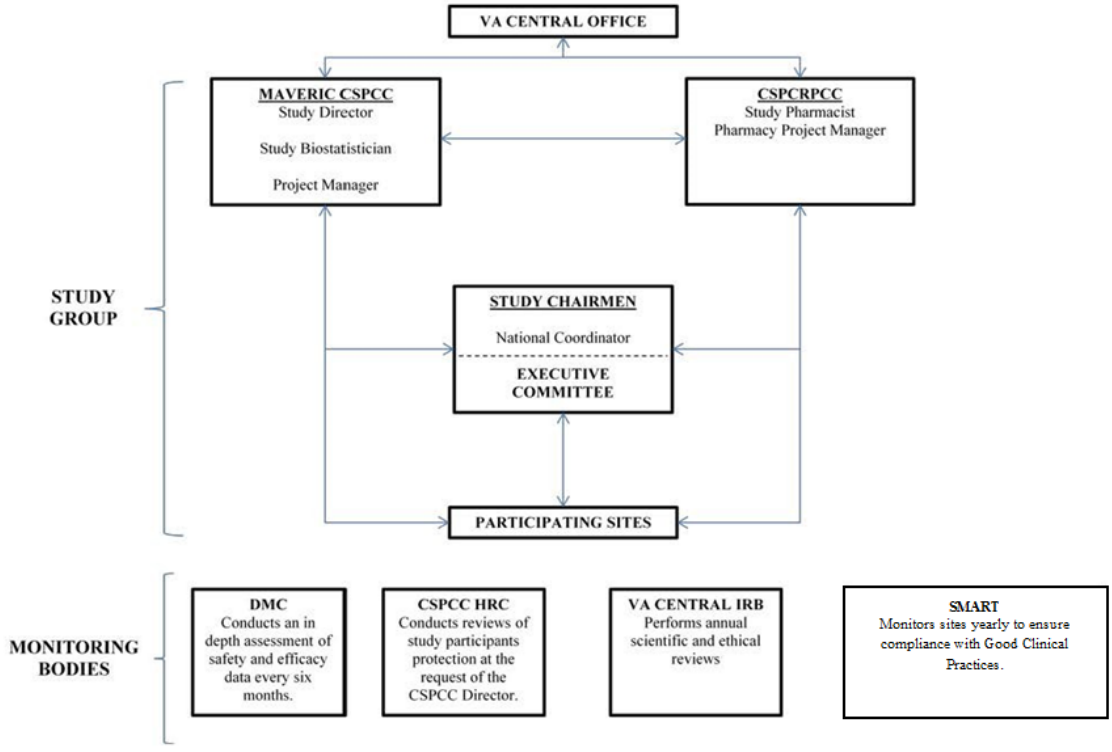
Losses to follow up and missing data

We conservatively estimate that up to 3% of subjects may be lost to follow up before 90 days. The site coordinators will make every effort to locate such subjects including at least three telephone contact attempts and one registered letter. Research staff are permitted to mail a letter to the participant for the purpose of appointment scheduling/reminders or follow-up contact. If such efforts fail and we have no information indicating the outcome for these subjects, then we will exclude them from the primary analysis and then carry out a worst case analysis to confirm the result of the primary analysis.

XVIII. STUDY ORGANIZATION AND ADMINISTRATION

The Cooperative Studies Program Central Office in Washington, D.C. will oversee the CSP#578 Study Group, which is responsible for all aspects of operational oversight of this trial including monitoring protocol adherence. The Study Group includes the following components: the MAVERIC CSPCC, Boston, MA; the Study Chairmen's Office at the VA Pittsburgh Healthcare System; the Cooperative Studies Program Clinical Research Pharmacy Coordinating Center (CSPCRPCC) at the Albuquerque VA Medical Center; and the participating VA medical centers. The Study Group will meet face-to-face prior to study initiation and at least annually thereafter and in addition, will communicate at least quarterly via conference call. In addition to the Study Group, an Executive Committee headed by the Study Chairmen and including selected site investigators, selected members of the Planning Committee, and members of the Study Group from the MAVERIC CSPCC, will be responsible for internal operational oversight of the study. The study management structure is depicted in Figure 5.

