

**ADVANCES IN CARDIAC  
ARRHYTHMIAS**  
*and*  
**GREAT INNOVATIONS  
IN CARDIOLOGY**

XXVII GIORNATE CARDIOLOGICHE TORINESI

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From Caliper to Catheter  
JM  
JOINT MEETING  
OF CARDIOLOGY

# Contrast induced acute kidney injury following coronary angiography: major adverse cardiac events in a long term follow up



CARLO BUDANO  
DIPARTIMENTO CARDIOVASCOLARE E TORACICO  
A.O.U. CITTA' DELLA SALUTE E DELLA SCIENZA DI TORINO

# Insufficienza Renale Acuta

Responsabile dell' 1 - 2% dei ricoveri in ambiente ospedaliero

Si verifica in circa il 5% di tutti i ricoveri ospedalieri

Complica fino al 30% i ricoveri in Unità Intensive

Anche quando reversibile è tra le prime cause di morbilità e mortalità nei pazienti ricoverati

È elemento prognostico sfavorevole nel decorso di molteplici processi patologici, aumentando la morbilità e la mortalità

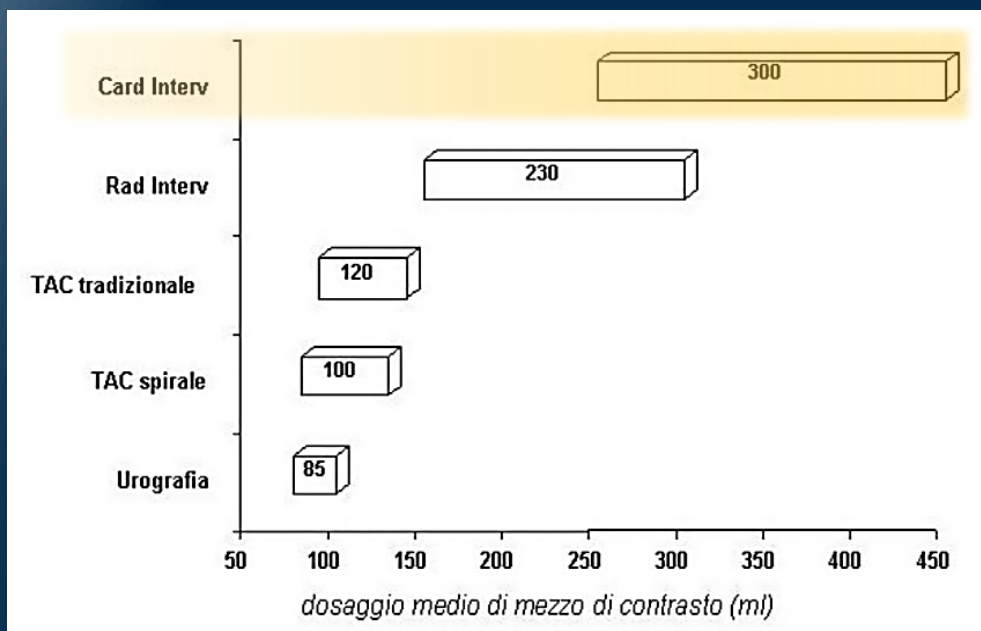
# DEFINITION

- An increase in serum creatinine generally occurring within 24hrs, peaking up to 5 days after, and returning to baseline within 3 weeks.
- Definition varies, increase in Cr of >25-50% from baseline and/or >0.5-1.0 mg/dL after 48-72 hrs.
- European Society of Urogenital Radiology 25% or 0.5 mg/dl
- Second International Consensus Conference of the Acute Dialysis Quality Initiative – defines renal failure in terms of GFR and urine output.

# DEFINITION

**Danno renale acuto  
da mezzo di contrasto (CI-AKI)**  
(incremento creatininemia di +0,3 mg/dl  
entro 48 ore oppure +50% entro 7 giorni)

KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int* (2012).



**INCIDENZA**  
nei pazienti con IRC:  
tra il **20** e il **60%**  
a seconda dei fattori  
di rischio compresenti

Rihal, C. S. et al. *Circulation* (2002).

Mehran, R. et al. *J. Am. Coll. Cardiol.* (2004).

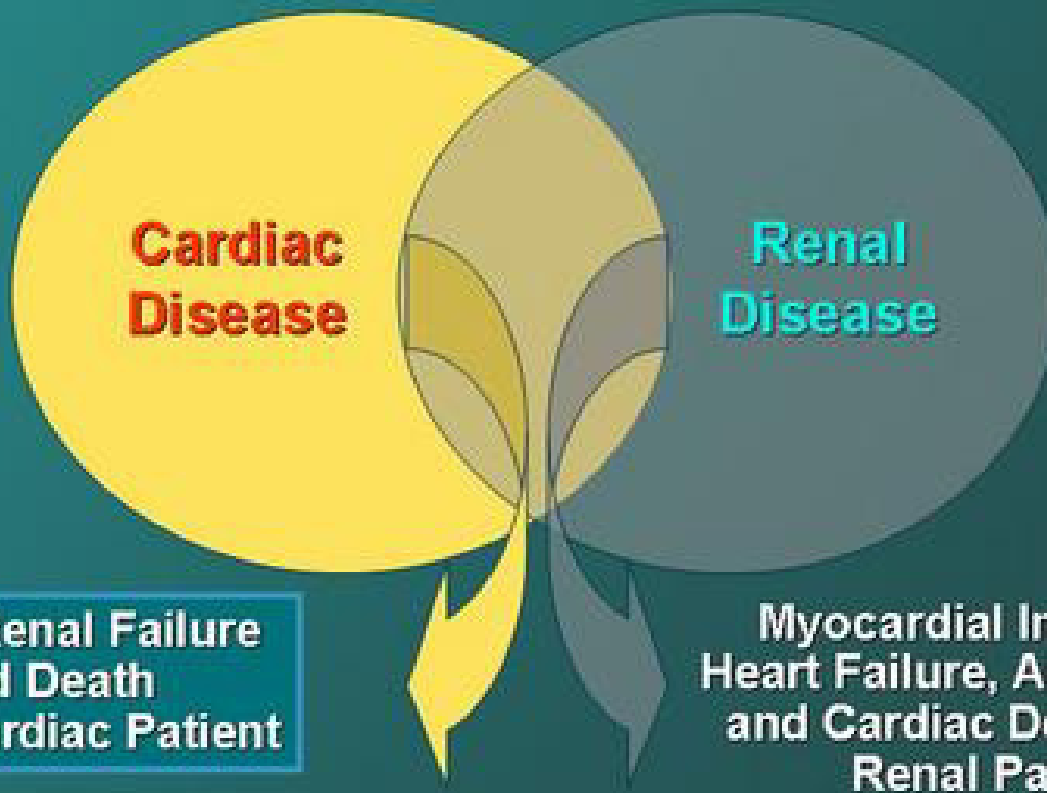
Cigarroa, R. G. et al. *Am. J. Med.* (1989).



