

Recombinant human C1 esterase inhibitor (Conestat alfa) in the prevention of contrast-induced nephropathy in high-risk subjects (PROTECT): a randomized, placebo-controlled, double-blind single-center trial

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26th October 2019

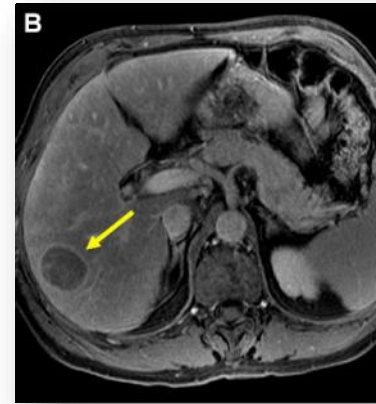


Disclosures

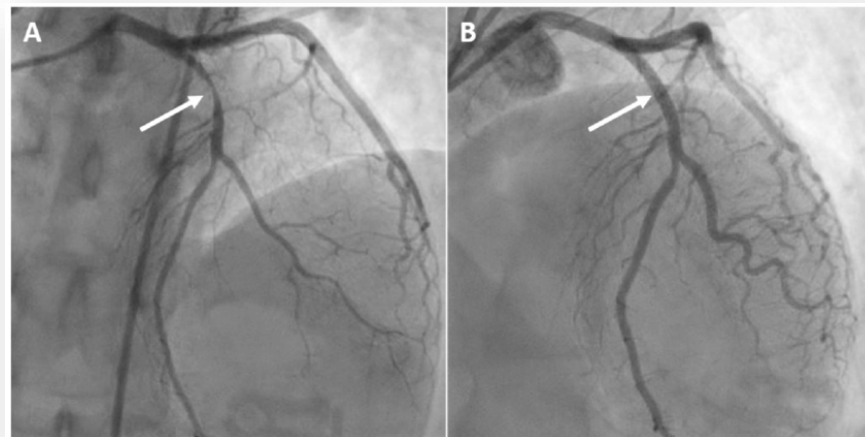
- **Research grants:** Pharming Biotechnologies B.V., Fondation Machaon, University Basel
- **Travel grants:** MSD, Gilead, Pfizer, Pharming Biotechnologies B.V.
- **Lecture fee:** MSD, Mundipharma
- **Consultation fee:** Pharming Biotechnologies B.V.

Radiographic contrast media (CM)

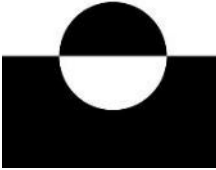
- **Essential tool in modern radiology and medicine**
 - Diagnostic



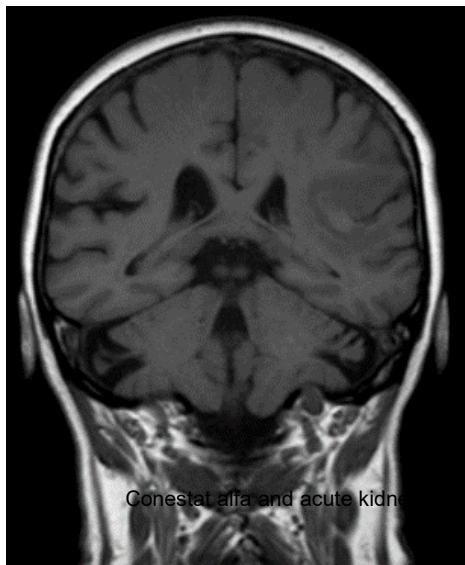
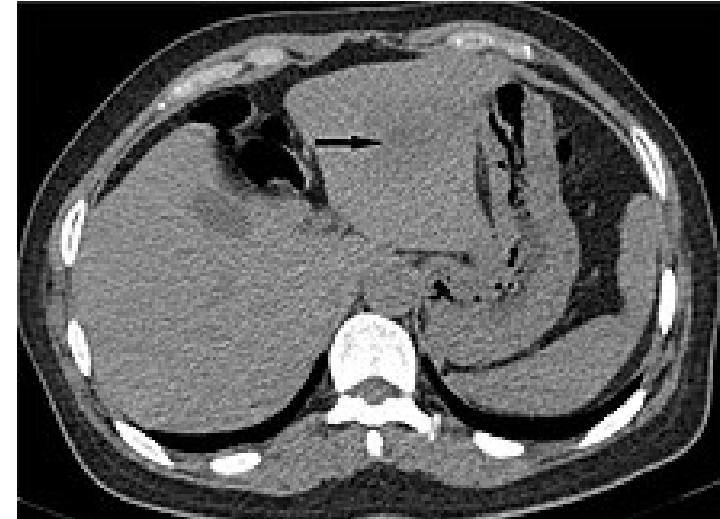
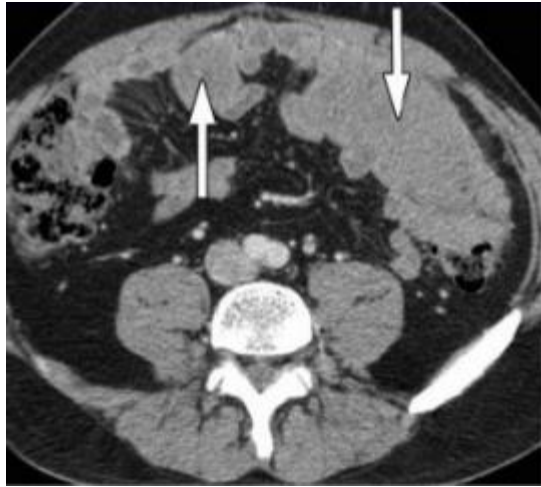
- Therapeutic



Radiographic contrast media (CM)



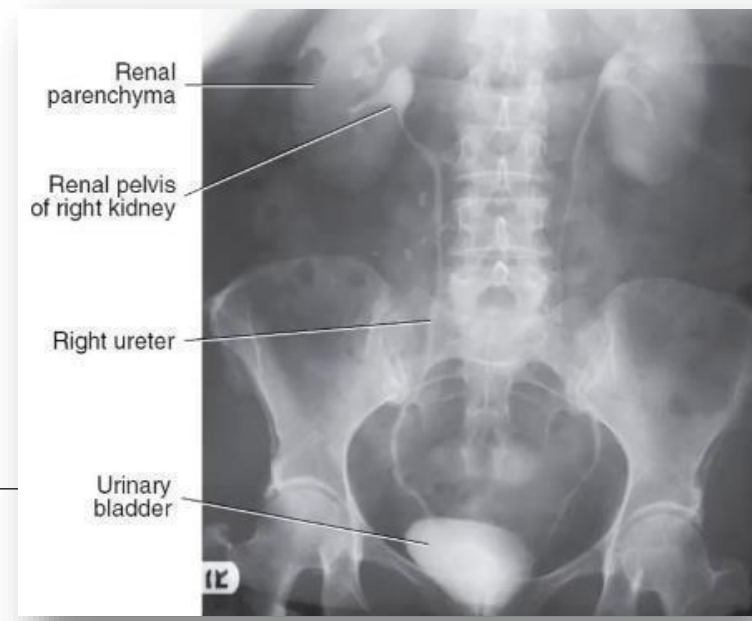
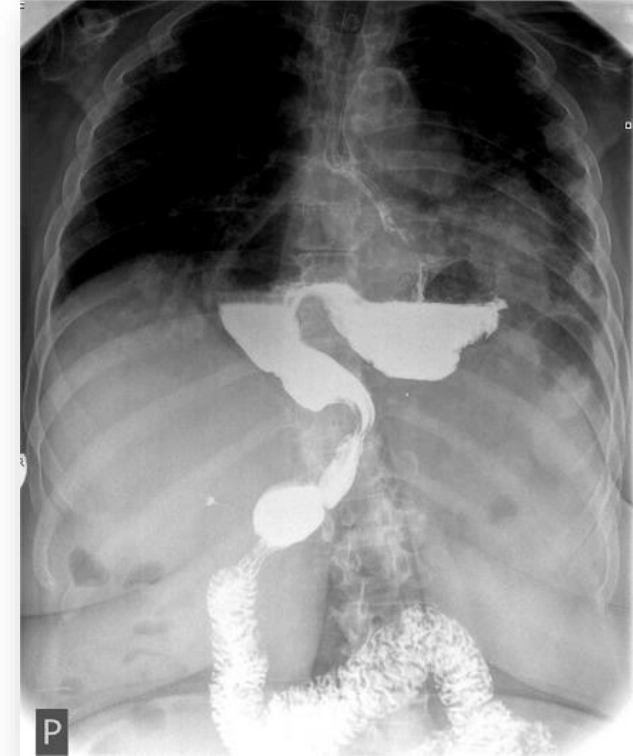
- CM makes fluid visible by increasing absorbance (>10% compared to blood)



Conestat alfa and acute kidn

History

- **1910:** Barium sulphate for gastrointestinal contrast study
- **1920's:** sodium iodide used to treat syphilis. Was found to be radio opaque on x-rays
- **Iodinated CM most commonly used today for**
 - ✓ CT scans
 - ✓ Angiographies
 - ✓ Arthrography
 - ✓
 - ✓ Oral, rectal, intravenous....





