A Randomized Controlled Trial of Prevention of Contrast Induced Nephropathy with Single Bolus Erythropoietin in Diabetic Patients with eGFR<60 ml/min/1.73m^2 Undergoing Coronary Angiography or PCI

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בית החולים לגליל המערבי

Disclosures

We have no conflicts of interest

Acute Renal Failure Post Cath/PCI

- Renal atheroemboli
- Hemodynamic instability with decreased renal perfusion
- Contrast induced nephropathy

Contrast Induced Nephropathy (CIN)

- **Definition:** "new-onset or an exacerbation of renal dysfunction after contrast administration in the absence of other causes"

- **Cr Increase of >25% or absolute increase of >0.5mg/dl**

CIN Timeline

- Creatinine increase is seen 24-72 hours after exposure
- Peaks at 5-7 days
- Normalizes usually within 7-10 days

CIN Incidence

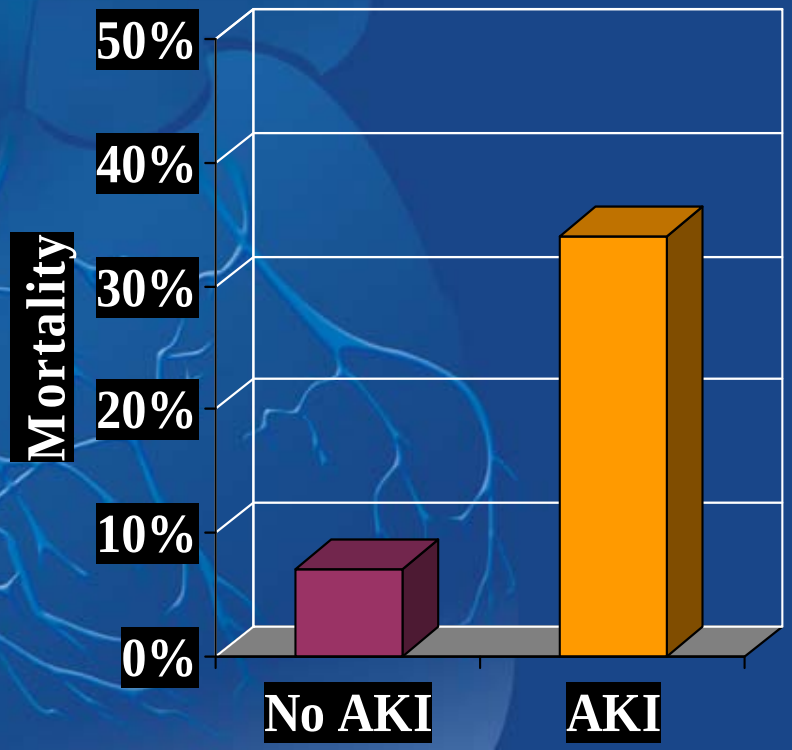
- 3rd most common hospital acquired renal failure
- >5% of patients with cath experience transient increase Cr > 1.0 from baseline

Implications of CIN

- Delay in discharge of patient
- Permanent kidney damage
- Dialysis
- Increased patient mortality. Case control study 1600 pts, mortality rate with CIN 5.5 times of matched controls
- Increase in cost of $10,345 for hospital stay

Dangas G et al. *Am J Cardiol*. 2005;95:13-19.

