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A Randomized Trial of Recombinant Human C1-Esterase-Inhibitor in the Prevention of Contrast-Induced Kidney Injury

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ABSTRACT

OBJECTIVES This study sought to determine the efficacy profile and safety of recombinant human C1 esterase inhibitor (rhC1INH) in the prevention of contrast-associated acute kidney injury after elective coronary angiography.

BACKGROUND Contrast-associated acute kidney injury is caused by tubular cytotoxicity and ischemia/reperfusion injury. rhC1INH is effective in reducing renal ischemia/reperfusion injury in experimental models.

METHODS In this placebo-controlled, double-blind, single-center trial 77 patients with chronic kidney disease were randomized to receive 50 IU/kg rhC1INH before and 4 h after elective coronary angiography or placebo. The primary outcome was the peak change of urinary neutrophil gelatinase-associated lipocalin within 48 h, a surrogate marker of kidney injury.

RESULTS Median peak change of urinary neutrophil gelatinase-associated lipocalin was lower in the rhC1INH group (4.7 ng/ml vs. 22.5 ng/ml; $p = 0.038$) in the per-protocol population but not in the modified intention-to-treat analysis, and in patients with percutaneous coronary interventions (median, 1.8 ng/ml vs. 26.2 ng/ml; $p = 0.039$ corresponding to a median proportion peak change of 11% vs. 205%; $p = 0.002$). The incidence of a cystatin C increase ≥10% within 24 h was lower in the rhC1INH group (16% vs. 33%; $p = 0.045$), whereas the frequency of contrast-associated acute kidney injury was comparable. Adverse events during a 3-month follow-up were similarly distributed.

CONCLUSIONS Administration of rhC1INH before coronary angiography may attenuate renal injury as reflected by urinary neutrophil gelatinase-associated lipocalin and cystatin C. The safety profile of rhC1INH was favorable in a patient population with multiple comorbidities. (Recombinant Human C1 Esterase Inhibitor in the Prevention of Contrast-induced Nephropathy in High-risk Subjects [PROTECT]; NCT02869347) (J Am Coll Cardiol Intv 2020;13:833–42)
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ABBREVIATIONS AND ACRONYMS

C1INH = C1-esterase inhibitor

CA-AKI = contrast-associated acute kidney injury

CIN = contrast-induced nephropathy

CM = contrast media

eGFR = estimated glomerular filtration rate

I/R = ischemia/reperfusion

IQR = interquartile range

mITT = modified intention-to-treat

NGAL = neutrophil gelatinase-associated lipocalin

PCI = percutaneous coronary intervention

PP = per-protocol

rhC1INH = recombinant human C1 esterase inhibitor

Iodinated contrast media (CM) are an indispensable component of contemporary diagnostic imaging and interventional intravascular procedures. However, their use has been associated with an often transient decrease in renal function known as contrast-associated acute kidney injury (CA-AKI) (1). Although recent studies challenge the existence of CA-AKI (in particular after intravenous CM administration) (2), previous data indicate an association of a temporary decline in renal function with future adverse renal events (3,4). Hence, prevention of CA-AKI is of importance, in particular in high-risk patients, such as patients with pre-existing renal disease, diabetes mellitus, congestive heart failure, or undergoing arterial and interventional contrast procedures with a larger amount of CM. Still, interventions to prevent CA-AKI are scarce and largely confined to intravenous hydration with sodium chloride.

Although the exact mechanisms of decline in renal function has not yet been completely elucidated, direct renal tubular and endothelial cell cytotoxicity and in particular renal ischemia/reperfusion (I/R) injury as a result of prolonged renal vasoconstriction have been entertained (5).

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C1-esterase inhibitor (C1INH) is a human plasma protein with manifold targets and biologic functions, including a strong inhibition of the complement and kinin system (6) and interactions with endothelial cells. Conestat alfa (rhC1INH) is a recombinant human version derived from the breast milk of transgenic rabbits, that shares an identical protein structure with plasma-derived C1INH (7), and is approved for the substitution treatment of hereditary angioedema. In experimental models of renal I/R injury, rhC1INH administration led to a significant reduction in complement deposition, renal infiltration of inflammatory cells, tubular damage, and apoptosis, and was associated with improved renal function and diminished fibrosis (8,9).

Given that renal I/R injury is postulated as an important mechanism of CA-AKI, the objective of the current proof-of-concept study was to evaluate the efficacy profile and safety of rhC1INH in the prevention of CA-AKI in high-risk patients undergoing elective coronary angiography.