Physiology / Pathophysiology

Iodinated CM

- Majority water soluble, >90% renal elimination
- Does not enter the cells



- FATIGUE
- WEIGHT LOSS
- SENSITIVITY TO COLD
- DEPRESSION
- MEMORY PROBLEMS
- GOITER
- HAIR LOSS
- MUSCLE PAIN
- TREMBLING HANDS
- INFERTILITY

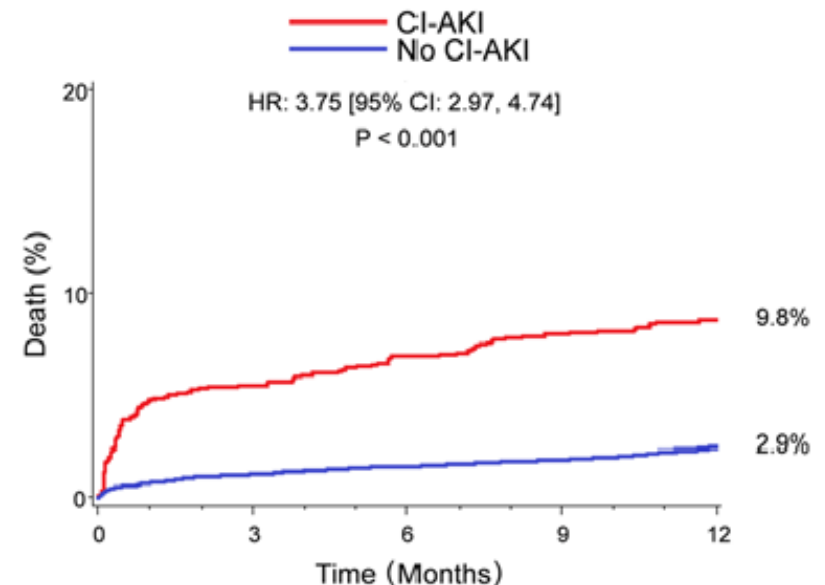
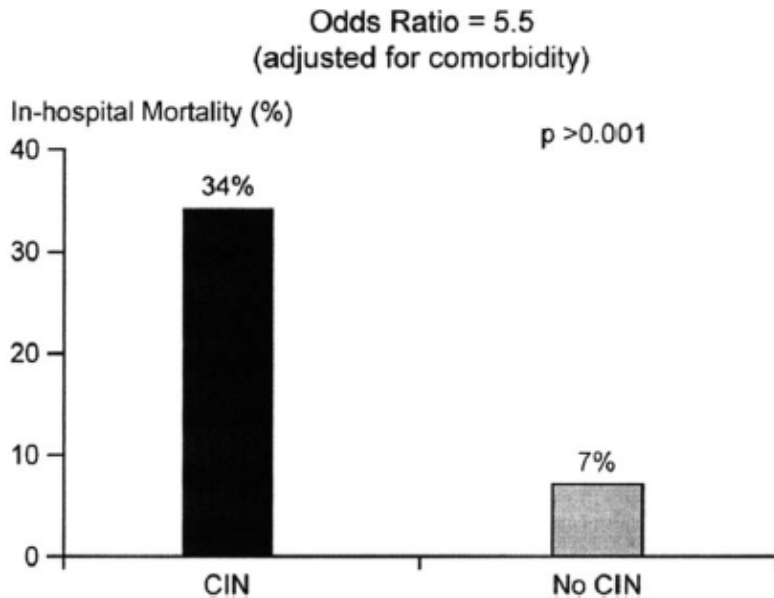
Adverse events

- «Allergic» reaction
- Contrast-associated acute kidney injury
- Exacerbation of pre-existing hyperthyroidism



Contrast-associated acute kidney injury (CI-AKI)

- Third leading cause of acute kidney failure (ARF) in the hospital.¹
- **Definition:**
 - Exposure to iodinated CM
 - Alternative major injuries are ruled out
- **Consequences:**
 - Prolonged hospitalization, significant morbidity and mortality and increased health care costs



¹ Tublin ME et al., AJR 1998

Conestat alfa and acute kidney injury

Rudnick M et al., Clin J Am Soc Nephrol 2008; Levy EM et al., JAMA 1996,
Giacoppo D, Circ Cardiovasc Interv 2015
McCullough PA, Am J Cardiol 2006

CI-AKI – risk factors

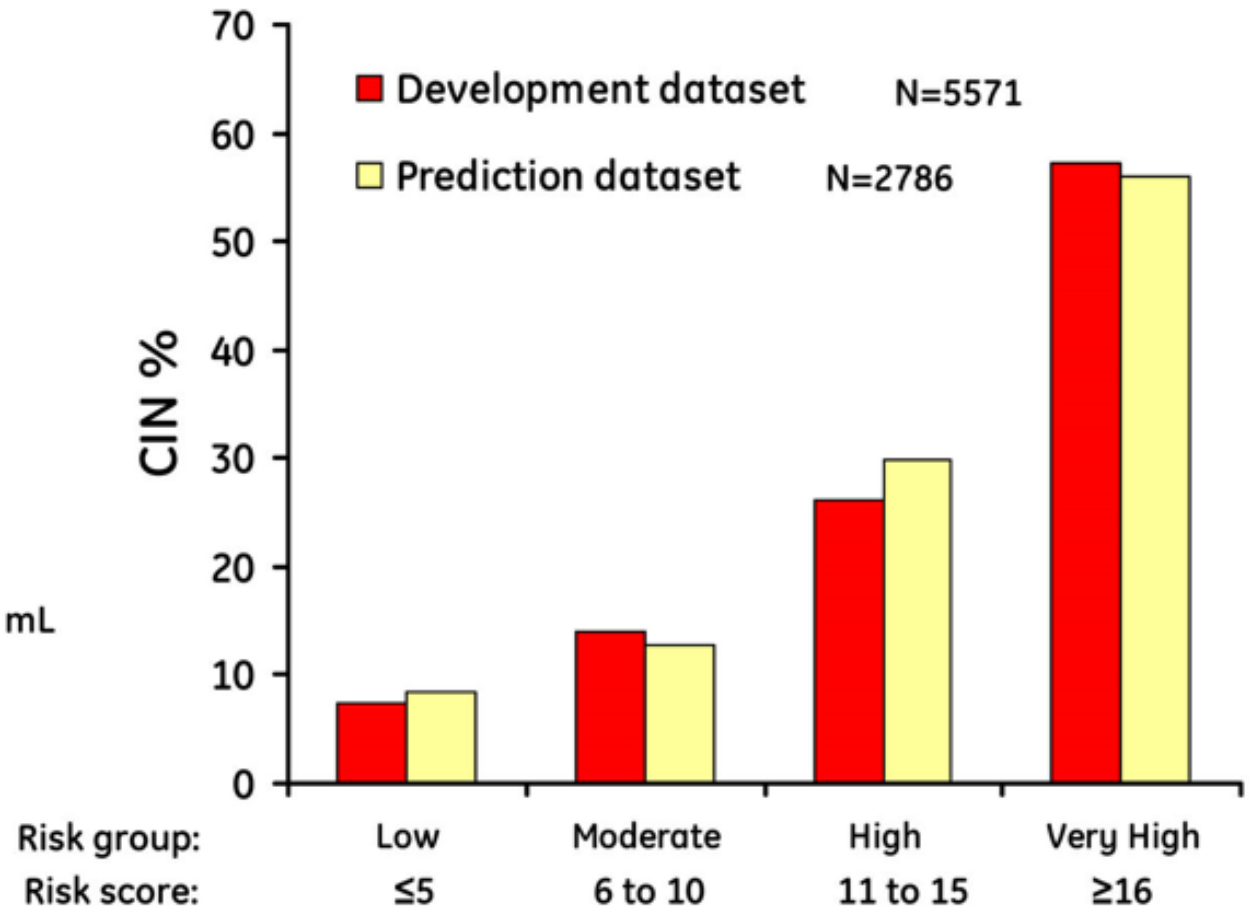
Non-modifiable	Modifiable
Renal disease	Anemia
Diabetes mellitus	Shock/Sepsis
Heart failure	Hypotension
Hypercholesterolemia	CM > 100ml
Age > 75 years	Nephrotoxic drugs
	Dehydration
	Repeat administration of CM

CI-AKI – risk score

Multivariate Predictors

Hypotension	5 points
IABP use	5 points
CHF	5 points
SCr >1.5 mg/dL (>132 µmol/L)	4 points
Age >75 y	4 points
Anemia	3 points
DM	3 points
Contrast volume	1 point/100 mL

Risk of contrast media associated kidney injury



CIN, contrast-induced nephropathy; DM, diabetes mellitus; IABP, Intra-aortic balloon pump

Mehran R, J Am Coll Cardiol 2004

CI-AKI – Prevention

- Hydration with 0.9% sodium chloride
- Low-osmolar/iso-osmolar CM
- Lowest amount of CM possible
- Stop of nephrotoxic drugs (e.g. certain pain killer and antibiotics)



N-acetylcysteine

RenalGuard Therapy®

??