CIN and mortality

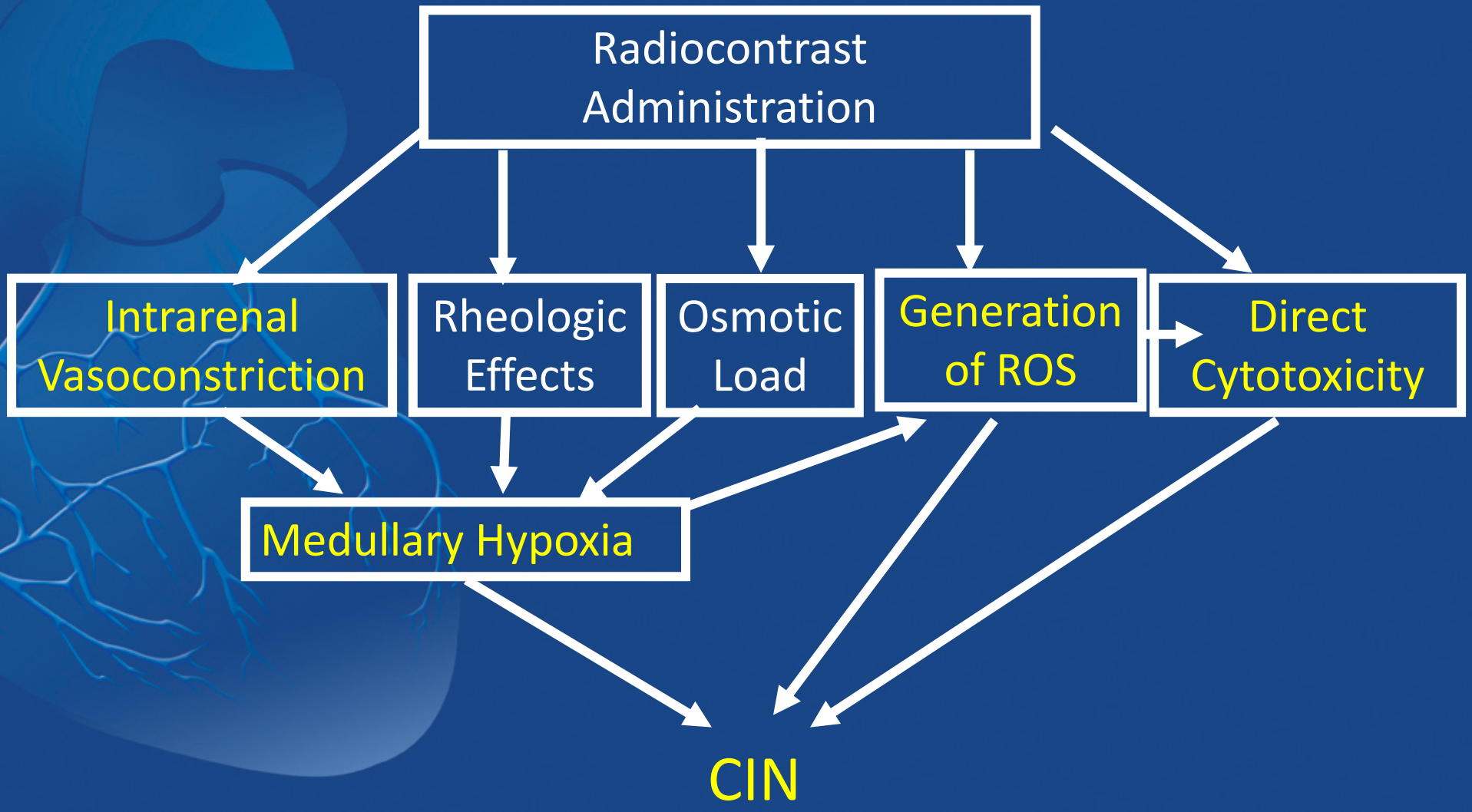


Adjusted OR: 5.5; p<0.01

	Mortality	
Apache II	No AKI	AKI
0-3	4% →	17%
4-7	5% →	40%
8-11	28% →	52%
>12	33% →	62%

Levy et al. *JAMA* 1996; 275:1489-1494

Pathophysiology of CIN



CIN and Coronary Procedures

- Higher mortality than other types of CIN
- 3% primary PCI for ACS (Marenzi et al 2004)
- 1800 pts with coronary interventions

  - ARF 14%, dialysis 0.8%
  - In house mortality for those with HD 36% (1% for those without HD)
  - 2 yr survival 19% in those needing HD

Risk factors for CIN

Patient-related

- **Renal insufficiency**
- **Diabetes mellitus***

} **additive risk**

- Intravascular volume depletion
- Reduced cardiac output
- Concomitant nephrotoxins

Procedure-related

- ↑ volume of radiocontrast
- Multiple procedures w/i 72 hours
- Intra-arterial administration
- Type of radiocontrast

*** Diabetes alone not strong risk factor**

Renal Insufficiency and Diabetes Mellitus

Creatinine Clearance (mL/min)	CIN Requiring Dialysis	
	Non-Diabetic	Diabetic
50	0.04%	0.2%
40	0.3%	2%
30	2%	10%
20	12%	43%
10	48%	84%

McCullough PA et al. *Am J Med*. 1997;103:368-375.

Preventive strategies for CIN

Ineffective	Unclear benefit	Effective
CCB Loop diuretics* Mannitol* Dopamine* Fenoldopam* ANP Hemodialysis*	NAC Theophylline Aminophylline Ascorbic acid Statins Hemofiltration	• IVF • Choice of contrast

* Possibly harmful

Erythropoietin

- Erythropoietin (EPO), a cytokine that was originally identified as a hematopoietic factor, has been widely used for the treatment of anemia in patients with CKD.