METHODS

STUDY DESIGN AND OVERSIGHT. The PROTECT (Prophylactic RhC1-inhibitor to Prevent Contrast-induced Nephropathy) trial was an investigator-initiated, single-center, randomized, double-blind, placebo-controlled, phase II clinical trial to determine the effect size and safety of prophylactic administration of rhC1INH in patients undergoing elective coronary angiography. In accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, the study protocol was approved by the local ethics committee before patient recruitment. All subjects provided written informed consent before randomization for participation. The clinical trial was overseen by an independent data safety monitoring board (NCT02869347).

STUDY POPULATION. Patients scheduled for an elective coronary angiography between January 2017 and May 2018 were eligible to participate if they were at least 18 years of age, had an estimated glomerular filtration rate (eGFR) of ≤50 ml/min/1.73 m^2 (as calculated by the Chronic Kidney Disease Epidemiology Collaboration study equation), and at least 1 of the following risk factors for CA-AKI: diabetes mellitus, age ≥75 years, anemia (baseline hematocrit value ≤39% for men and ≤36% for women), congestive heart failure functional class III or IV by New York Heart Association classification, or history of pulmonary edema. Exclusion criteria were contraindications to the class of drugs under study; a history of allergy to rabbits; current treatment with *N*-acetylcysteine, sodium bicarbonate, fenoldopam, mannitol, dopamine, or theophylline; pregnancy or breastfeeding; multiple myeloma; acute heart failure or myocardial infarction in the previous 2 weeks; dialysis; and exposure to iodinated CM in the previous 7 days.

RANDOMIZATION AND PROCEDURES. Patients were randomly assigned (1:1 ratio) to receive either rhC1INH (50 U/kg with a maximum of 4,200 U administered) or an equal volume of placebo

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(intravenous 0.9% sodium chloride) intravenously and immediately before and 4 h after coronary angiography. rhC1INH (conestat alfa [Ruconest]) was supplied by the manufacturer (Pharming Technologies, B.V., Leiden, the Netherlands) free of charge. The chosen dose of rhC1INH is expected to increase plasma C1INH activity by approximately 100% and is identical to the licensed dosage for the treatment of hereditary angioedema. Repeated administration was chosen because of the short half-life of rhC1INH (2.5 h [7]) and a documented duration of vasoconstriction and ischemia of up to 4 h after administration of CM (10).

Randomization was done with a randomly permuted block size of 4 using a computer-generated randomization list, and patients were stratified by the planned procedure (angiography as work-up before transcatheter aortic valve replacement or angiography and potentially angioplasty). Patients, care providers, investigators, laboratory personnel, and data assessors were blinded to the treatment assignment.

After informed consent was obtained and patients randomized, baseline blood and urine samples were collected. Study drugs were prepared in opaque syringes by an unblinded study nurse and administered by a blinded team member as intravenous injection over a period of 5 min immediately before and again 4 h after the angiography. Coronary angiography was performed as per standard operating procedures at the study site predominantly using a radial artery access, and the amount and type of CM was recorded.

All patients received standard intravenous hydration with 0.9% sodium chloride at a rate of 1 ml/kg/h starting after inclusion into the study (maximum 12 h before angiography) until 12 h after coronary angiography. Patients with heart failure and a reduced ejection fraction of <30% or symptoms consistent with functional class III or IV by New York Heart Association functional classification) received 500 min/24 h. Metformin and nonsteroidal anti-inflammatory drugs were withheld on the day of the procedure. Repeat urine and blood samples were collected at 4, 24, and 48 h. Assessment of adverse events, renal and cardiac events, readmission to hospital, and death was done by a structured telephone interview after 3 months.

ENDPOINTS AND DEFINITIONS. The primary efficacy outcome was the peak change of neutrophil gelatinase-associated lipocalin (NGAL) (a surrogate marker for kidney injury [11]) in urine within 48 h after coronary angiography compared with baseline. Secondary efficacy outcomes included the development of contrast-induced nephropathy (CIN; defined as serum creatinine increase of ≥25% or ≥0.5 mg/dl) and CA-AKI (defined as serum creatinine increase of ≥0.3 mg/dl or ≥50%) within 48 h; the occurrence of an increase of serum cystatin C ≥10% within 24 h (3); the peak change of serum troponin T within 24 h; the peak change of urinary TIMP-2*IGFBP7 within 48 h (a cell-cycle arrest and "alarm" marker [12]); and the occurrence of a composite cardiovascular and renal endpoint including death, acute coronary syndrome, hospitalization for heart or renal failure, or dialysis during a 3-month follow-up.

Creatinine, cystatin C, high-sensitivity troponin T, C1INH protein concentration, and C4 concentration were determined on automated standard platforms at the clinical laboratory of the University Hospital Basel or by the Viollier laboratories (a large commercial clinical laboratory in Switzerland). NGAL and TIMP-2*IGFBP7 were measured with commercially available assays (Bioporto [Hellerup, Denmark] and Abcam [Cambridge, United Kingdom], respectively) according to the manufacturer's protocol.