**PERCHE' IL  
PROBLEMA E'  
RILEVANTE  
IN CARDIOLOGIA  
INTERVENTISTICA ?**



# Cardiorenal Risk



**Acute Renal Failure  
and Death  
in the Cardiac Patient**

**Myocardial Infarction,  
Heart Failure, Arrhythmias,  
and Cardiac Death in the  
Renal Patient**

# BACKGROUND

Insufficienza Renale Cronica  
(GFR  $\leq$  60 ml/min)



**PREVALENZA:**

Fino al **30%** dei pazienti  
ricoverati in Cardiologia

Best, P.J. et al. *J. Am. Coll. Cardiol.* (2002)  
Shlipak, M. G. et al. *Ann. Intern. Med.* (2002)  
Santopinto, J.J. et al. *Heart* (2003)



## QUALI RISCHI CORRELATI ALLA CORONAROGRAFIA ?

Danno renale acuto da mezzo di contrasto (CI-AKI)

Aumentato rischio emorragico

Ristenosi coronarica precoce in caso di angioplastica

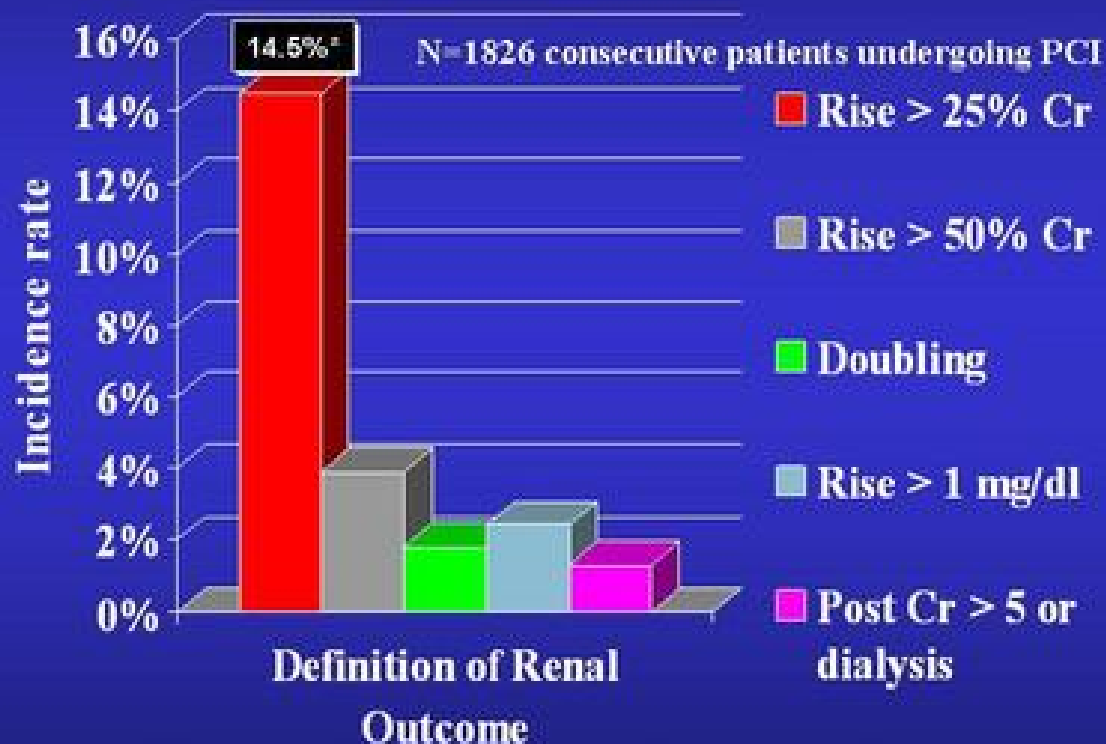
Sadeghi, H. M. et al. *Circulation* (2003).

Culleton, B. F. et al. *Kidney Int.* (1999).

Palmer, S. C. et al. *Ann. Intern. Med.* (2012).

## Frequency of CIN

The incidence of any complication depends on how it is defined



\*Validated at 16.5% in 8,628 consecutive series at Washington Hospital Center, Iakovou, et al. Submitted to ACC for publication in 2002.

# INCIDENCE

- Large scale studies in general hospital patients provide best estimate of healthcare impact
- CIN has decreased over the past decade from ~15% to ~7% recently
  - Nash et al. 4622 patients, 7.2% CIN
- Thought to be due to
  - Greater awareness of the problem
  - Better risk prevention measures
  - Improved iodinated contrast media
- Total number of cases did not decline due to increasing number of procedures requiring contrast



# IMPACT

- Radiographic contrast media is the third most common cause of hospital acquired renal failure (after decreased renal perfusion and nephrotoxic medications), accounting for 11% of cases
- In-hospital mortality rate of CIN as high as 14%<sup>1</sup>
- In patients with multiple risk factors, incidence of CIN can rise to 50% or greater<sup>2</sup>
- Differential diagnosis: cholesterol embolism-can be difficult to distinguish, but typically occurs over 3-8 weeks, in elderly men, may have cutaneous signs

1 Nash et al. Am J Kidney Dis 2002

2 McCullough PA et al. Am J Cardiol 2006

## Contrast-induced Nephropathy In-hospital Mortality

% In-hospital death



Profound increase in in-hospital mortality in patients developing acute renal failure (ARF), particularly in diabetic patients

# MORTALITY RISK

- Levy et al., 1996, retrospective study of >16,000 patients with 2% CIN incidence, but 34% vs. 7% risk of death for CIN
- After adjustment the odds of dying was 5.5 for patient with CIN
- Rihal et al., 2002, retrospective study of 7,586 patients noted a CIN incidence of 3.3% and a 22% vs. 1.4% in-hospital mortality for patients with CIN
- McCullough et al., 1997 reported a mortality rate of 7.1% for CIN, 35.7% if patient required HD, vs. 1.1% for no CIN. 2 year mortality was 81.2% for HD patients
- Significant association was found between >25% Cr increase and one year mortality (Gruberg et al, 2000)