- More recently, EPO was found to induce a range of cytoprotective cellular responses (mitogenesis, angiogenesis, promotion of vascular repair, and inhibition of apoptosis), which are independent of EPO's effects on erythropoiesis.[1]

- EPO was reported to attenuate renal injury in acute renal failure models in experimental animals with ischemia-reperfusion and radiocontrast medium injuries.

- In human studies, EPO administered after reperfusion – failed to reduce infarct size.

Study Background

- we have previously reported that in several high risk patient subgroups, such as patients with renal insufficiency and diabetes mellitus, the prevalence of CIN is significantly higher (14.1%-44%), and is associated with poor outcome including increased hospital length of stay and higher in-hospital mortality rates.

Shema L, et al. *IMAJ* 2009; 8: 460-464.

Study hypothesis

- We hypothesized that EPO can prevent contrast-induced nephropathy in diabetic patients with eGFR<60 ml/min/1.73m^2 undergoing coronary angiography or PCI (elective, urgent or emergent).

- We hypothesized that the administration of a single bolus of EPO prior to reperfusion in PPCI may reduced infarct size.

Study Methods

- A prospective, randomized, double blind, placebo controlled trial.
- Diabetic patients with eGFR<60 ml/min/1.73m^2 in 2 consecutive measurements, schedule for coronary angiography (CA) ± PCI.
- Pts randomly received either a single dose of 50,000U of EPO (Recormon, Roche, Epoietin beta) or saline intravenously before given 30 minutes before CA.
- CIN was defined as an increase in SCr level, compared to basal value, of at least 0.5 mg/dl during 1–3 days after exposure to contrast media.

Study Methods

- Patients with STEMI undergoing PPCI – were randomized regardless of their kidney function.
- Measurements of Troponin I and CK for infarct size assessment.
- TTE for LV function assessment at discharge and after 3 months.

Study Methods (2)

- Primary outcome was the incidence of CIN.
- Secondary outcomes was enzymatic infarct size as measured by TnI curve (in primary PCI patients), hospital length of stay, the need for renal replacement therapy and in-hospital mortality.

Exclusion criteria

- Non diabetic patients
- Chronic renal replacement therapy.
- Subject with active malignancy.
- Subject with any known history of seizure disorders.
- Subject with polycythemia defined as Hb >16.5 g/dl or Hct >48 in women and Hb >18.5 g/dl or Hct >52 in men.
- Uncontrolled hypertension defined as systolic blood pressure of >180 mm/Hg and/or diastolic > 110 mm/Hg in any recording in 24 hours prior to procedure.
- Use of long acting EPO (CERA) during 1 month prior to randomization.
- Use of NAC or bicarbonate during 3 days prior to randomization.
- Contrast media exposure during the last 7 days before randomization.
- Pregnant or lactating women.

Study Protocol

- standard hydration (1cc/kg/min saline 0.9% 12 h before and after the procedure or 0.5cc/kg/h for patients with CHF or 2cc/kg/min saline 0.9% for primary PCI patients prior to PCI, and then 1cc/kg/min saline 0.9% for 12 h after the PCI).

- N-Acetylcystein 600mg po BID x 4 doses (2 doses the day prior and 2 the day of)

Study protocol (2)

- Blood samples for SCr determination were taken twice before the procedure in order to identify patients with AKI in evolution. The last sample prior to PCI was referred as baseline Scr.
- Scr post PCI was taken at 24 and 48 h post procedure. Blood sample for cystatin C were taken once before the procedure and at 24h post procedure.
- Urine sample for Cr and NGAL were taken once before the procedure and at 8h post procedure.