STATISTICAL ANALYSIS. Because previously published data suggested a low overall incidence of CA-AKI (13) at our center, we chose NGAL as primary outcome parameter. A formal power calculation was not performed for the primary endpoint of this exploratory study, because of a lack of suitable data on preventive therapy studies with rhC1INH at time of study design and therefore the use of potentially poor estimates of parameters for sample size calculations. In analogy to previous interventional studies using different prophylactic regimens (14,15) and similar surrogate parameters of renal function, we calculated that 40 subjects are required in each study arm to allow for the detection of a difference in mean urinary peak NGAL concentration of 100 ng/ml assuming a standard deviation of 150 ng/ml, a power of 80%, and a 2-sided type 1 error of 5%. This difference has been shown to be predictive of AKI (16).

A modified intention-to-treat (mITT) analysis was primarily used for this trial including all participants that had received at least 1 dose of study medication and underwent coronary angiography. The per-protocol (PP) population consisted of patients fully complying with the trial protocol. A post hoc analysis of patients receiving a larger amount of CM and undergoing percutaneous coronary intervention (PCI) was performed.

Continuous variables were reported as median (interquartile range [IQR]) and were compared using nonparametric tests (Mann-Whitney *U* and Wilcoxon test for unpaired and paired observations, respectively), if not normally distributed or as mean ± SD

FIGURE 1 Flow Diagram of the Study

eGFR = estimated glomerular filtration rate; mITT = modified intention-to-treat population; NSTEMI = non-ST-segment elevation myocardial infarction; PP = per-protocol population; rhC1INH = recombinant human C1 esterase inhibitor; STEMI = ST-segment elevation myocardial infarction. *Patient received only 1 dose of study medication. #One patient received only 1 dose of study medication, the second patient retrospectively violated the exclusion criteria (dialysis).

and were compared using the Student's *t*-test. Categorical variables were expressed as proportions and counts and compared using the chi-square test. Tests were done at the 2-sided 5% significance level. All analyses were performed with the use of SPSS version 22 software (IBM, Chicago, Illinois).

RESULTS

PATIENTS. We enrolled 80 eligible patients in the trial and randomized them to either rhC1INH or placebo treatment (Figure 1). Three patients did not undergo the scheduled angiography and did not receive any study medication. Hence, 38 and 39 patients were allocated to the rhC1INH and placebo groups, respectively, comprising the mITT population. For the PP population, 3 patients were excluded (not meeting eligibility criteria [dialysis], or noncompliance with study protocol). Baseline demographic, clinical, and procedural characteristics were well balanced in the 2 groups (Table 1). Mean age was 77 years (range 52 to 93 years), and 54 (70%) of 77 were men. The burden of comorbidities was high, including diabetes mellitus (42%), congestive heart

failure (48%), pre-existing coronary artery disease (58%), and a history of myocardial infarction (33%). Mean serum creatinine and eGFR at study entry were 1.7 ± 0.8 mg/dl and 40 ± 9.6 ml/min/1.73 m^2, respectively. CA-AKI risk was moderate with a median Mehran score of 8 (IQR: 6 to 10). Patients received a moderate amount of nonionic low-osmolar CM (iomperol or iopamidol; median, 112 ml; IQR: 81 to 171 ml) and 39% of patients underwent a PCI. Total hydration volume was similar (**Table 1**).

PRIMARY ENDPOINT. There was a large numerical difference in mean baseline NGAL concentrations of the 2 groups (118 vs. 50 ng/ml) because of 2 outliers with baseline concentrations >1,000 ng/ml, possibly caused by dialysis in 1 patient and an acute urinary tract infection in the other (17). In contrast, mean urinary NGAL values at baseline were comparable between the groups in the PP population (Supplemental Figure 1).

Median peak change of urinary NGAL within 48 h was lower in the rhC1INH group only in the PP (4.7 [IQR: −0.1 to 50.4] ng/ml vs. 22.5 [IQR: 4.2 to 84.5] ng/ml; p = 0.038), but not in mITT analysis (7.2 [IQR: −0.7 to 54.5] ng/ml vs. 22.5 [IQR: 4.2 to 84.5] ng/ml; p = 0.119) (**Table 2**). A similar trend was observed when analyzing the relative peak change of urinary NGAL (mITT analysis, 45% [IQR: −3% to 129%] vs. 121% [IQR: 22% to 300%]; p = 0.060).