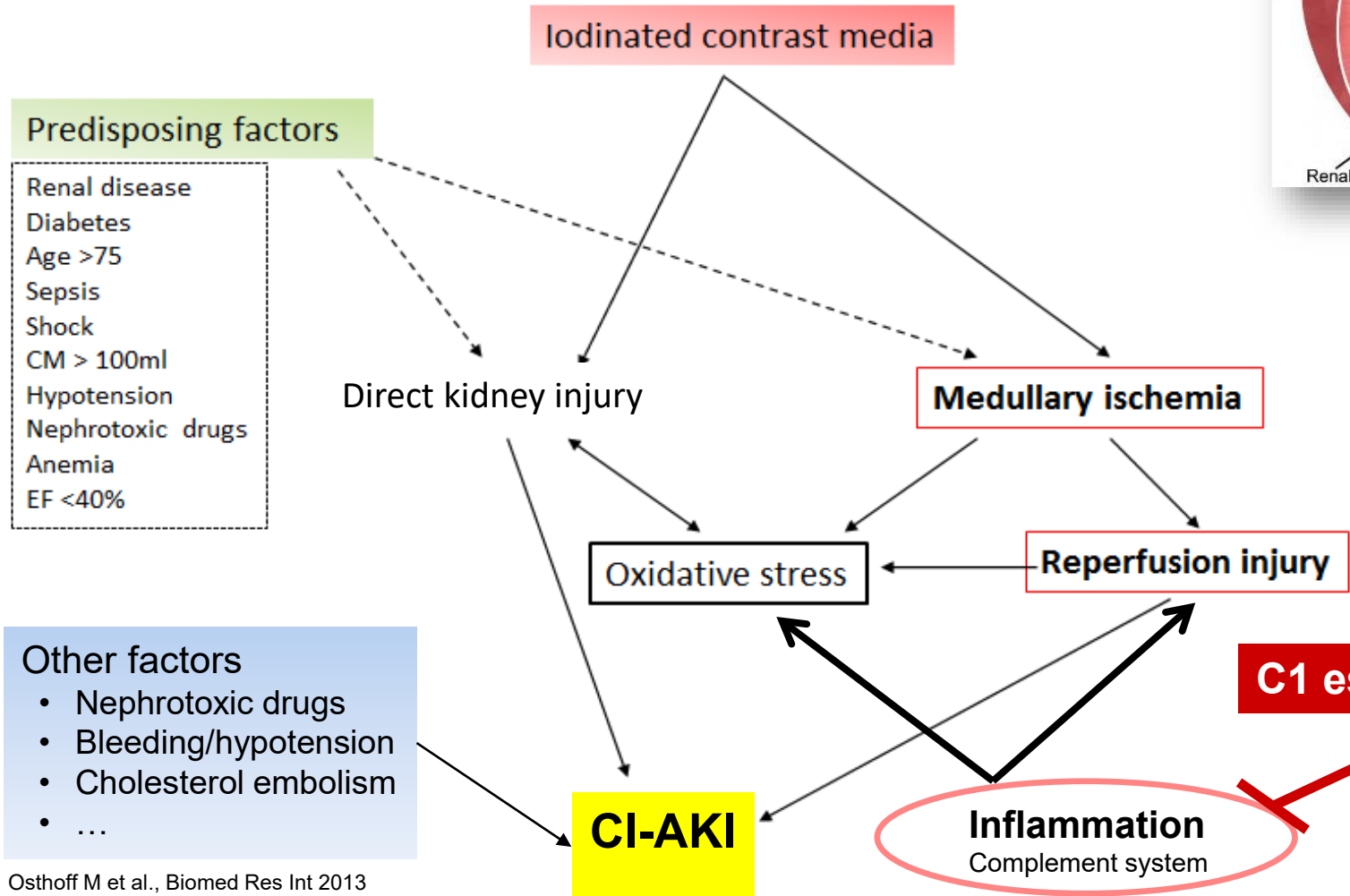
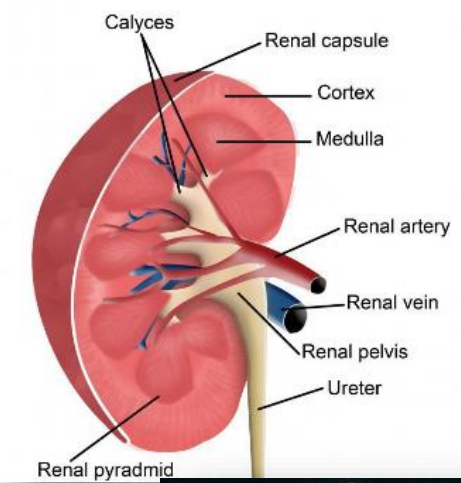
Sodium bicarbonate

Mannitol

Statins

Forced diuresis

CI-AKI - Pathophysiology



Predisposing factors

- Renal disease
- Diabetes
- Age >75
- Sepsis
- Shock
- CM > 100ml
- Hypotension
- Nephrotoxic drugs
- Anemia
- EF <40%

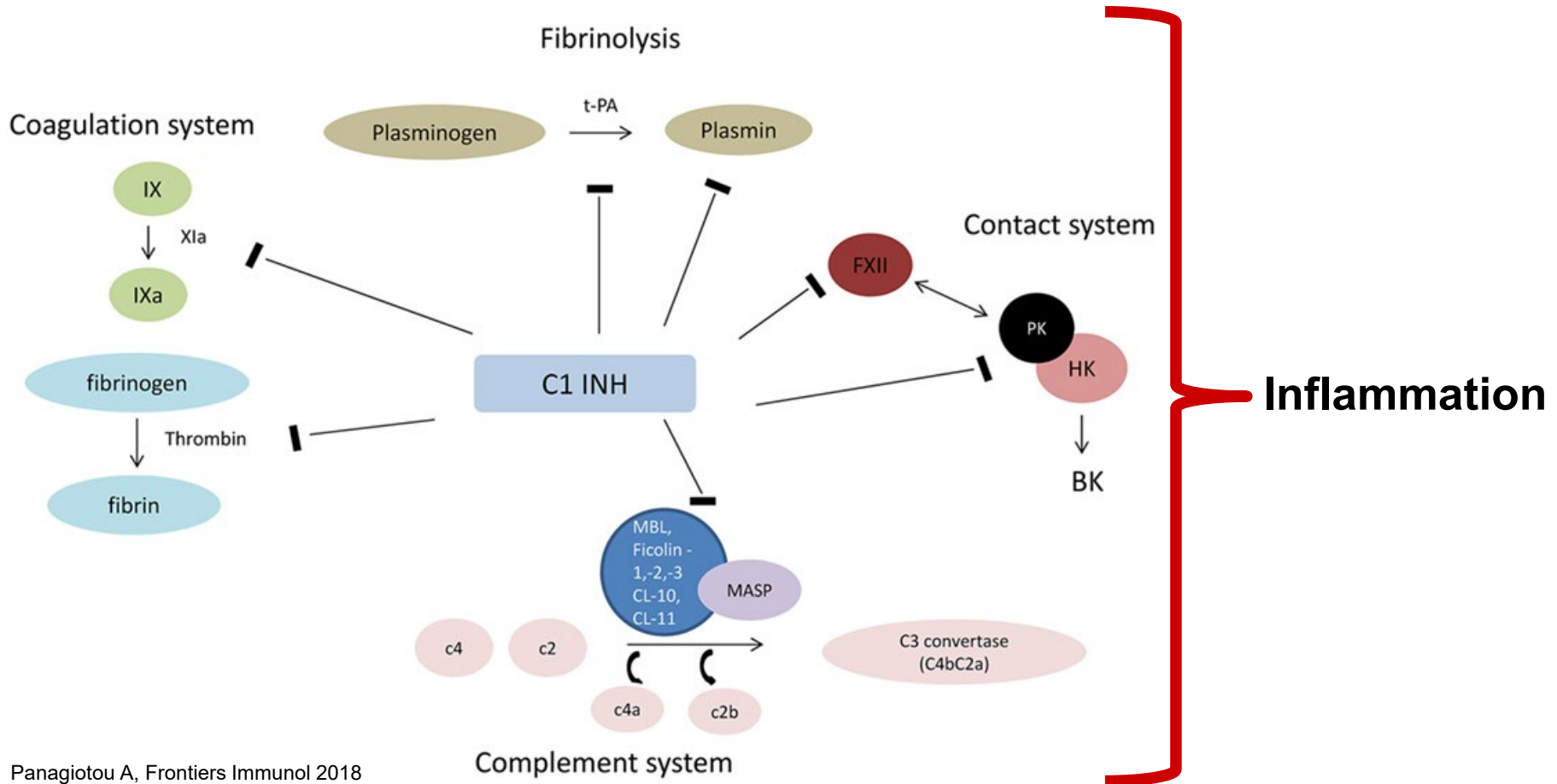
Other factors

- Nephrotoxic drugs
- Bleeding/hypotension
- Cholesterol embolism
- ...