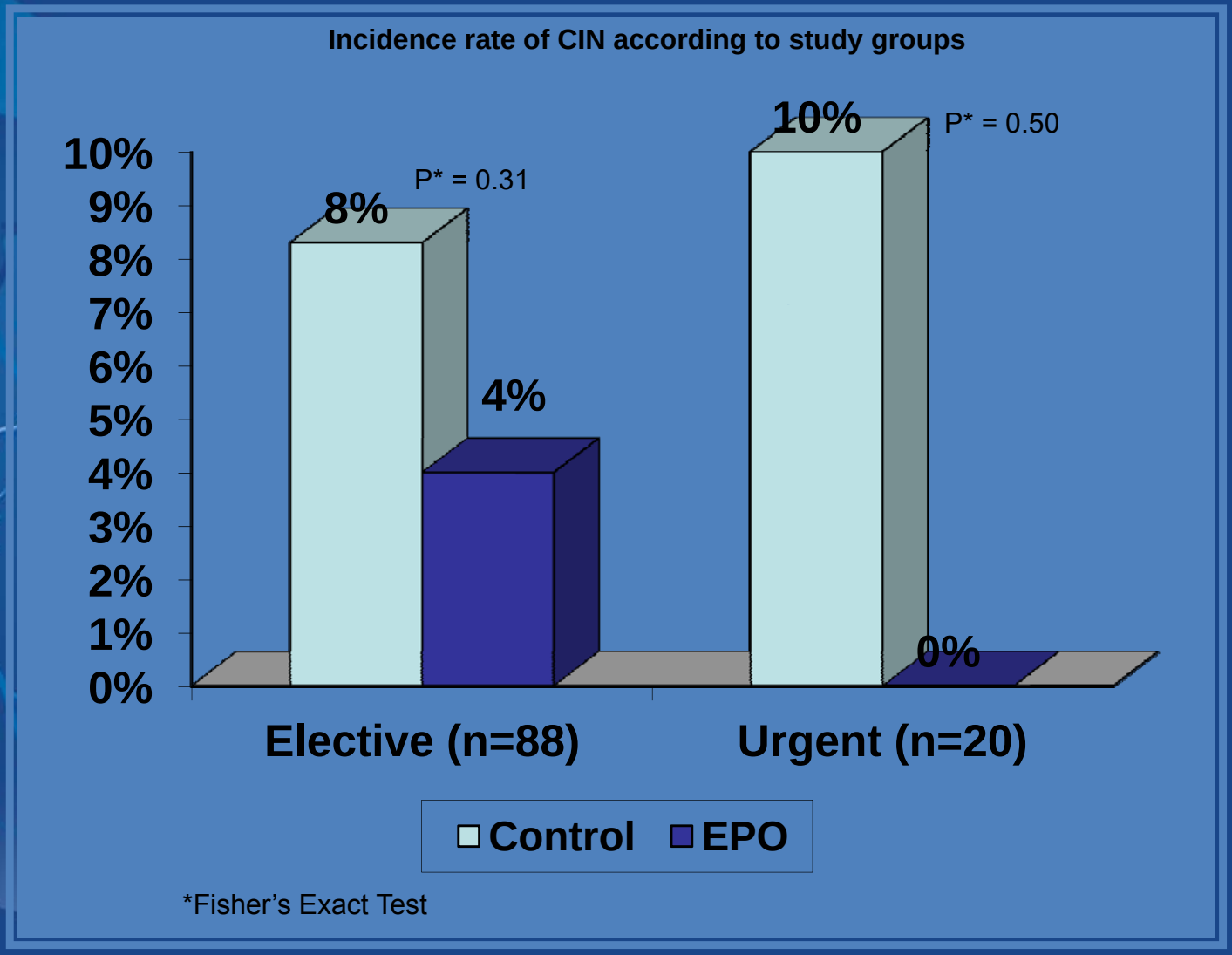
Results

- We studied 118 patients (58 control, 60 EPO).
- There were no differences with regard to the following parameters: age, gender, weight, BP, HR, creatnine, hemoglobin and hematocrit, albumin, procedure length and contrast-media volume.
- There were no safety issues in any of the patients.

Incidence of CIN by groups

CIN (0.5 mg/dl)			
Elective (n=98)		**PPCI (n=20)**	
Group	**CIN**	**Group**	**CIN**
Control (48)	4 (8.3%)	Control (10)	1 (10.0%)
EPO (50)	2 (4.0%)	EPO (10)	0
Total (n=98)	6 (6.0%)	Total (n=20)	1 (5.0%)

Incidence of CIN by groups



Incidence of CIN by contrast media volume

Mean	90.6729
Std. Deviation	53.97969
Minimum	26.00
Maximum	250.00

	N	Mean±SD	P.V*
No CIN	111	88.9±53.6	0.13
CIN	7	120.0±55.6	

	Elective (n=88)			PPCI (n=20)		
	N	Mean±SD	P.V*	N	Mean±SD	P.V*
No CIN	82	83.5±53.5	0.15	19	114.2±47.9	---
CIN	6	112.0±58.1		1	160.0	

The value of NGAL for detection of CIN

		N	Mean&SD	PV
No CIN	NGAL before	90	60.6±221.5	0.92
	NGAL after	90	59.5±157.7	
CIN	NGAL before	4	**55.0±23.3**	0.72
	NGAL after	4	**68.0±48.1**	

The value of Cystatin C for detection of CIN

		N	Mean&SD	PV*
CC before	No CIN	100	1.9±0.67	0.28
	CIN	6	2.2±0.58	
CC after	No CIN	99	**1.9±0.67**	0.01
	CIN	6	**2.6±0.61**	