Differences in the course of urinary NGAL concentrations were most pronounced during the first 24 h with an initial decline in the rhC1INH group (median increase of −25 and −8% at 4 and 24 h, respectively) compared with a steady increase (median increase of 4 and 25%) without a complete return to baseline in the placebo group (mITT population) (**Figure 2**, Supplemental Table 1).

Because patients undergoing a PCI are at higher risk of ischemic renal damage secondary to a larger amount of CM used (18), a post hoc analysis of these patients was performed (n = 15 each, mITT analysis). Indeed, PCI patients received a larger amount of CM (median, 157 [IQR: 113 to 93] ml vs. 95 [IQR: 67 to 135] ml in non-PCI patients; p < 0.0001). In this subgroup of patients, median absolute and relative peak change of urinary NGAL were significantly smaller in the rhC1INH group compared with the placebo group (1.8 [IQR: −2.7 to 12.5] ng/ml vs. 26.2 [IQR: 16.0 to 133.8] ng/ml; p = 0.039; and 11% [IQR: −5% to 74%] vs. 205% [IQR: 84% to 469%]; p = 0.002), whereas there was no difference evident in non-PCI patients (data not shown).

SECONDARY OUTCOMES (mITT POPULATION). rhC1INH treatment was associated with a significantly lower incidence of a relevant cystatin C increase ≥10% within 24 h (16% vs. 33%; p = 0.045). In contrast, the numbers of patients developing CIN and CA-AKI were similarly distributed in both groups (**Table 2**). There was no difference in the peak change of urinary TIMP2*IGFBP7 and of troponin T (**Table 2**).

Median C1INH concentration rose from 0.30 (IQR: 0.27 to 0.36) g/l at baseline to 0.58 (IQR: 0.53 to 0.64) g/l after the first administration and from 0.36 (IQR: 0.32 to 0.42) g/l before the second

TABLE 1 Baseline Demographic, Clinical, and Procedural Characteristics

	All Patients (N = 77)	Placebo (n = 39)	rhC1INH (n = 38)
Age, yrs	76.9 ± 8.3	77.6 ± 9.4	76.2 ± 7.0
Male	54 (70)	28 (72)	26 (68)
Comorbidities			
Diabetes mellitus	32 (42)	14 (36)	18 (47)
Hypertension	71 (92)	37 (95)	34 (90)
Dyslipidemia	48 (62)	23 (60)	26 (66)
Congestive heart failure	37 (48)	21 (54)	16 (42)
Coronary artery disease	44 (58)	20 (51)	24 (63)
Previous myocardial infarction	25 (33)	12 (31)	13 (34)
Previous CABG	8 (10)	3 (8)	5 (13)
Ejection fraction, %	50 (40-60)	50 (38-60)	51 (44-60)
Medication			
ACE-I or ARB	62 (81)	29 (74)	33 (87)
Beta-blocker	48 (62)	20 (51)	28 (74)
Statin	50 (65)	21 (54)	29 (76)
Loop diuretic	35 (46)	19 (49)	16 (42)
Thiazide diuretic	27 (35)	15 (39)	12 (32)
Metformin	16 (21)	8 (21)	8 (21)
Aspirin	45 (58)	21 (54)	24 (63)
Anticoagulant	29 (38)	17 (44)	12 (32)
NSAID	2 (3)	1 (3)	1 (3)
Procedural characteristics			
Reason of angiography			
Angina/positive stress test	46 (60)	22 (56)	24 (63)
Before surgery or TAVR	17 (22)	8 (21)	9 (24)
Planned staged PCI	8 (10)	4 (10)	4 (11)
Other	6 (8)	5 (13)	1 (3)
Contrast media, ml	112 (81-171)	112 (81-175)	110 (74-151)
PCI	30 (39)	15 (39)	15 (40)
Hydration volume, l	1.31 (1.03-1.65)	1.30 (0.89-16.00)	1.31 (1.20-1.77)
Laboratory parameters			
Creatinine, mg/dl	1.66 ± 0.76	1.60 ± 0.47	1.71 ± 0.98
eGFR, ml/min/1.73 m^2	40.1 ± 9.6	40.3 ± 9.1	39.9 ± 10.1
Cystatin C, ng/ml	1.68 ± 0.51	1.67 ± 0.44	1.68 ± 0.58
Urinary NGAL, ng/ml	19.7 (9.2-52.1)	17.7 (9.6-49.5)	21.1 (8.7-55.5)

Values are mean ± SD, n (%), or median (interquartile range). All comparison between the 2 groups yielded nonsignificant results (p > 0.05).