## Factors involved in CIN pathogenesis

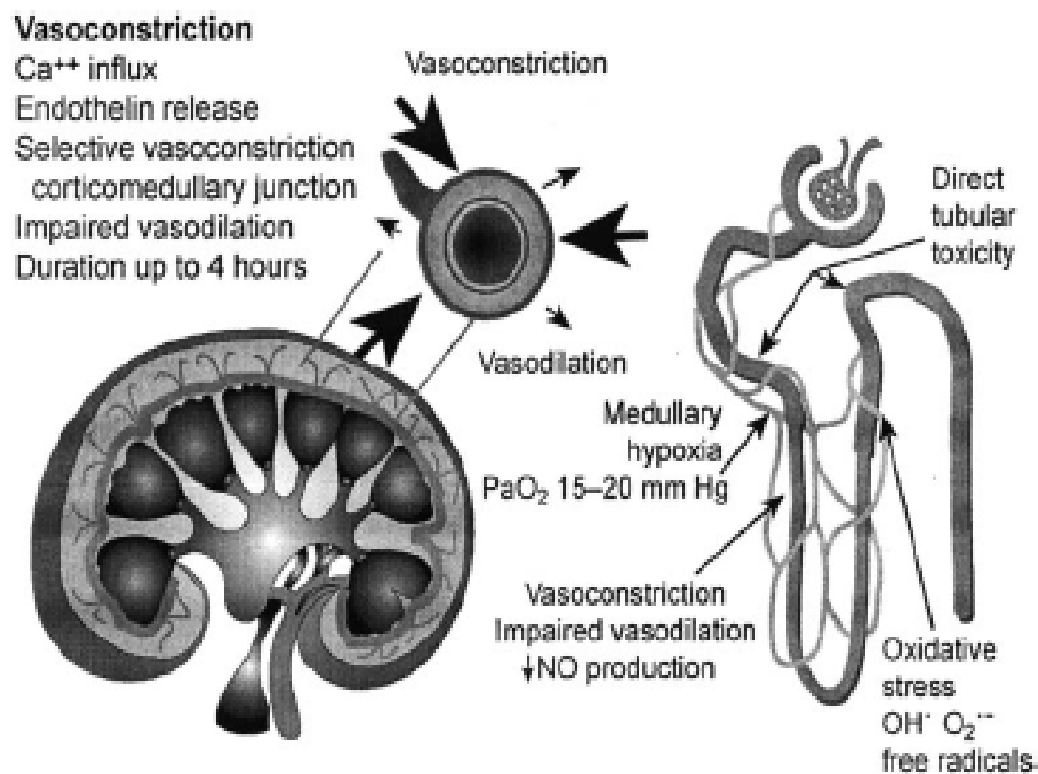
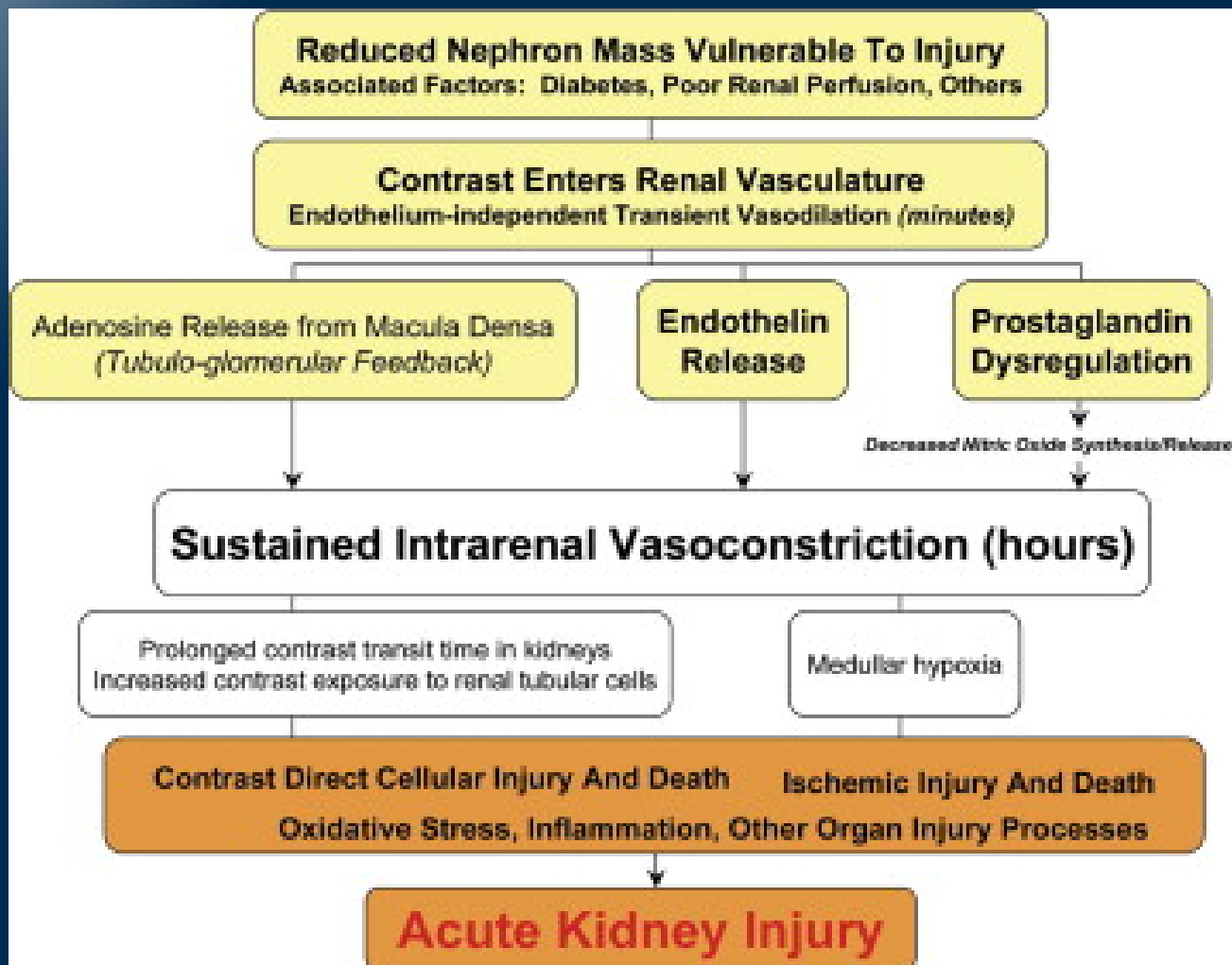


Figure 1. Overview of the factors involved in the pathogenesis of contrast-induced nephropathy. NO = nitric oxide; OH<sup>•</sup> = hydroxyl radical; O<sub>2</sub><sup>•-</sup> = superoxide radical; PaO<sub>2</sub> = arterial oxygen pressure.

## Postulated Pathophysiology of CIN



In the presence of a reduced nephron mass, the remaining nephrons are vulnerable to injury. Iodinated contrast, after causing a brief (minutes) period of vasodilation, causes sustained (hours to days) intrarenal vasoconstriction and ischemic injury. The ischemic injury sets off a cascade of events largely driven by oxidative injury causing death of renal tubular cells. If a sufficient mass of nephron units are affected, then a recognizable rise in serum creatinine will occur