Osthoff M et al., Biomed Res Int 2013
www.msmanuals.com

C1 esterase inhibitor (C1INH)

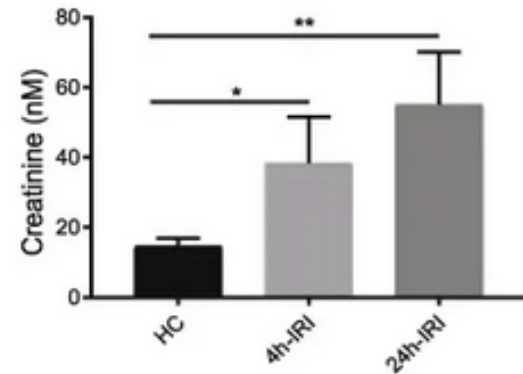
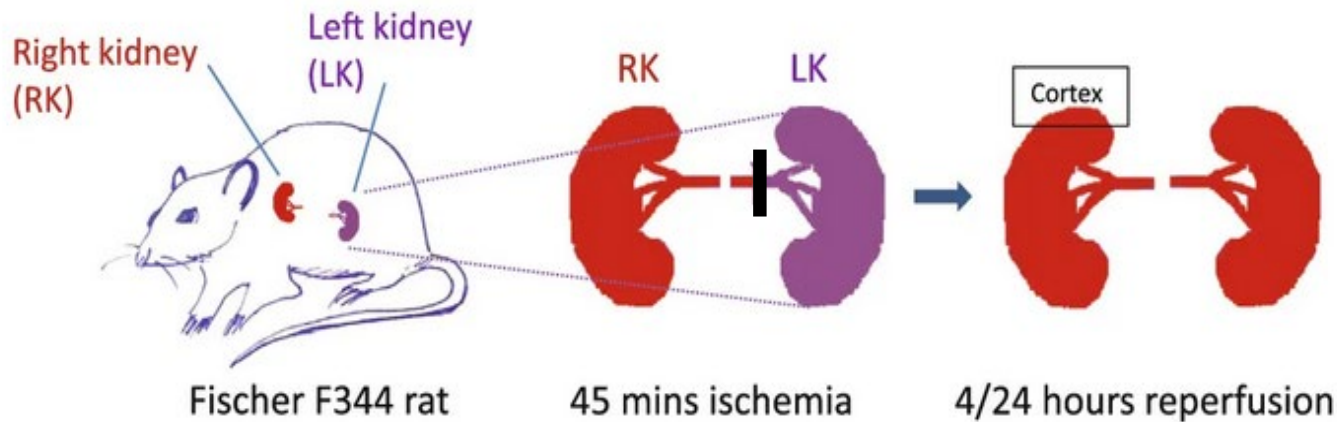
- Human plasma protein – **multiple-action-multiple-target inhibitor** (complement, coagulation and contact (kinin) system, fibrinolysis)



Panagiotou A, Frontiers Immunol 2018

C1 esterase inhibitor (C1INH)

- Human plasma protein – **multiple-action-multiple-target inhibitor** (complement, coagulation and contact (kinin) system, fibrinolysis)
- Approved for hereditary angioedema
- Plasma-derived or recombinant version (**rhC1INH/conestat alfa**)
- **Ameliorates experimental renal ischemia/reperfusion injury**

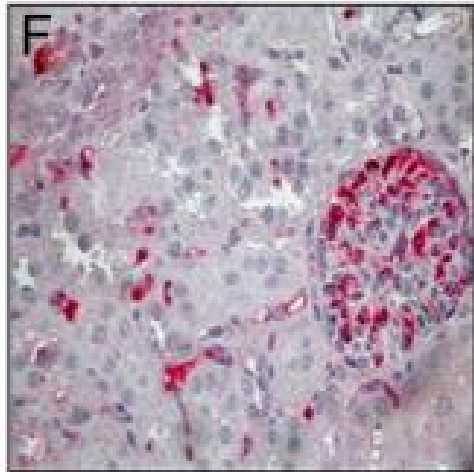


Huang H, Scientific Reports 2018

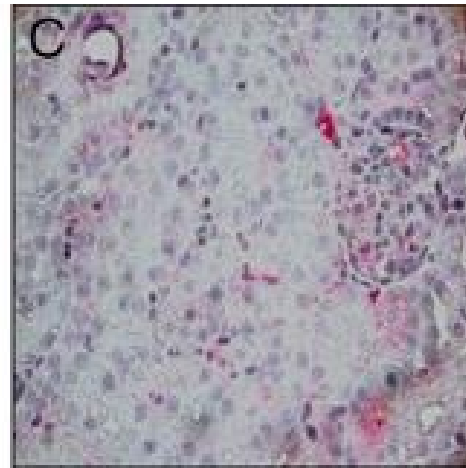
C1 esterase inhibitor (C1INH)

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Complement deposition in the kidneys

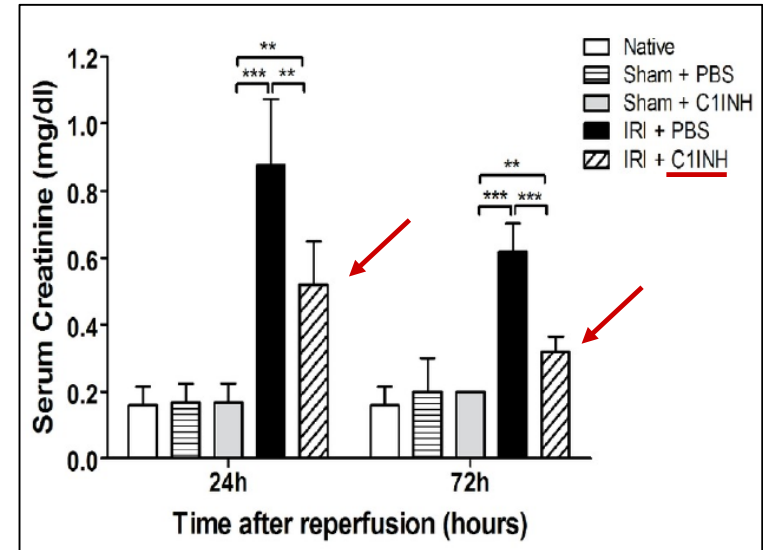


Placebo



rhC1INH

Serum creatinine increase

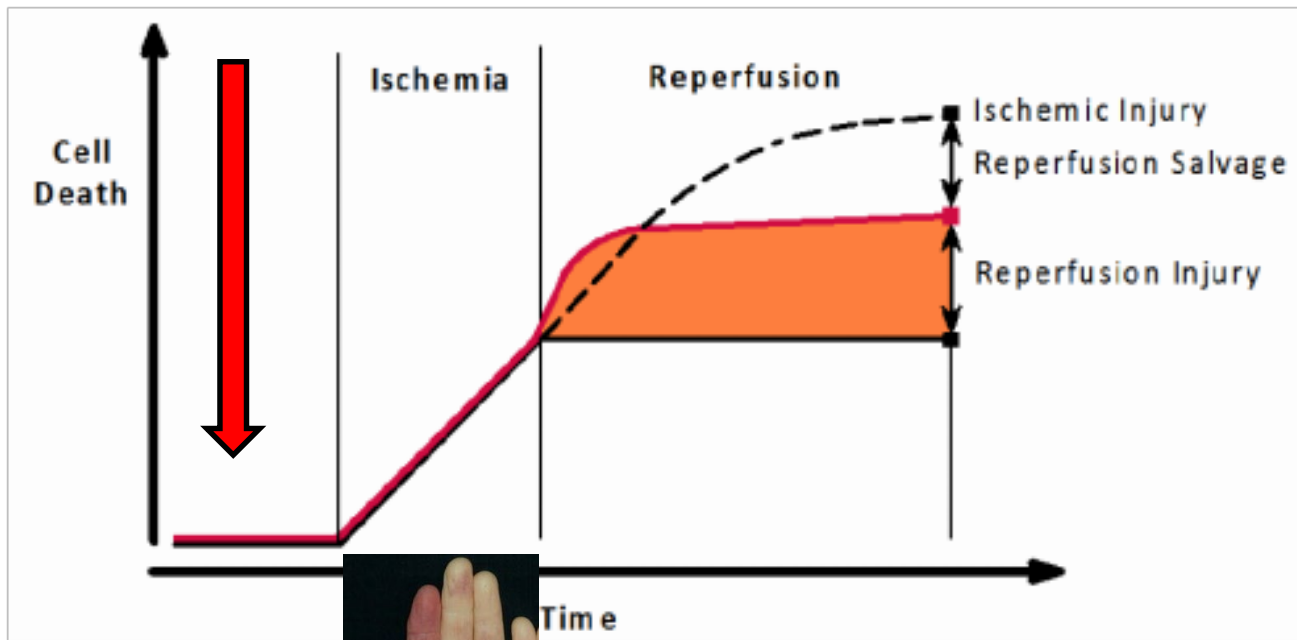


Van der Pol et al., Am J Transplant 2012; Danobeitia JS et al., PLOS one 2017

Study rationale

- Ischemia/reperfusion injury contributes to CI-AKI
- rhC1INH reduces experimental renal ischemia/reperfusion injury

Is prophylactic rhC1INH treatment associated with a reduced risk of CI-AKI in high-risk patients?