ACE-I = angiotensin-converting-enzyme inhibitor; ARB = angiotensin II receptor blockers; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration equation); NGAL = neutrophil gelatinase-associated lipocalin; NSAID = nonsteroidal anti-inflammatory drugs; PCI = percutaneous coronary intervention; rhC1INH = recombinant human C1-esterase inhibitor; TAVR = transcatheter aortic valve replacement.

TABLE 2 Primary and Secondary Endpoints

	Placebo	rhC1INH	p Value
Primary endpoint			
mITT: absolute peak increase urinary NGAL within 48 h, ng/ml	22.5 (4.2 to 84.5)	7.2 (-0.7 to 54.5)	0.119
PP: absolute peak increase urinary NGAL within 48 h, ng/ml	22.5 (4.2 to 84.5)	4.7 (-1.0 to 50.4)	0.038
mITT: relative peak increase urinary NGAL within 48 h, %	121 (22 to 300)	45 (-2 to 129)	0.060
PP: relative peak increase urinary NGAL within 48 h, %	121 (22 to 300)	29 (-4 to 149)	0.052
Secondary endpoints (mITT)			
Cystatin C increase >10% within 24 h	13 (33.3)	6 (15.8)	0.045
Acute kidney injury*	7 (17.9)	6 (15.8)	0.765
Contrast-induced nephropathy†	2 (5.6)	4 (10.5)	0.675
Peak urinary TIMP-2*IGFBP7 peak increase within 48 h (ng/ml†/1,000)	0.09 (0.02 to 0.28)	0.07 (0.01 to 0.21)	0.283
Peak troponin T increase within 24 h, ng/l	8.0 (0 to 33)	10.5 (4 to 60)	0.130

Values are median (interquartile range) or n (%). *Increase in serum creatinine of ≥0.3 mg/dl or ≥50% within 48 h. †Increase in serum creatinine of ≥0.5 mg/dl or ≥25% within 48 h.

mITT = modified intention-to-treat; PP = per-protocol; other abbreviations as in Table 1.

administration to 0.66 g/l (IQR: 0.58 to 0.71 g/l), corresponding to a median relative increase of 91% (IQR: 66% to 105%) and 76% (IQR: 65% to 94%) after the first and second administration, respectively. As expected, C1INH concentrations remained unchanged in the placebo group (Figure 3). C4 concentration did not change in any of the 2 study groups during the first 4 h (data not shown).

SAFETY ASSESSMENTS. A total of 59 adverse events (rhC1INH group n = 29; placebo group n = 30) occurred in 30 patients enrolled (14 [37%] vs. 16 [41%]) during a 3-month follow-up. Sixteen patients experienced 21 serious adverse events (n = 10 vs. n = 11). All serious adverse events were considered not to be related to rhC1INH treatment. Two patients that died within 24 h after angiography and 1 patient that died during follow-up were in the placebo group. A complete summary of serious adverse events is shown in Table 3.

Safety measures PP included assessment of anaphylactic reaction within 24 h after administration of rhCINH and assessment of a composite cardiovascular and renal endpoint and of thromboembolic events during a 3-month follow-up. Median follow-up duration was 88 days in both groups. There was no difference in the incidence of the composite cardiovascular and renal endpoint (n = 3 [8%] in both groups) within 3 months (Supplemental Table 2), and no anaphylactic reactions occurred. One patient in the rhC1INH group developed a deep-vein thrombosis 35 days after receiving the study medication, which resolved with anticoagulation.

DISCUSSION

In the present randomized clinical trial, prophylactic administration of rhC1INH attenuated the rise in urinary NGAL, a marker of renal injury, and decreased the incidence of a relevant cystatin C increase compared with placebo in patients with chronic renal disease undergoing elective coronary angiography (Central Illustration), although this association was only significant in the PP population.

CA-AKI is a commonly observed phenomenon after iodinated contrast procedures, in particular in the setting of pre-existing renal impairment, intra-arterial administration of CM, and therapeutic interventions (1). Although the short-term effect of this condition may be subtle (confined to only a minor change in eGFR), the association with adverse outcomes has been demonstrated previously (3,4). Still, prophylactic interventions are mostly limited to intravenous hydration with sodium chloride.

In the present study, the difference in urinary NGAL increase was most pronounced during the first 24 h. This is in line with the concept of a non-sustained acute renal injury in the setting of CM exposure, which is reflected by the increased secretion of NGAL into the urine in the placebo group lasting up to 24 h and approaching baseline secretion afterward. Previous evidence from human and experimental studies in piglets demonstrated local renal vasoconstriction followed by a gradual decline in renal blood flow after repeat injection of nonionic low-osmolar CM (19,20). Hypoxic injury is aggravated by an increased renal tubular cell oxygen demand after administration of CM. Consequently, oxidative stress, which triggers local inflammatory responses including activation of the complement system, causes additional cell injury during the reperfusion phase (21).