Figure 5- Study Management Structure



A. Cooperative Studies Program Central Office

The Cooperative Studies Program Central Office in Washington, D.C. establishes overall policies and procedures that are applied to all VA cooperative studies through the Study Chairmen's Office, the MAVERIC CSPCC, and the CSPCRPCC.

B. Study Chairmen's Office and MAVERIC CSPCC

The Study Chairmen's Office and the MAVERIC CSPCC will jointly perform the day-to-day scientific and administrative coordination of the study. This includes developing the study protocol, preparing the Operations Manual and source document worksheets, ensuring that appropriate support for the participating centers is provided, scheduling of meetings and conference calls, answering questions about the protocol, publication of newsletters, preparing interim and final progress reports, and archiving of study data at the end of the study. Patient accrual and data quality will be monitored closely to ensure that the study is progressing satisfactorily.

C. CSP Clinical Research Pharmacy Coordinating Center

The CSP Clinical Research Pharmacy Coordinating Center acts as a liaison in all VA cooperative studies between the study participants and the manufacturer of the study drug. This center will take the lead in developing a drug information report and drug handling procedures, obtaining and distributing the study medications, and providing advice and consultation about drug-related matters during the course of the study.

D. Executive Committee

The Executive Committee will oversee study operations, the performance of participating medical centers, and the quality of data collected. This Committee will also monitor adherence to the protocol. The Executive Committee formulates plans for publications and oversees the publication and presentation of all data from the study. Permission must be granted by the Executive Committee before data from the study may be used for presentation or publication. The members of the Executive Committee will be selected by the Study Chairmen from members of the Planning Committee and Participating Investigators. The Executive Committee may meet quarterly by conference call and in-person as necessary.

XIX. PUBLICATIONS

A. Publication policy

It is the policy of the CSP that outcome data will not be revealed to the participating investigators until the data collection phase of the study is completed. This policy safeguards against possible biases affecting the data collection. The regular and ex-officio members of the DMC will be monitoring the outcome results to ensure that the study is stopped if a definitive answer is reached earlier than the scheduled end of the study.

All presentations and publications from this study will be done in accordance with current CSP guidelines. The presentation or publication of any or all data collected by participating investigators on patients entered into the VA Cooperative Study is under the direct control of the study's Executive Committee. This policy is applicable whether the publication or presentation is concerned with the results of the principal undertaking or is associated with the study in some other way. No individual participating investigator has any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any or all of the data other than under the auspices and approval of the Executive Committee.

The Executive Committee has the authority to establish one or more publication committees, usually made up of sub-groups of participating investigators and some members of the Executive Committee, for the purpose of producing manuscripts for presentation and publication. Any presentation or publication, when formulated by the Executive Committee or its authorized representatives, should be circulated to all investigators participating in manuscript preparation for their review, comments, and suggestions at least four weeks prior to submission of the manuscript to the presenting or publication body. All publications must give proper recognition to the study's funding source, including the Department of Veterans Affairs, and should list all investigators in the study. If an investigator's major salary support and/or commitment is from the VA, it is obligatory for the investigator to list the VA as his/her primary institutional affiliation. Submission of manuscripts or abstracts must follow the current VA policy. Since all publications should state that it is a publication from a VA Cooperative Study, ideally, a sub-title is used stating, "A VA Cooperative Study." The DVA contributions to the research project

should be acknowledged in all written and oral presentations of the research results, including scientific articles, news releases, news conferences, public lectures, and media interviews.

All clinical study reports and journal manuscripts must be reviewed and approved by the MAVERIC CSPCC Director prior to submission for publication. After approval for submission is granted by the MAVERIC CSPCC Director, the MAVERIC CSPCC Associate Center Director for Administrative Operations must be notified as it is their responsibility for sending all scientific publications from CSP related studies to VA Central Office upon acceptance. This includes minor publications such as abstracts and poster presentations.

B. Planned publications

A plan outlining intended study publications is provided in Table 12.

Table 12 – Planned study manuscripts

Manuscript	Projected Time of Submission
Design paper	1 year following study initiation
90-day outcomes (primary)	6-12 months after end of primary outcome data collection
1-year outcomes	6-12 months after primary manuscript
Comparison of prediction scores for the development of CIAKI	12-24 months after primary manuscript
Assessment of risk factors for serious, adverse outcomes at 90 days post-angiography	12-24 months after primary manuscript

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