Study design – PROTECT study

Recombinant Human C1 Esterase Inhibitor in the Prevention of Contrast-induced Nephropathy in High-risk Subjects

Study type	Randomized, double-blind, placebo-controlled, exploratory (phase 2) study
Study population	Individuals with chronic kidney disease scheduled for elective coronary angiography (+/- angioplasty)

Pilot study

- small study often done to assist the preparation of a larger, more comprehensive study
- to demonstrate feasibility of key components
- to estimate key parameters for a larger trial
- to identify a target population for a larger trial

«Good results»: to demonstrate

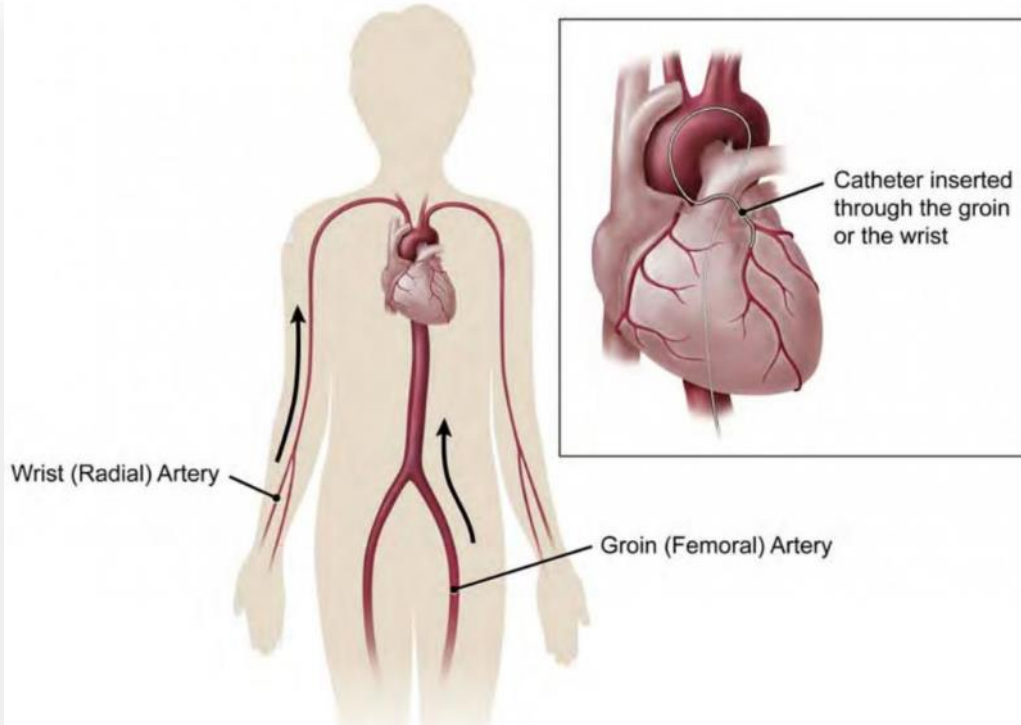
«Some signal» of efficacy

No safety concern

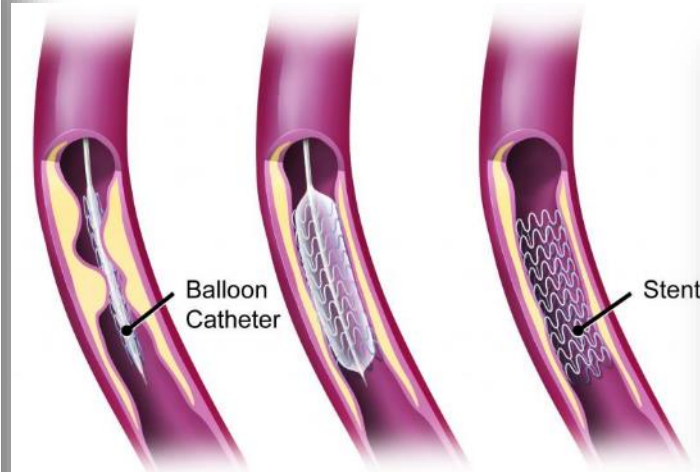
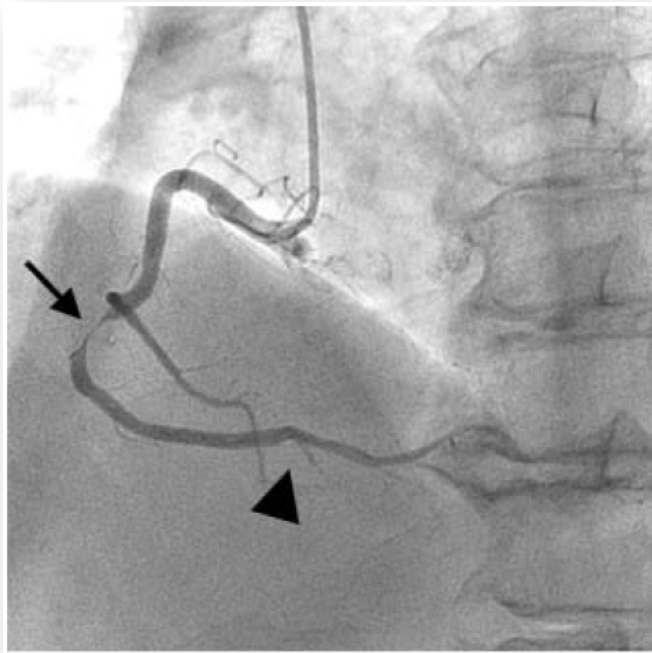
Study design – elective coronary angiography

Chest pain (worsening)
Progressive shortness of breath
Positive cardiac stress test
Before major surgery

....



Study design – elective coronary angiography



- 30 - 90 minutes
- 50 - 400 ml contrast media
- Usually safe, most common side effect: bleeding

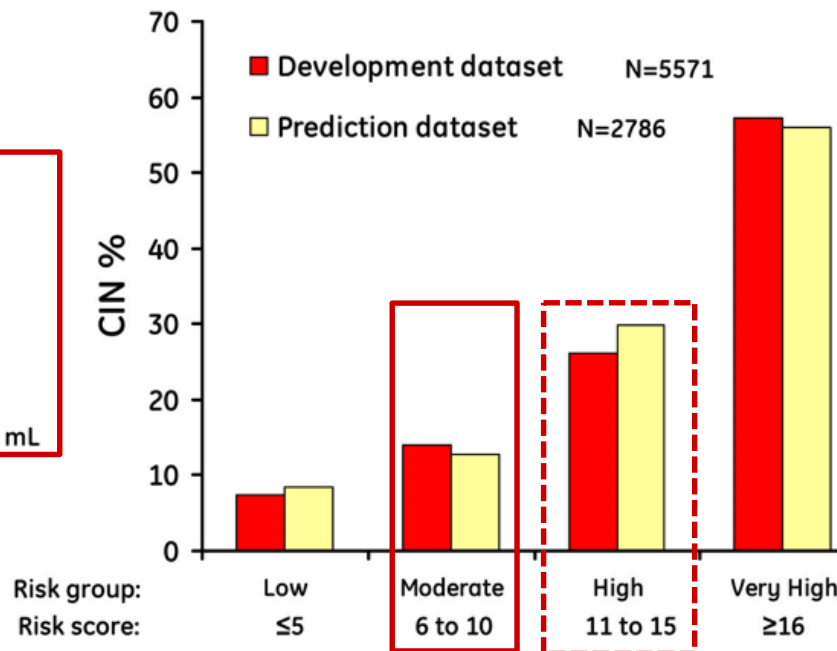


Study design

Study type	Randomized, double-blind, placebo-controlled, exploratory (phase 2) study
Study population	Individuals with chronic kidney disease scheduled for elective coronary angiography (+/- angioplasty)
Inclusion criteria	≥ 18 a, $eGFR \leq 50$ ml/min/1.73m ² plus ≥ 1 of the following: Age ≥ 75 y, congestive heart failure NYHA III/IV, diabetes mellitus, anemia (hematocrit $\leq 39\%$ for men and $\leq 36\%$ for women), history of pulmonary edema