Despite being a multitarget multiple-action inhibitor, it seems plausible that the beneficial effects of rhC1INH observed in the current proof-of-concept study are predominantly mediated by its strong local complement inhibiting activity (8). In this regard, the current clinical study may confirm for the first time experimental data suggesting that complement inhibition by rhC1INH is effective in the setting of renal I/R injury (8,9).

Interestingly, we observed an initial decline in urinary NGAL secretion in the rhC1INH group compared with a steady increase in the placebo group. Recent evidence suggests that urinary NGAL levels are a marker of chronic kidney disease and

severity thereof, and correlate with serum creatinine and eGFR (22). Hence, the administration of rhC1INH may not only prevent CM-induced renal damage, but may also shortly interfere with chronic inflammatory processes as a result of the underlying chronic kidney disease (23).

Several facts argue against an artificial decrease of urinary NGAL secretion in the rhC1INH group independent of a renal injury. Hydration regimens were similar in both groups. When taking into account different urine dilutions (using the urinary NGAL/urinary creatinine ratio), the time course and the difference between the groups did not change (data not shown). Although rhC1INH may theoretically interfere with NGAL secretion by blood neutrophils independently of renal injury and dysfunction, the major fraction of urinary NGAL results from secretion of the distal tubule as a consequence of renal injury (24). Finally, a lower incidence of a significant cystatin C increase, a second biomarker of renal dysfunction independent of the NGAL pathway, supports the observed difference in urinary NGAL increase being most likely related to an attenuated renal injury after prophylactic administration of rhC1INH.

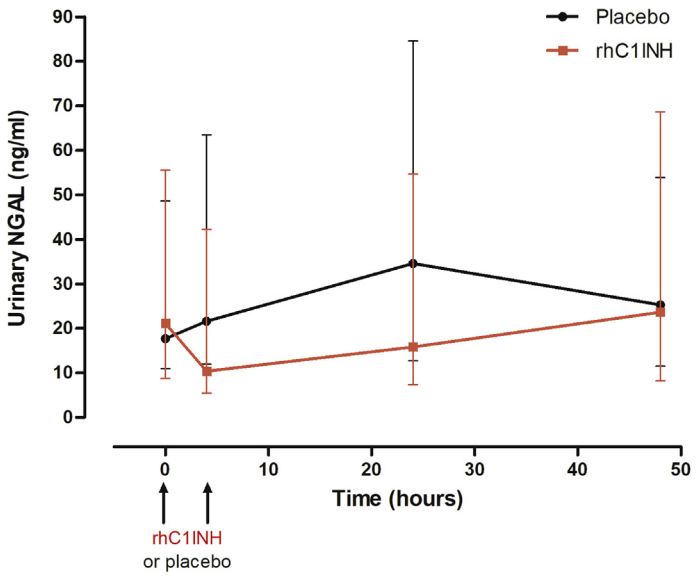
Patients undergoing coronary revascularization are at higher risk of ischemic kidney damage because of the fact that embolization of cholesterol crystals during the procedure may cause mechanical occlusion and trigger complement-mediated inflammation (25), but more importantly because they receive a larger amount of CM. Hence, these patients may therefore be more likely to benefit from an intervention with rhC1INH.

Indeed, the observed difference in the relative peak change of urinary NGAL concentrations (11% vs. 205% in the placebo group) was even more pronounced in the subgroup of patients undergoing a PCI. Although limited by the sample size, these data may indicate a target population for future trials, which may benefit the most from rhC1INH treatment.

The definition of CA-AKI is still based on the course of serum creatinine measurements over time. In the present study, treatment of rhC1INH was not associated with a lower incidence of CA-AKI or CIN. However, the analysis was hampered by the low incidence of CIN in the study population (7.8%), which limits the power of the study when assessing this endpoint.

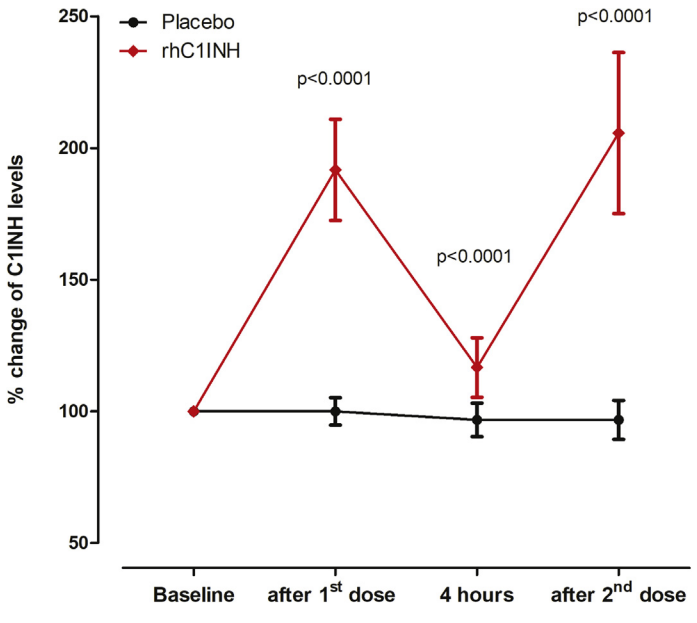
A more reliable marker for the early diagnosis and prognosis of CA-AKI injury is cystatin C. Compared with serum creatinine, cystatin C has been shown to rise earlier, to peak as early as 24 h after CM