# RISK FACTORS

Table 1

Risk factors identified in multivariate analyses

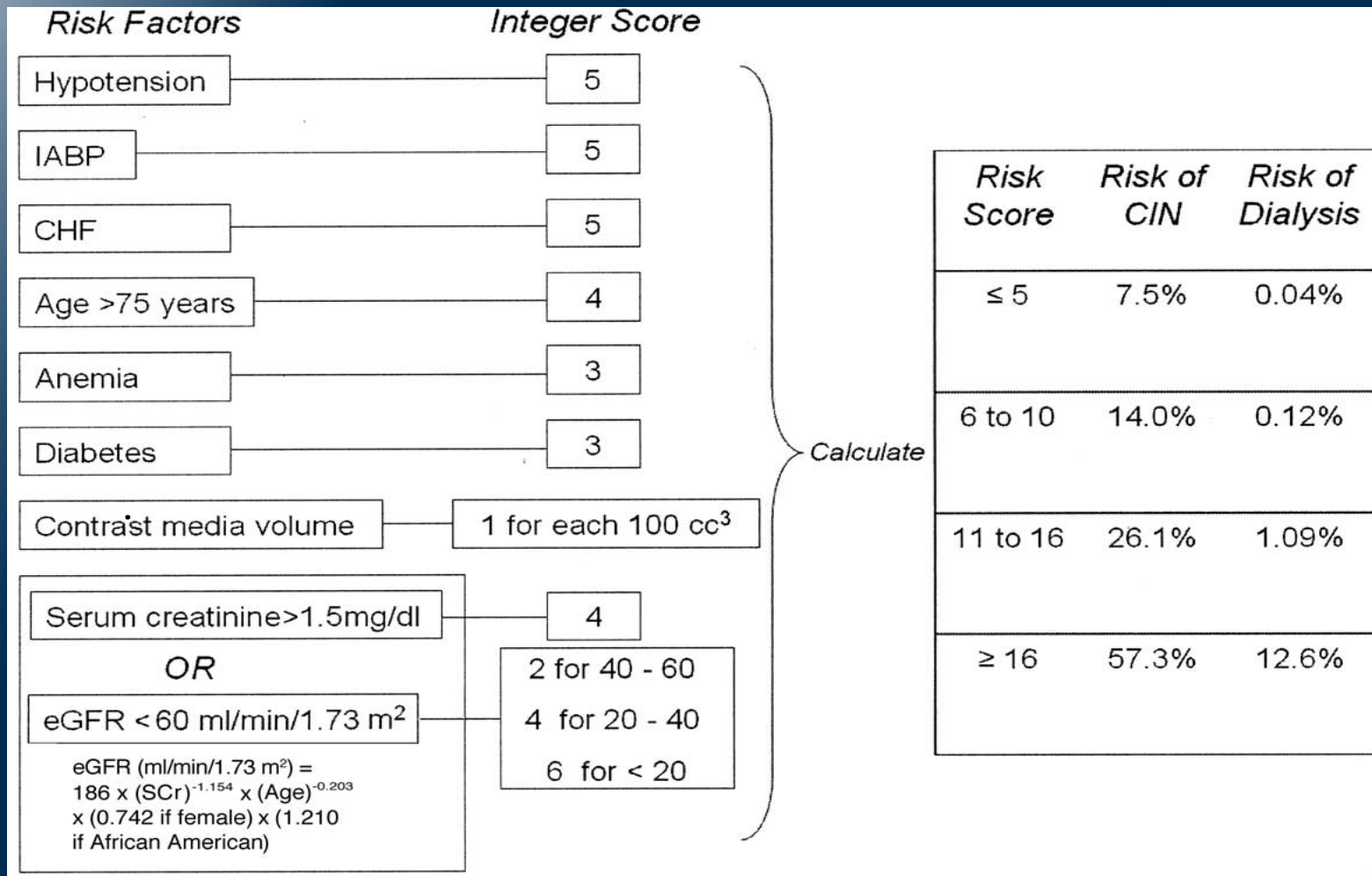
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- Chronic kidney disease (stage III or greater; eGFR <60 mL/min/1.73 m<sup>2</sup>)
  - Diabetes mellitus (type 1 or type 2)
  - Volume depletion
  - Nephrotoxic drug use (NSAIDs, cyclosporine, aminoglycosides)
  - Preprocedural hemodynamic instability
  - Other comorbidities
    - Anemia
    - Congestive heart failure
    - Hypoalbuminemia
- 

eGFR = estimated glomerular filtration rate; NSAIDs = nonsteroidal anti-inflammatory drugs.

# OTHER RISK FACTORS

- Increasing age
- Gender data inconsistent
- Earlier studies reported higher incidence in nonwhites (Lindsay, 2003) and African Americans (Dangas, 2005) but these findings have not been replicated
- Intraarterial administration and osmolality and volume of contrast
- The effect of risk factors is additive. If a patient has 4 or 5 risk factors, risk of CIN is 50%

# CIN MEHRAN RISK SCORE





# RISK REDUCTION STRATEGIES

- Contrast
- IVF
- NaHCO<sub>3</sub>
- N-Acetylcysteine
- Ascorbic acid
- Statin
- ACEi
- Theophyllin/aminophylline
- Diuresis
- Dopamine/Fenoldopam
- Prostaglandin/prostacyclin
- ANP
- Mechanical (HD, hemofiltration, RenalGuard)

# RISK REDUCTION STRATEGIES

Intervention	Trial Design	Result
Hydration	RCT	Reduced incidence of CIN
Furosemide	RCT	Increased incidence of CIN
Mannitol	RCT	Increased incidence of CIN
Atrial Natriuretic Peptide	RCT	No benefit
Endothelin Antagonist	RCT	No benefit
Dopamine	RCT	No benefit
Adenosine Antagonist	RCT	Potential benefit
Calcium Channel Blocker	Prospective	Not adequately studied
n-Acetylcysteine	RCT	Reduced incidence of CIN after low volume I.V. contrast
Low Osmolar Contrast	RCT	Reduced incidence of CIN vs. high osmolar contrast
Pre-emptive Dialysis	Prospective	No benefit
Fenoldopam	RCT	<i>Ongoing Studies; Results Pending</i>
Ioxaglate vs. Iodixanol	RCT	<i>Ongoing Studies; Results Pending</i>

**RCT = Randomized Clinical Trial**

# RISK REDUCTION STRATEGIES

**HYDRATION-Goal: Produce both volume expansion and a large volume of dilute urine**



- Various protocols in the literature
- Should be suited to the clinical situation

# RISK REDUCTION STRATEGIES

2014 ESC/EACTS Guidelines on myocardial revascularization

## Recommendations for prevention of contrast-induced nephropathy

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
<b>Patients undergoing coronary angiography or MDCT</b>		
Patients should be assessed for risk of contrast-induced AKI.	IIa	C
<b>Patients with moderate-to-severe CKD</b>		
Hydration with isotonic saline is recommended. <sup>d</sup>	I	A
Use of low-osmolar or iso-osmolar contrast media is recommended.	I	A
Short-term, high-dose statin therapy should be considered.	IIa	A
Iso-osmolar contrast media should be considered over low-osmolar contrast media	IIa	A
Volume of contrast media should be minimized	IIa	B
Furosemide with matched hydration may be considered over standard hydration in patients at very high risk for CIN or in cases where prophylactic hydration before the procedure cannot be accomplished.	IIb	A
N-Acetylcysteine administration instead of standard hydration is not indicated.	III	A
Infusion of sodium bicarbonate 0.84% instead of standard hydration is not indicated.	III	A
<b>Severe CKD</b>		
Prophylactic haemofiltration 6 hours before complex PCI may be considered.	IIb	B
Prophylactic renal replacement therapy is not recommended as a preventive measure.	III	B

PROFILASSI



Danno renale acuto

da mezzo di contrasto (CI-AKI)  
(incremento creatininemia di +0,3 mg/dl entro 48 ore oppure +50% entro 7 giorni)

KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int (2012)



CONSEGUENZE

Aumento COMPLICANZE (vascolari al sito d'accesso, IMA periprocedurale, shock cardiogeno, arresto card.)