Multivariate Predictors

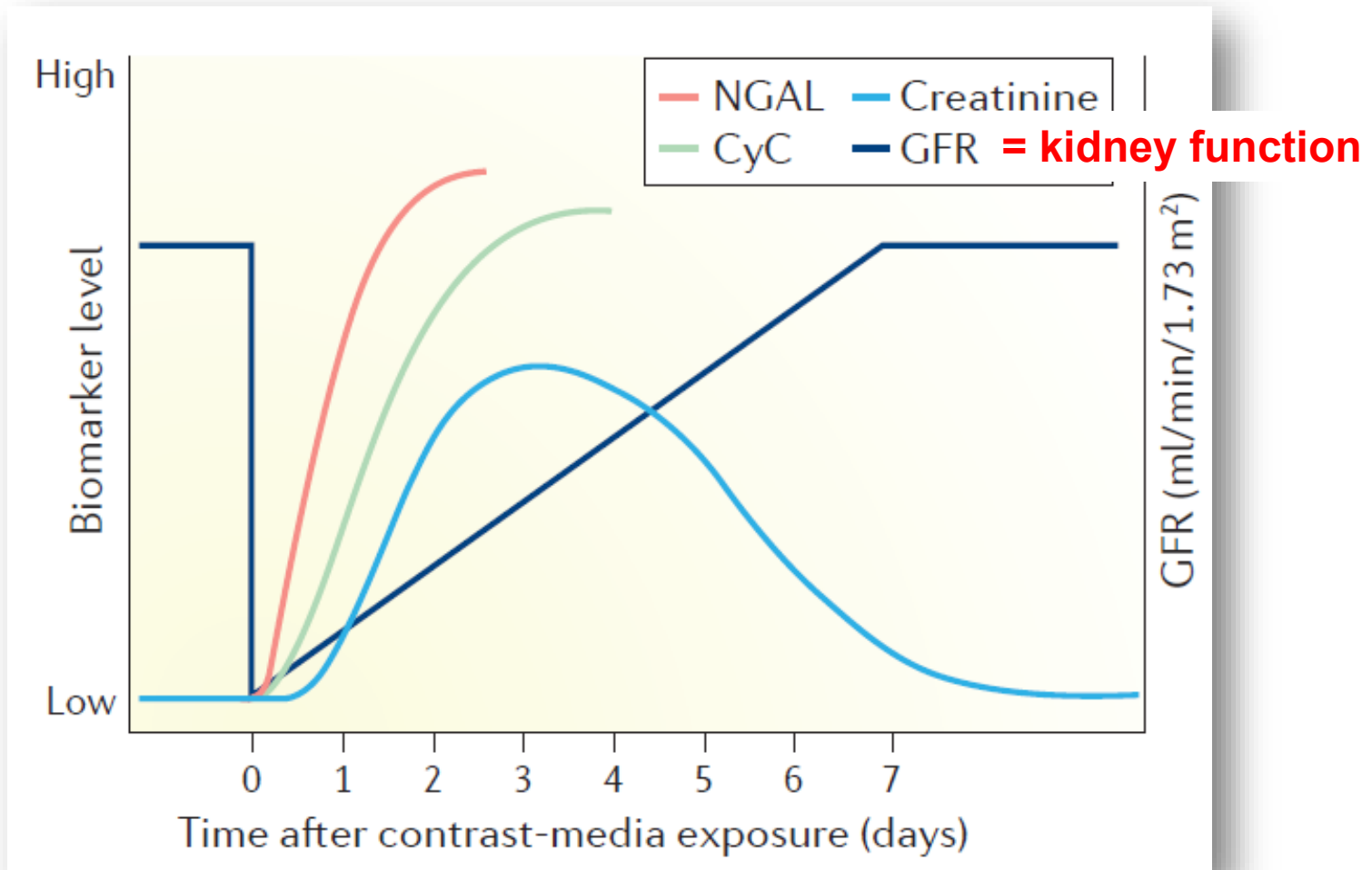
Hypotension	5 points
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Exclusion criteria	Allergy to rabbits, recent (≤ 2 wk) pulmonary edema or myocardial infarction, dialysis, multiple myeloma, recent (≤ 7 d) exposure to contrast media, pregnancy/lactation, treatment with N-acetylcystein or sodium bicarbonate

Biomarker of acute kidney injury



Malyszko J, Scientific Reports 2015; Briguori C, J Biomedicine Biotechnology 2014
Fähling M, Nature Rev Nephrology 2017

Intervention

- Screening
- Informed consent
- Randomization
- Baseline samples
- Hydration

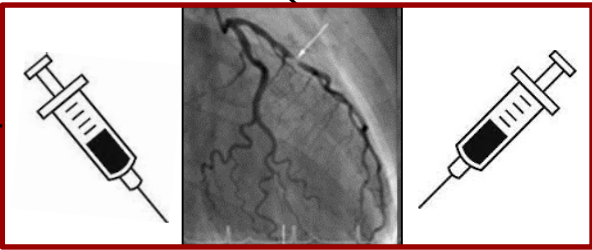


- Blood/urine sampling
- Discharge

Telephone interview



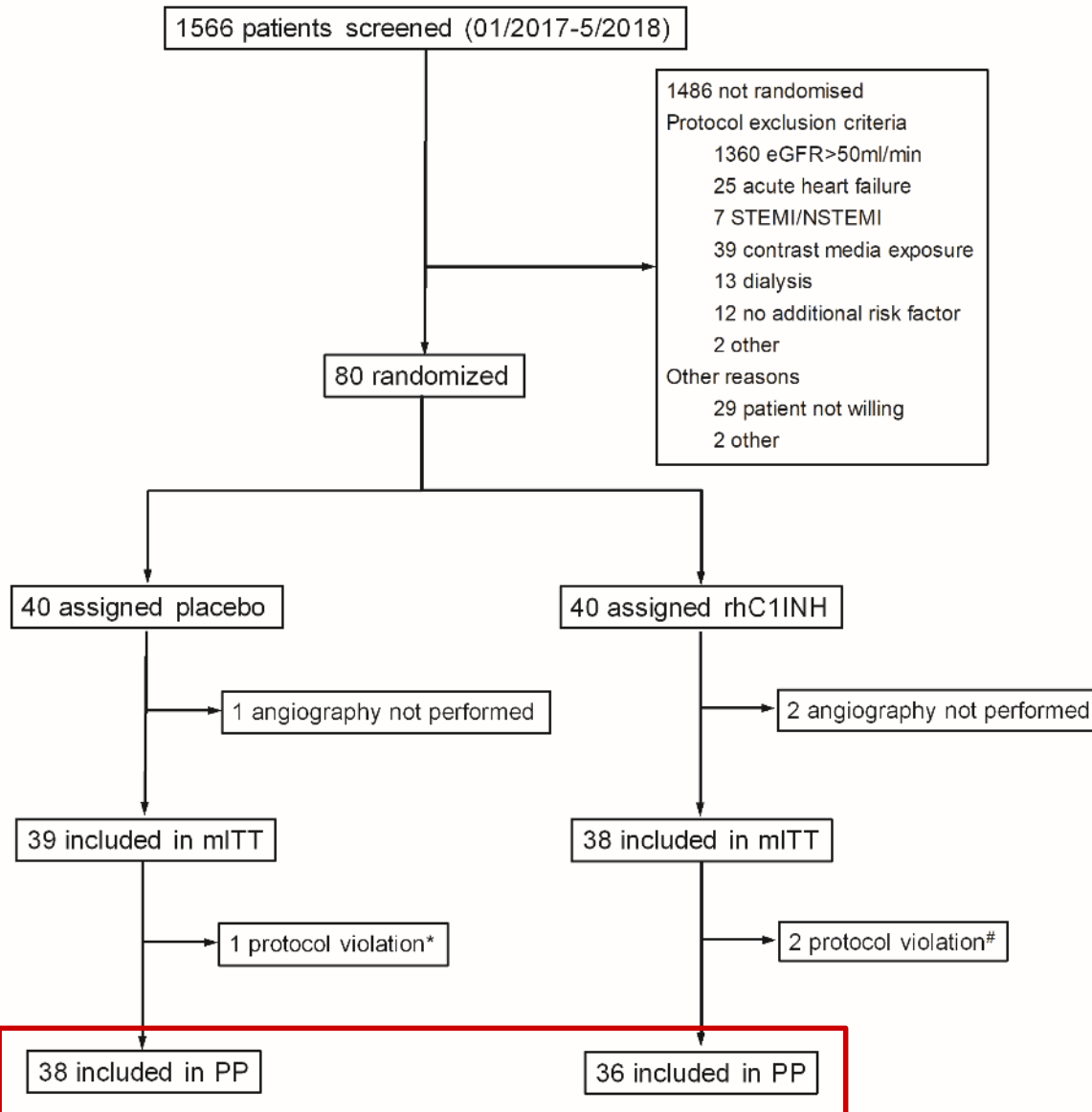
- Group 1: rhC1INH**
 - <84kg: 50 U/kg
 - >84kg: 4200 U
- Group 2: placebo**
 - Sodium chloride



Blood/urine sampling

- Outpatient visit**
 - Blood/urine sampling

Trial profile and baseline characteristics



Abbreviation: rhC1INH, recombinant human C1 inhibitor; eGFR, estimated glomerular filtration rate; mITT = modified intention-to-treat analysis (participants who have received at least one dose of study medication and have undergone the planned elective angiography); PP = per protocol analysis (two doses of study medication)