FIGURE 2 Course of Urinary NGAL Levels During 48 h After Coronary Angiography (mITT)



Medians and interquartile ranges are depicted. NGAL = neutrophil gelatinase-associated lipocalin; other abbreviations as in Figure 1.

FIGURE 3 Relative Change in C1INH Concentration After the First and Second Administration of Study Medication Compared With Baseline (mITT)



Medians and interquartile ranges are depicted. Abbreviations as in Figure 1.

TABLE 3 Serious Adverse Events (Number)

Serious Adverse Events	rhC1INH (n = 10)	Placebo (n = 11)
Cardiac disorders	Acute myocardial infarction (1) Decompensated heart failure (2) Coronary artery occlusion (1)	Acute myocardial infarction (1)* Atrial fibrillation (1) Cardiogenic shock (2)*
Gastrointestinal disorders	Acute abdominal pain (1)	
Infections		Gangrene (1) *Clostridioides difficile* colitis (1)
Musculoskeletal disorders	Progressive osteoarthritis (1)	
Neoplasm		Malignant neoplasm (2)
Nervous system disorders	Seizure (1) Transient ischemic attack (1)	Cerebrovascular accident (1)*
Vascular disorders	Hemorrhage (1) Hypertensive emergency (1)	Hemorrhage (2)

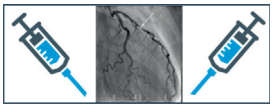
*Serious adverse events leading to death.
Abbreviation as in Table 1.

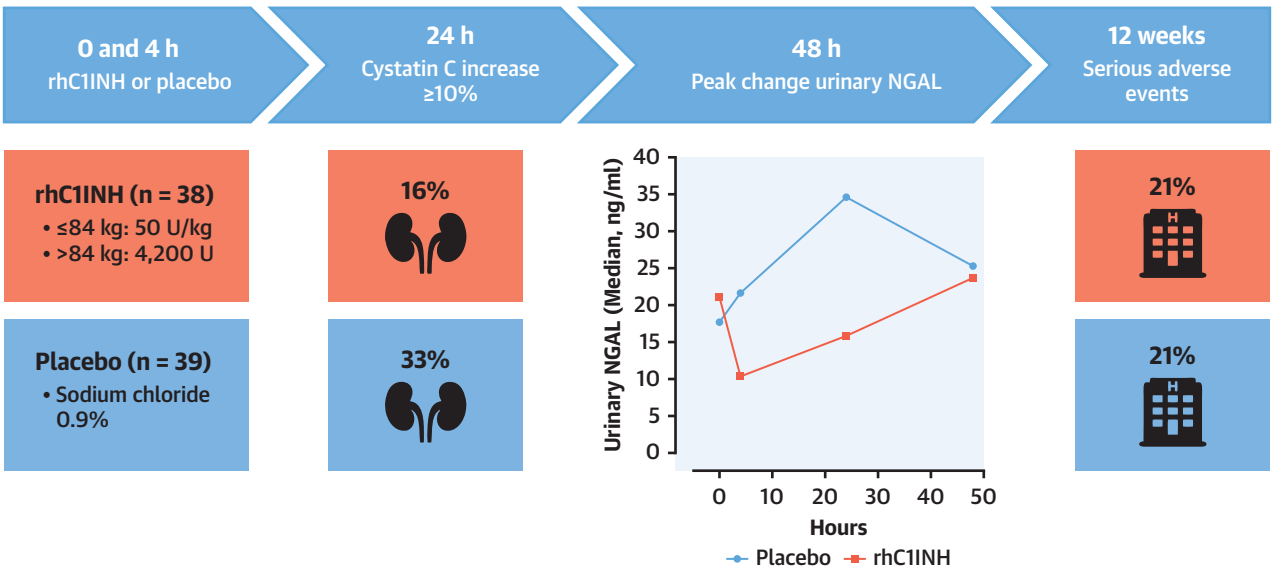
administration, and to detect even subtle changes in renal function after AKI (26). In the present study, a relevant cystatin C increase occurred twice as often in the placebo treatment group (33%) compared with the rhC1INH-treated group (16%). This difference was in line with the analysis results of the "damage" marker NGAL, and confirms that rhC1INH treatment may indeed attenuate some of the detrimental effects of CM.