Aumento MORTALITA'

Aumento EVENTI AVVERSI CARDIOVASCOLARI

Gruberg, L. et al. JACC (2000), Rihal, C.S. et al. Circulation (2002)

## 2011 ACCF/AHA/SCAI Guidelines for Percutaneous Coronary Intervention

Recommendations	COR	LOE
Contrast-induced AKI		
Patients should be assessed for risk of contrast-induced AKI before PCI.	I	C
Patients undergoing cardiac catheterization with contrast media should receive adequate preparatory hydration	I	B
In patients with CKD (creatinine clearance <60 mL/min), the volume of contrast media should be minimized.	I	B
Administration of N-acetyl-L-cysteine is not useful for the prevention of contrast-induced AKI.	III: No Benefit	A

# Limitations of CIN Studies

- Small numbers – not megatrials that cardiologists are used to
- Varying treatments used
  - Differing hydration regimens
- Varying definitions
  - Outcomes vary by definitions
- Serum Cr- not Creatinine Clearance

## Incidence & Prognostic Importance of Acute Renal Failure Following PCI

- Mayo Clinic Retrospective Analysis
- Circulation. 105,2259-2264,2002
- N=7586
- ARF defined as increase in Cr  $>0.5$  mg/dl
- Incidence 3.3%
- Incidence related to baseline serum Cr & presence of diabetes

## Long Term Prognostic Implications of ARF after PCI (Hospital Survivors)

- 6890 non ARF patients: mortality at 6 months, 1 year and 5 years 2.3%, 3.7%, 14.5%.
- 185 ARF patients: 9.8%, 12.1%, 44.6% ( $p < 0.0001$ )
- Non ARF patients – risk of MI: 2.7%, 3.8%, 10.5%

Gennaio - Settembre 2007

1000 pazienti consecutivi arruolati nello studio

## Criteria di INCLUSIONE

- indicazione a coronarografia o PCI

## Criteria di ESCLUSIONE

- shock cardiogeno
- emodialisi

## End-point PRIMARIO

**Eventi avversi maggiori cardiovascolari e cerebrovascolari (MACCE) a 1 e 7 anni**  
*(sindrome coronarica acuta, edema polmonare acuto, shock cardiogeno, attacco ischemico transitorio, stroke, morte cardiovascolare o cerebrovascolare)*

## End-point SECONDARI

- **CIAKI post-procedura** (+0.3 mg/dl in 48h o +50% in 7 giorni)
- **Riospedalizzazioni in dipartimenti di cardiologia o nefrologia a 1 e 7 anni**



## PROTOCOLLO AZIENDALE DI NEFROPROTEZIONE

**IDRATAZIONE con NaCl 0.9% e.v. 12 ore prima della procedura**  
*500-1000 mL (tasso di infusione in base alla FE%)*

**BICARBONATO DI SODIO 1.4% e.v.**  
*3 mL/kg/h per 1 ora prima della procedura*  
*1 mL/kg/h per 6 ore dopo la procedura*

**N-ACETIL-CISTEINA per os**  
*1200 mg il giorno prima della procedura*  
*1200 mg il giorno successivo*

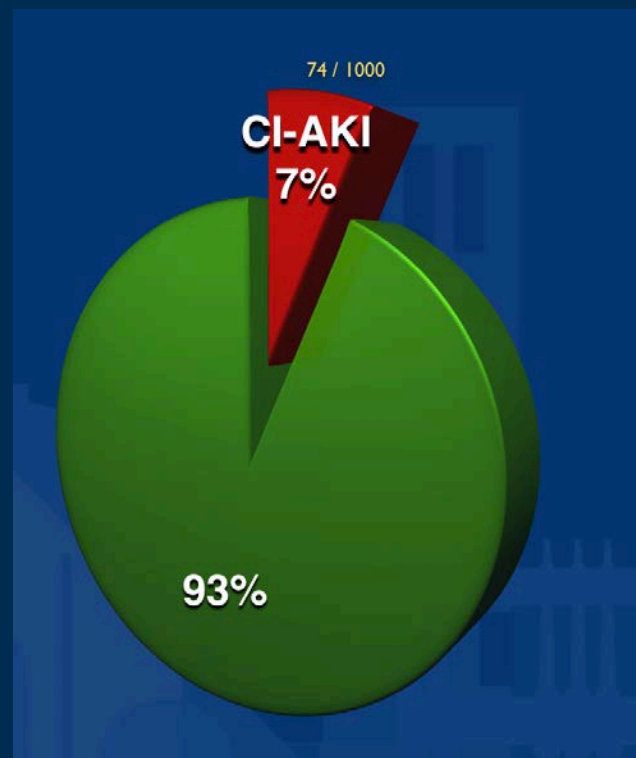
**ACIDO ASCORBICO per os**  
*3 gr prima della procedura, 2 gr dopo la procedura*  
*2 gr il giorno successivo*

# BASELINE

# CIAKI

Caratteristiche basali e procedurali	Popolazione (n = 1000)
Età	66 ± 11
Sesso femminile	280 (18%)
FE (%)	52 ± 13
Ipertesi	755 (75%)
Diabetici	200 (20%)
Dislipidemici	555 (55%)
CAD nota	474 (47%)
Precedente IMA	266 (27%)
Smokers	164 (16%)
Trapianto di rene	4 (3%)
Creatininemia (mg/dl)	1.1 ± 0.9
eGFR all'ingresso (ml/min)	77 ± 22
Mehran CIAKI risk score	9.6 ± 4.2
Volume di mezzo di contrasto (cc)	164 ± 83
PCI + stenting	571 (57%)
<b>Indicazione alla coronarografia</b>	
<i>NSTEMI o Angina Instabile</i>	506 (51%)
<i>Angina da sforzo</i>	126 (13%)
<i>STEMI</i>	164 (16%)
<i>Ischemia Strumentale</i>	172 (17%)
<i>Decompensated Heart Failure</i>	32 (3%)

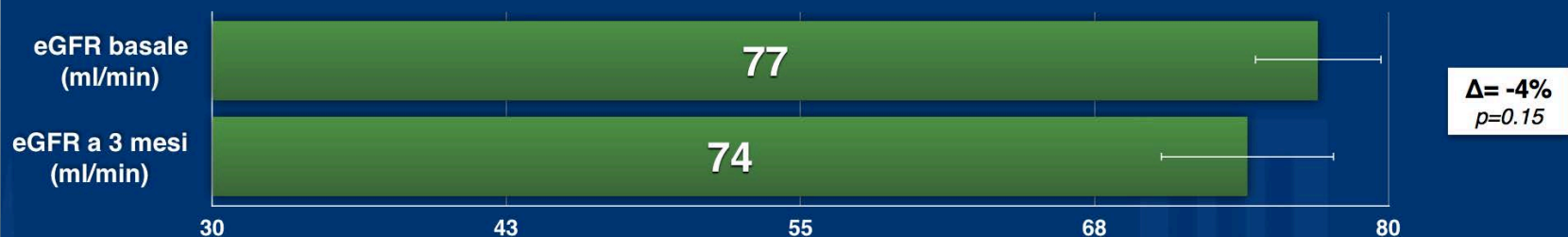
Incidenza di CI-AKI dopo coronarografia/PCI