Baseline characteristics

Parameter	Placebo N=39	rhC1INH N=38	P value
Female, n (%)	11 (28.2)	12 (31.6)	0.8
Age in years, mean (SD)	77.7 (9.4)	76.2 (7.0)	0.4
Dyslipidemia	23 (59.0)	25 (65.8)	0.5
Diabetes mellitus, n (%)	14 (35.9)	18 (47.4)	0.3
Heart failure, n (%)	21 (53.8)	16 (42.1)	0.3
Coronary artery disease, n (%)	20 (51.3)	24 (63.2)	0.3
Previous MI, n (%)	12 (30.8)	13 (34.2)	0.8
ACE-I or ATII-RA, n (%)	29 (74.4)	33 (86.8)	0.2
Loop diuretic, n (%)	19 (48.7)	16 (42.1)	0.6
Metformin, n (%)	8 (20.5)	8 (21.1)	1
Aspirin, n (%)	21 (53.8)	24 (63.2)	0.5
Statin, n (%)	21 (53.8)	29 (76.3)	0.06
Betablocker, n (%)	20 (51.3)	28 (73.7)	0.06

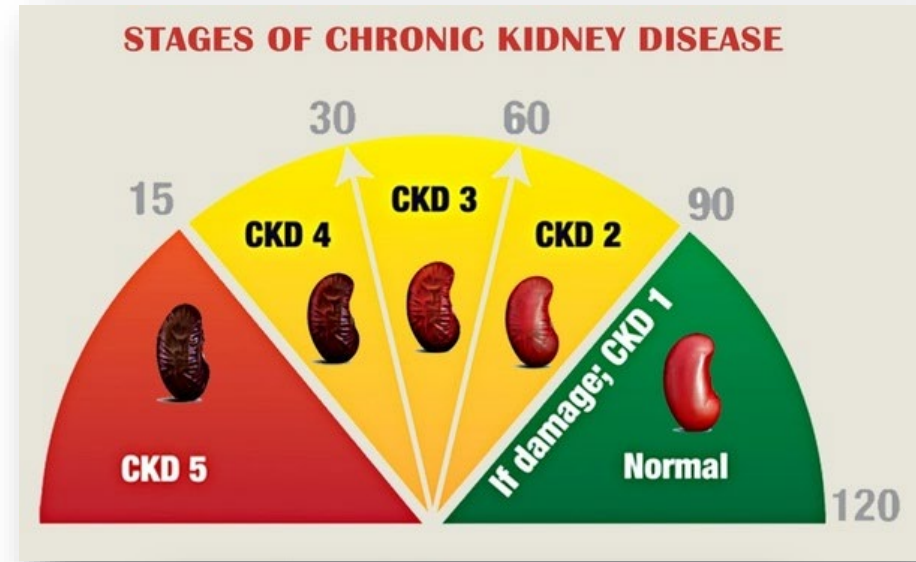


Abbreviation: RAAS, renin-angiotension-aldosterone system; CAD, coronary artery disease; MI, myocardial infarction;

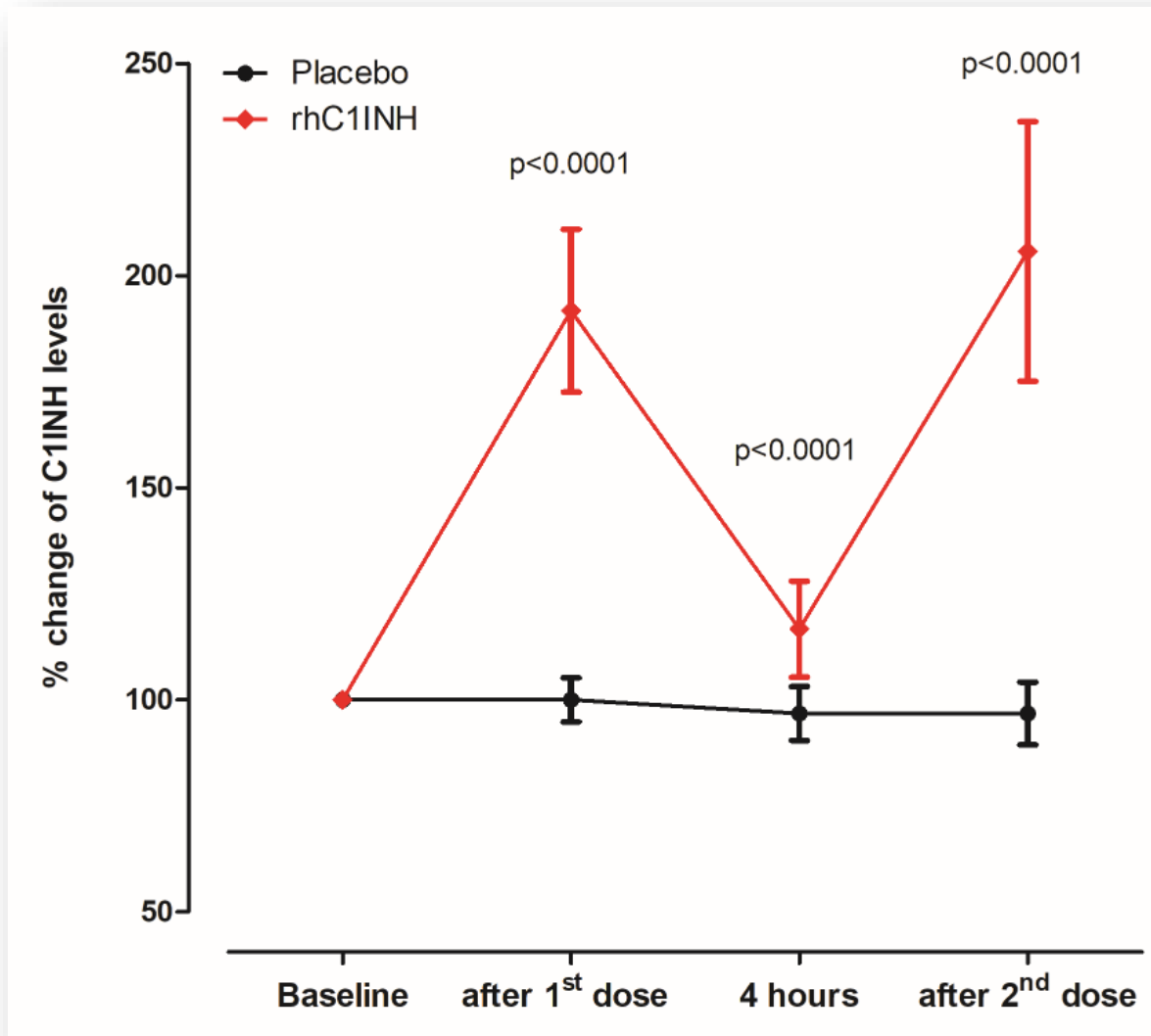
Intervention characteristics

Parameter median (IQR) or n (%)	Placebo N=39	rhC1INH N=38	P value
Creatinine (µmol/l)	128 (52)	133 (36)	0.9
eGFR (ml/min/1.73m²)	41 (15)	44 (10)	0.8
Urinary NGAL (ng/ml)	17.7 (39.9)	21.1 (46.8)	0.6
Cystatin C (mg/l)	1.58 (0.4)	1.55 (0.5)	0.8
Reason for angiography			0.7
Angina	13 (33.3)	17 (44.7)	
Before surgery or TAVR	8 (20.5)	9 (23.7)	
Positive stress test	9 (23.1)	7 (18.4)	
Coronary artery stenosis	4 (10.3)	4 (10.5)	
Other	5 (12.8)	1 (2.6)	
Contrast media (ml)	112 (94)	110 (83)	0.5
PCI	15 (38.5)	15 (39.5)	0.7

Abbreviations; eGFR, estimated glomerular filtration rate (calculated with the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-Epi)), PCI, percutaneous coronary intervention; TAVR, transcatheter aortic valve replacement