We did not observe any differences in the peak increase of the cell cycle biomarker urinary TIMP-2*IGFBP7 between the groups. Although identified as a very promising biomarker for the detection of AKI in intensive care unit patients (27), there is a lack of data suggesting its usefulness in the setting of AKI related to relatively mild injuries (e.g., CM) (28).

Previous interventional studies in the setting of CM exposure have assessed a variety of interventions, such as sodium bicarbonate, acetylcysteine, real-time urinary flow guided hydration, or remote ischemic pre-conditioning, yielding mixed results. A direct comparison of efficacy with the present study is hampered by the significant difference in the incidence of CIN, which occurred at least twice as often in many previous trials compared with the

CENTRAL ILLUSTRATION Recombinant Human C1 Esterase Inhibitor in the Prevention of Contrast-Induced Acute Kidney Injury





Panagiotou, A. et al. J Am Coll Cardiol Intv. 2020;13(7):833–42.

Safety and efficacy (change in urinary neutrophil gelatinase-associated lipocalin and serum cystatin C) of prophylactic administration of recombinant human C1 esterase inhibitor in high-risk patients undergoing elective coronary angiography. eGFR = estimated glomerular filtration rate; NGAL = neutrophil gelatinase-associated lipocalin; rhC1INH = recombinant human C1 esterase inhibitor.

present study (7.8%, in line with a previous study from our center in lower-risk patients [13]), which may be related to variations in the included study populations or procedural characteristics.

Importantly, no safety signal or unexpected adverse reactions related to rhC1INH administration emerged during the study, which is remarkable given the inclusion of an elderly patient population (mean age, 77 years) suffering from several comorbidities. In particular, there was no difference in the incidence of periprocedural events, which may be related to its interaction with the fibrinolysis and coagulation cascade (e.g., hemorrhage, stent thrombosis, or pulmonary embolism). Administration of rhC1INH was safe and well-tolerated in this study. A total of 3 death cases in the placebo group were related to periprocedural complications or underlying diseases. Hence, our date support future studies of rhC1INH in a similar patient population and other I/R settings.

STUDY LIMITATIONS. Our study has several limitations including the small sample size and its single-center performance. However, baseline and procedural characteristics were well balanced between the 2 groups with the exception of 2 outliers with excessively high NGAL values in the mITT population at baseline. Another limitation is the lack of assessment of the impact of rhC1INH on long-term renal function and outcomes (e.g., dialysis) and the inclusion of only a limited number of patients with severe renal impairment at baseline (eGFR <30 ml/min/1.73m^2). The pathophysiology of CA-AKI is complex and still under discussion, hence the precise mechanism of rhC1INH in attenuating NGAL and cystatin C increases is unknown. Because this was a pilot trial, only a single dosing regimen of rhC1INH was investigated, and the most appropriate regimens need to be determined in future studies. Last, the number of eligible subjects for this study was small which limits generalizability of our results.

CONCLUSIONS

Given the paucity of available prophylactic options to prevent CA-AKI, the present randomized controlled pilot study documents for the first time that administration of rhC1INH, a powerful complement inhibitor, before and 4 h after elective coronary angiography may be associated with less renal injury as reflected by 2 biomarkers (NGAL and cystatin C), in particular in patients undergoing more invasive procedures. In addition, the safety profile was favorable in an elderly patient population. These data justify larger clinical trials involving high-risk patients and investigating meaningful clinical outcomes.

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PERSPECTIVES

WHAT IS KNOWN: CA-AKI is a common event after coronary angiography and caused by direct cytotoxicity and local renal hypoperfusion. rhC1INH attenuated renal ischemia/reperfusion injury in experimental models.

WHAT IS NEW: In this randomized trial, rhC1INH attenuated acute renal injury as reflected by 2 biomarkers (urinary NGAL and serum cystatin C) in high-risk patients undergoing an elective coronary angiography and was well tolerated.

WHAT IS NEXT: RhC1INH is a promising intervention to attenuate renal damage. However, future trials with a larger patient population are required to determine its true efficacy, in particular regarding clinical outcomes.

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KEY WORDS contrast-induced acute kidney injury, coronary angiography, cystatin C, neutrophil gelatinase-associated lipocalin, recombinant C1 esterase inhibitor

APPENDIX For supplemental tables and a figure, please see the online version of this paper.