# RESULTS

## Funzionalità renale a 3 mesi

### pazienti senza CIAKI



### pazienti con CIAKI

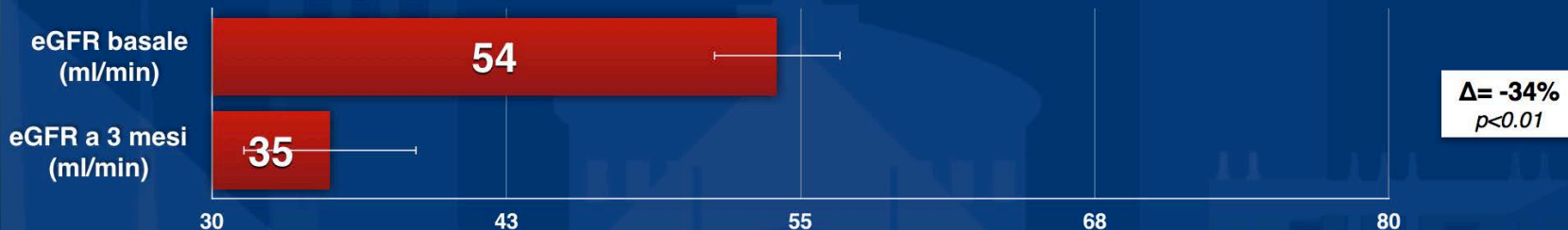
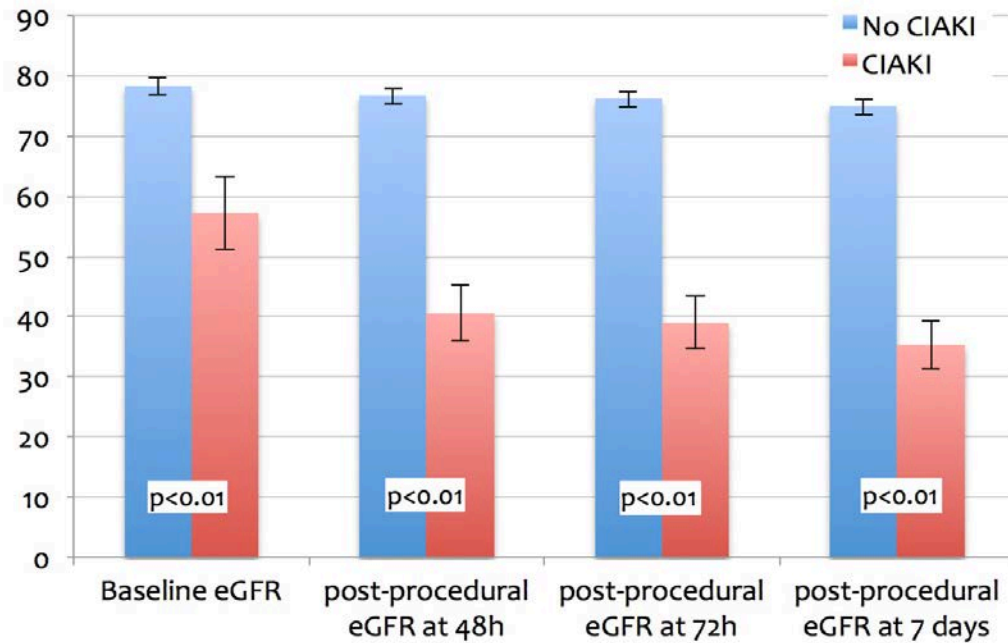


FIGURE 1 – eGFR variation after CA/PCI



eGFR < 60    212/1000    CIAKI 44/212 (21%)  
eGFR > 60    788/1000    CIAKI 30/788 (4%)

# RESULTS

## CKD Class

### CKD Class

	Patients	CKD Class
<i>CKD class G1 (eGFR ≥90 cc/min)</i>	315 (31%)	4%
<i>CKD class G2 (eGFR 60-89 cc/min)</i>	473 (47%)	4%
<i>CKD class G3a (eGFR 45-59 cc/min)</i>	123 (12%)	12%
<i>CKD class 3b (eGFR 30-44 cc/min)</i>	61 (5%)	33%
<i>CKD class G4-G5 (eGFR &lt;29 cc/min)</i>	28 (3%)	32%

## Mehran Class

### Mehran Class

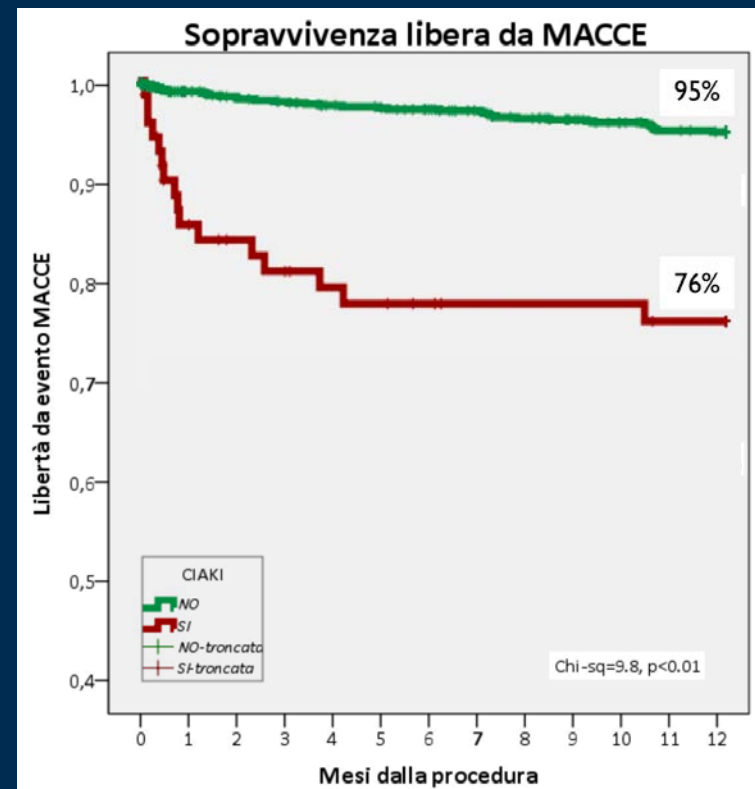
	Patients	CKD Class	Mehran Class
CLASS I	707	8%	4%
CLASS II	247	14%	13%
CLASS III	43	26%	28%
CLASS IV	3	57%	100%
Overall	1000	10%	7%

# RESULTS

## MACCE a 12 mesi

Tipo di evento	popolazione (n=1000)	no CIAKI (n=926)	CIAKI (n=74)
Sindrome coronarica acuta	5%	4%	6%
Necessità di PCI / CABG	2%	2%	4%
Shock cardiogeno / EPA	5%	3%	4%
TIA o stroke	2%	2%	0
Morte cardiovascolare	2%	1%	10%
Morte cerebrovascolare	0	0	0
<b>Totale eventi</b>	<b>16%</b>	<b>12%</b>	<b>24%</b>

Regressione di Cox sulle covariate	Odds Ratio	IC 95%	p-value
CIAKI	<b>3,15</b>	[1.2-7.9]	<b>0.02</b>
Pregresso IMA	<b>3,09</b>	[1.2-7.8]	<b>0.02</b>
FE < 40%	2,15	[0.8-5.6]	0.12
Età avanzata > 75	1,60	[0.6-4]	0.32
Diabete	0,96	[0.4-2.5]	0.93