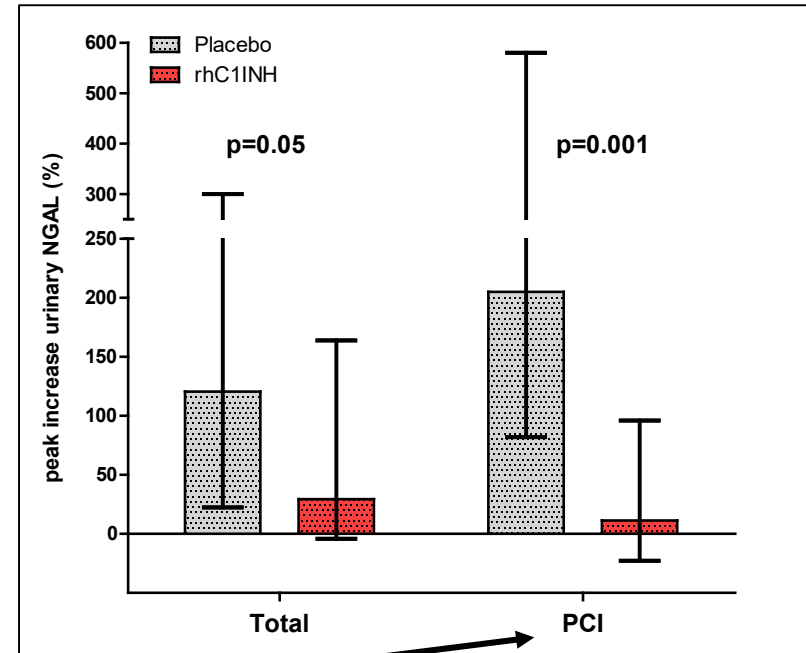
Change in C1INH concentration



Results – peak urinary NGAL increase within 48 h

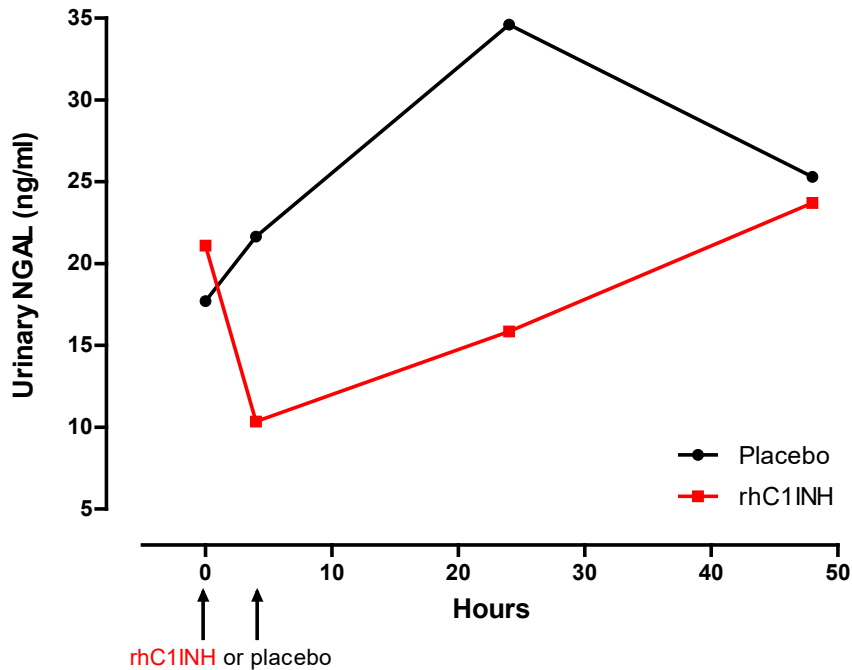
Median (IQR)	Placebo	rhC1INH	P value
Entire population			
Absolute (ng/ml)	22.5 (80.3)	4.7 (51.4)	0.038
Relative (%)	121 (277)	29 (152)	0.052
Percutaneous coronary intervention (PCI)			
Absolute (ng/ml)	26.2 (117.8)	1.8 (15.2)	0.039
Relative (%)	205 (385)	11 (79)	0.002

Relative peak increase (%)

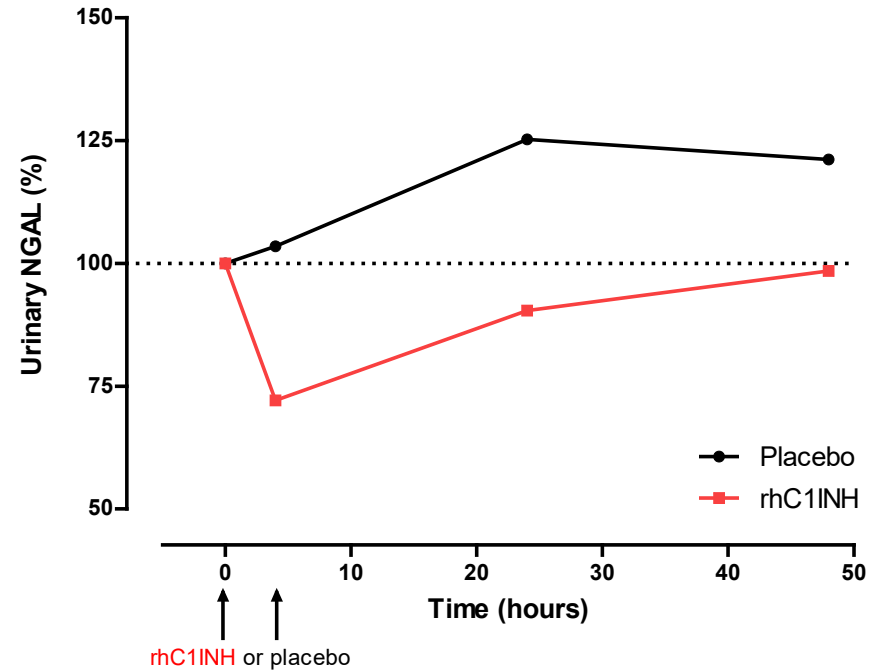


Results – course of urinary NGAL

Absolute concentration (ng/ml, medians)



Relative concentration (% , medians)



Results – secondary endpoints / safety

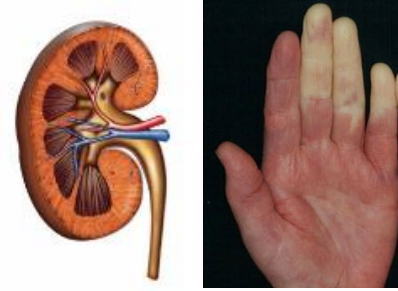
Secondary endpoint Median (IQR) or n (%)	Placebo	rhC1INH	P value
Cystatin C increase \geq 10% within 24h	13 (33.3)	6 (15.8)	0.045
Acute kidney injury ¹	7 (17.9)	6 (15.8)	0.7
Troponin T peak increase within 24h (ng/l)	8 (33.0)	10.5 (56.0)	0.13

¹ increase in serum creatinine of \geq 26 μ mol/l or \geq 50% within 48h

Safety (within 3 months)	Placebo	rhC1INH
Composite cardiovascular/renal outcome ¹ , n (%)	3 (8)	3 (8)
Any adverse event, n (%)	16 (41)	14 (37)
Any possible drug-related adverse event, n (%)	2 (5)	0 (0)
Serious adverse event, n (%)	8 (21)	8 (21)
Death, n (%)	3 (8)	0

¹ death, unstable angina/acute coronary syndrome, hospitalization for heart or renal failure or hemodialysis

Conclusion



1st human trial of rhC1INH in ischemia/reperfusion injury setting

Administration of rhC1INH before and 4 hours after coronary angiography

- was associated with less renal injury (as reflected by urinary NGAL and cystatin C)
- in particular in patients undergoing more invasive procedures

The safety profile was favorable in a patient population with multiple comorbidities and polypharmacy

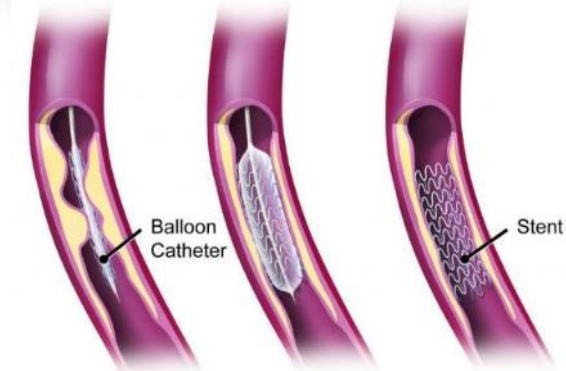
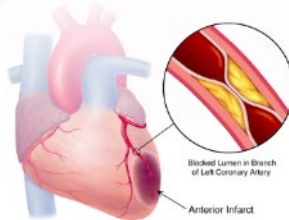
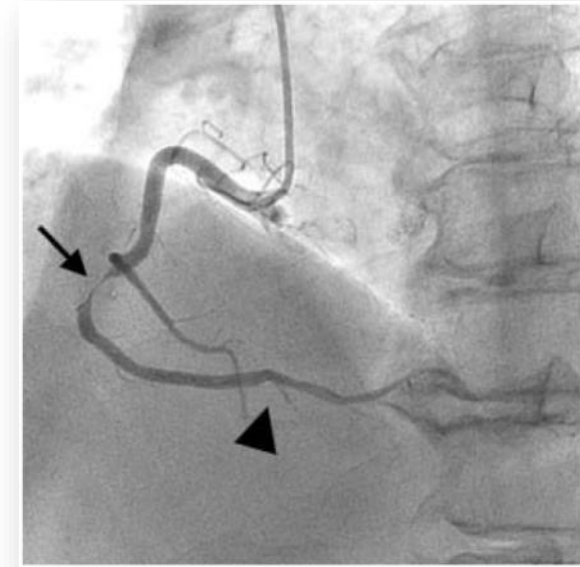
Future studies are warranted to investigate the nephroprotection by rhC1INH in more detail

To be continued....

Myocardial infarction and kidney injury



rhC1INH



Acknowledgements



Cardiology

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Anurag Relan



Freiwillige Akademische
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Thank you very much for your attention

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