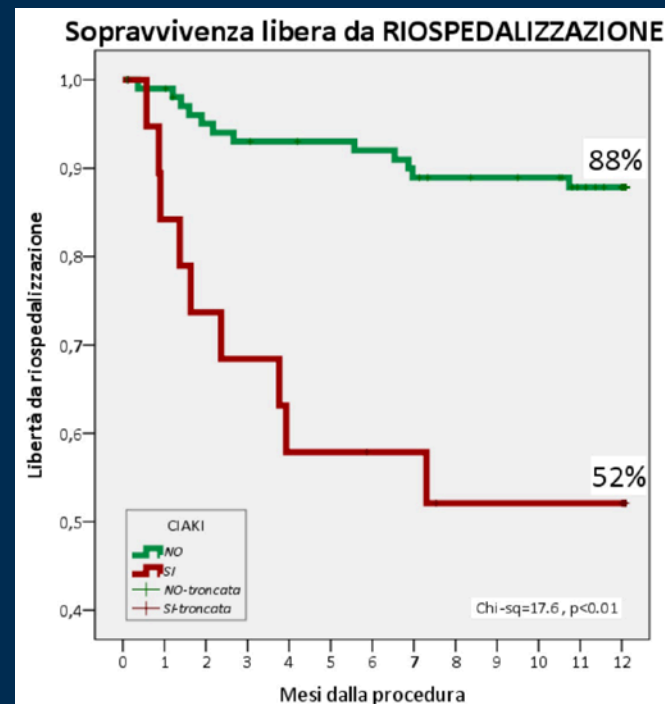


# RESULTS

## Riospedalizzazioni a 12 mesi

Reparto di ricovero	popolazione (n=1000)	no CIAKI (n=926)	CIAKI (n=74)
Cardiologia	15%	12%	35%
Nefrologia	2%	0	10%
<b>Totale eventi</b>	<b>17%</b>	<b>12%</b>	<b>45%</b>

Regressione di Cox sulle covariate	Odds Ratio	IC 95%	p-value
CIAKI	<b>4,33</b>	[1.8-10.6]	<b>&lt;0.01</b>
FE < 40%	2,06	[0.8-5.3]	0.13
Pregresso IMA	1,97	[0.8-4.8]	0.14
Età avanzata > 75	0,89	[0.4-2.1]	0.79
Diabete	0,78	[0.3-2]	0.61



# RESULTS

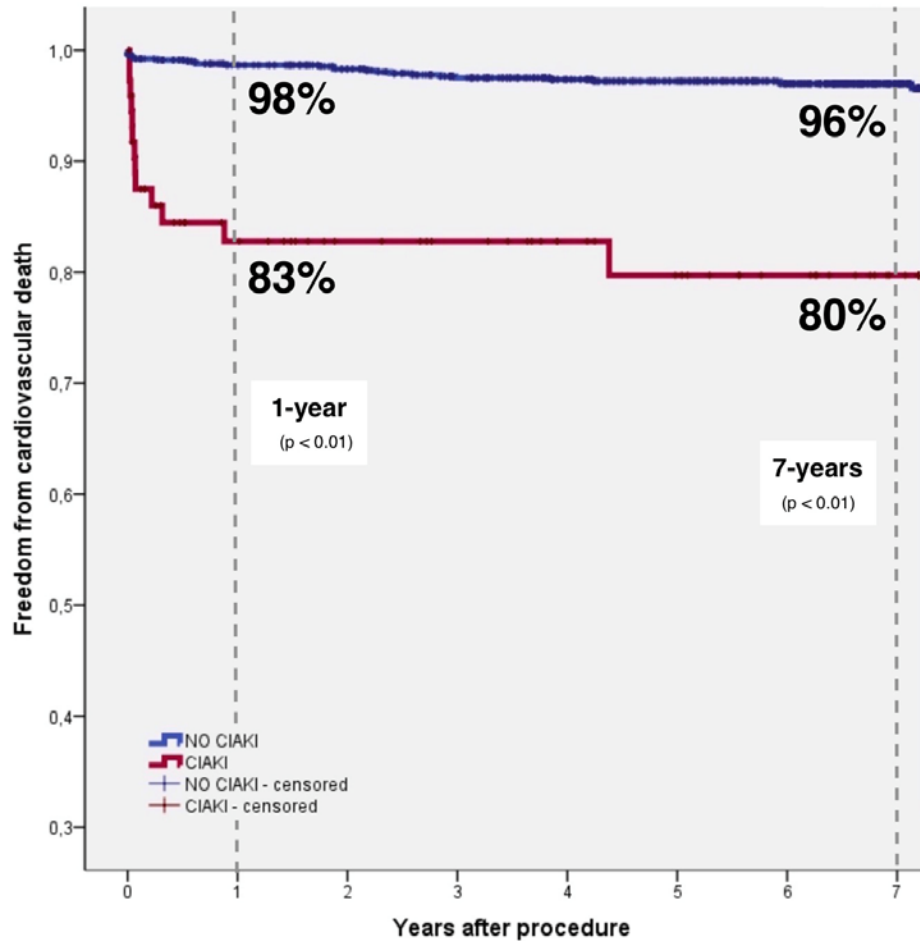
MACCE a 7 anni

	Population (1000 pts)	CIAKI (74 pts)	No-CIAKI (926 pts)	p
ACS	65 (6%)	6 (8%)	59 (6%)	0,69
Cardiogenic Shock or APE	15 (1%)	4 (5%)	11 (1%)	0,04
TIA or Stroke	19 (2%)	2 (3%)	17 (2%)	0,83
Cardiovascular Death	39 (4%)	13 (18%)	26 (3%)	<0,01
Cerebrovascular Death	5 (0,5%)	2 (3%)	3 (0,3%)	0,09
Overall	143 (14%)	27 (36%)	116 (12%)	<0,01

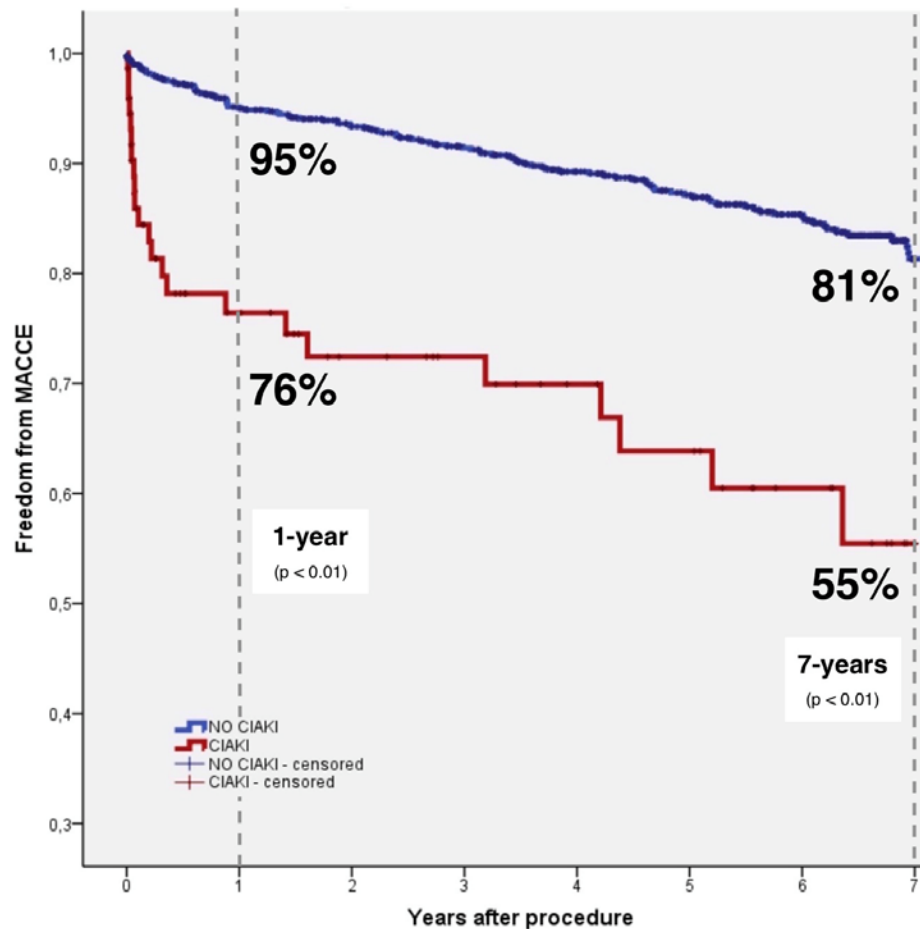


# RESULTS

## A 7-year freedom from cardiovascular death



## B 7-year freedom from MACCE

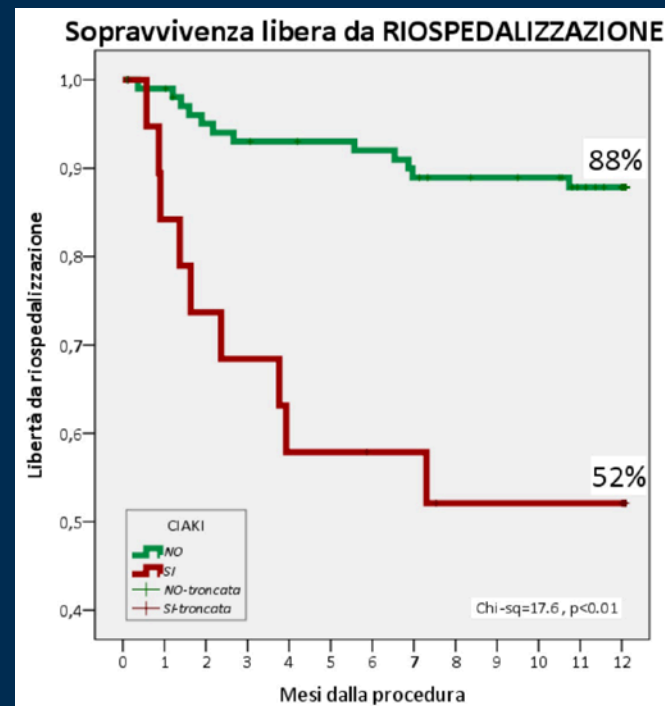


# RESULTS

## Riospedalizzazioni a 7 anni

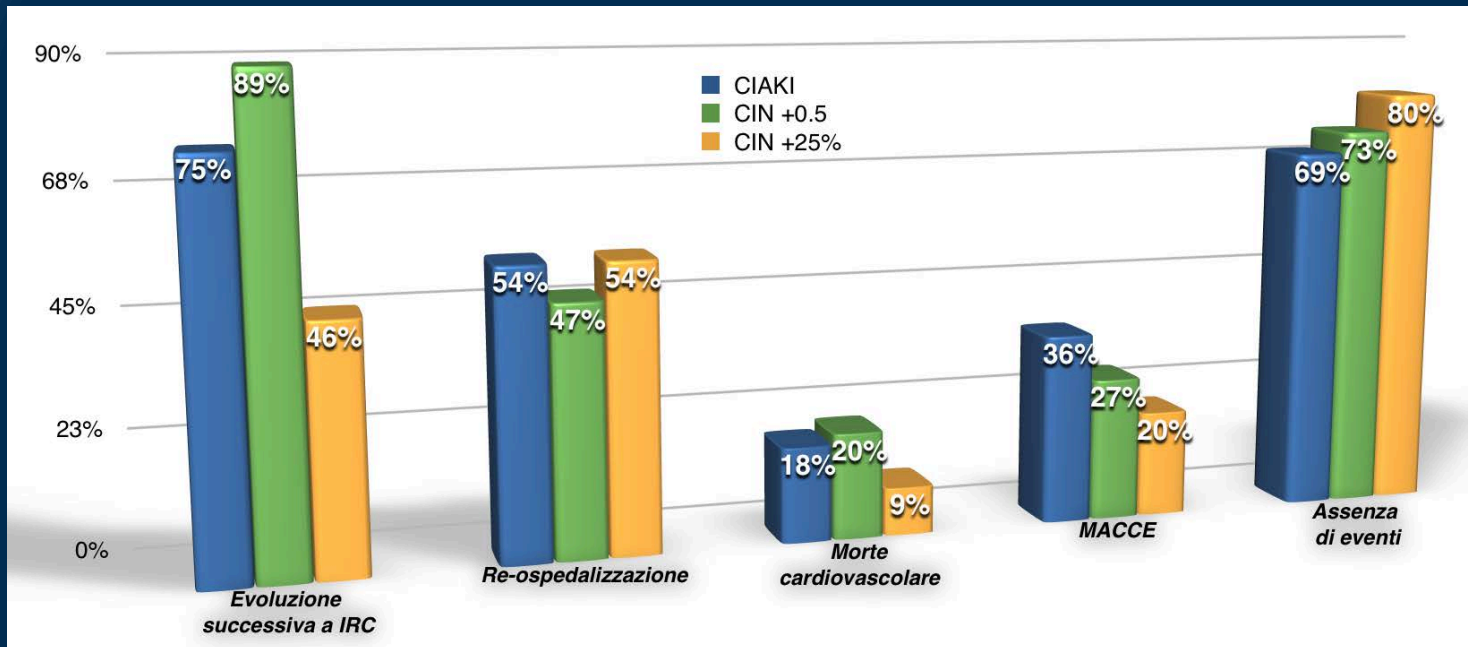
Reparto di ricovero	popolazione (n=1000)	no CIAKI (n=926)	CIAKI (n=74)
Cardiologia	38%	33%	45%
Nefrologia	2%	1%	13%
<b>Totale eventi</b>	<b>35%</b>	<b>33%</b>	<b>54%</b>

Regressione di Cox sulle covariate	Odds Ratio	IC 95%	p-value
CIAKI	<b>4,33</b>	[1.8-10.6]	<b>&lt;0.01</b>
FE < 40%	2,06	[0.8-5.3]	0.13
Pregresso IMA	1,97	[0.8-4.8]	0.14
Età avanzata > 75	0,89	[0.4-2.1]	0.79
Diabete	0,78	[0.3-2]	0.61



# Follow up a 7 anni

Definizione di CI-AKI	CI-AKI (inc. 7.4%)	CIN +0.5 (inc. 3%)	CIN 25% (inc. 10%)
Evoluzione successiva a IRC	75%	89%	46%
Re-ospedalizzazione	40%	47%	54%
Morte cardiovascolare	18%	15%	9%
MACCE	40%	27%	20%
Assenza di eventi	69%	73%	80%



# CONCLUSIONS

- Se sottoposti a coronarografia o PCI, i pazienti con IRC hanno un rischio più elevato rispetto alla popolazione generale di sviluppare CIAKI.
- Lo sviluppo di CIAKI era un fattore prognostico indipendentemente associato con un maggior tasso di MACCE (OR=3.15) e di riospedalizzazioni (OR=4.33) durante 12 mesi di follow-up.
- I pazienti con CIAKI mostravano una più rapida evoluzione dell'insufficienza renale nei 3 mesi successivi alla dimissione.
- Un singolo episodio di CIAKI può aumentare il rischio di eventi avversi al follow-up accelerando la progressione dell'IRC, che amplifica il danno vascolare, endoteliale e aterosclerotico.
- Una attenta profilassi di CIAKI in pazienti a rischio è di primaria importanza.

*Grazie per l'attenzione*