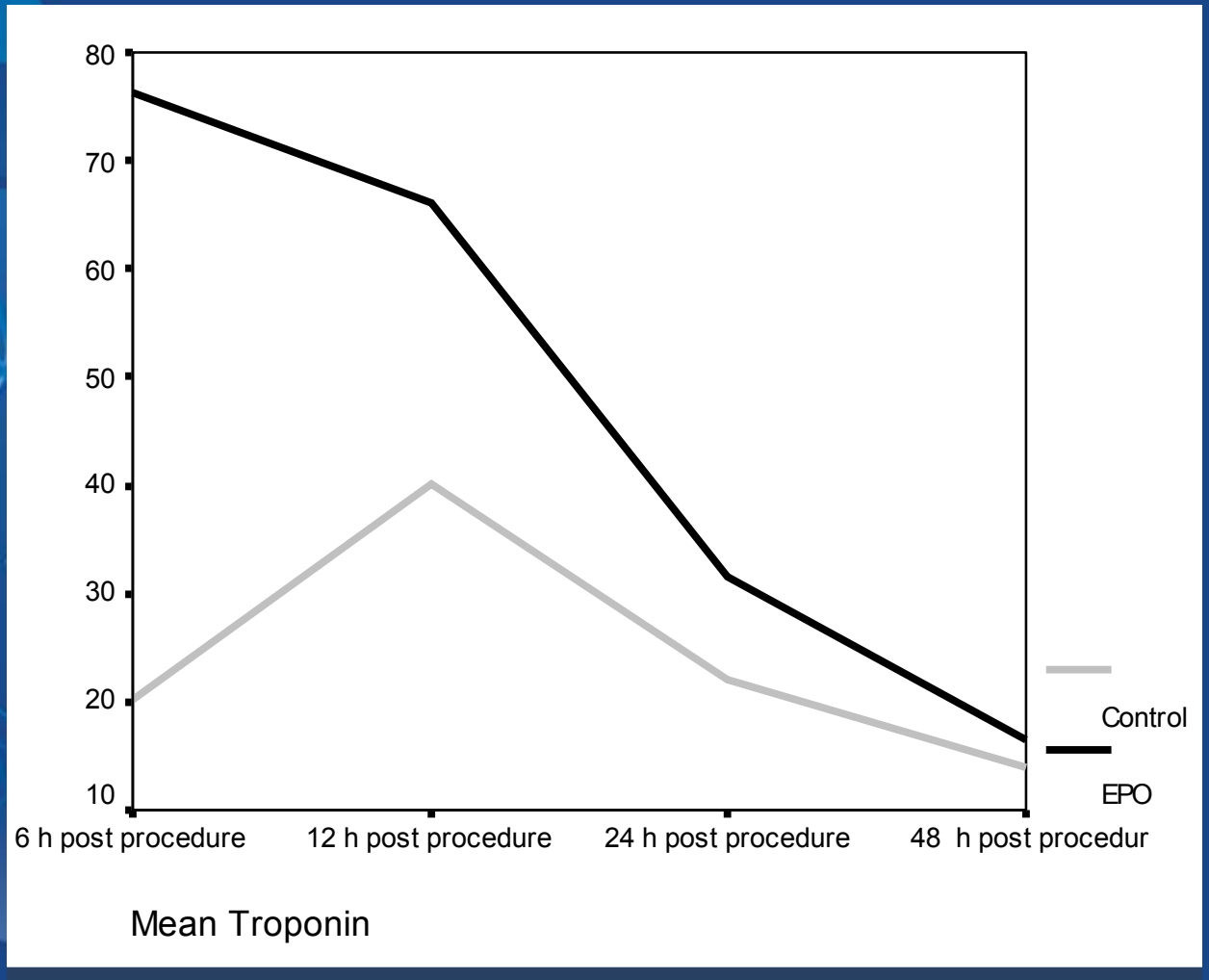
Cystatin C for detection of CIN

		N	Mean&SD	PV
No CIN	CC before	98	1.9±0.67	0.15
	CC after	98	1.9±0.67	
CIN	CC before	6	2.2±0.58	0.11
	CC after	6	2.6±0.61	

The effect of EPO on infarct size in STEMI with PPCI

Troponin	Control		EPO		P.V*
	N	Mean±SD	N	Mean±SD	
6h post procedure	7	20.25±30.0	10	76.32±81.7	0.42
12h post procedure	8	40.14±69.6	9	66.0±62.0	0.37
24h post procedure	9	22.11±40.6	8	31.59±34.0	0.67
48h post procedure	8	13.98±23.2	9	16.48±24.1	0.96

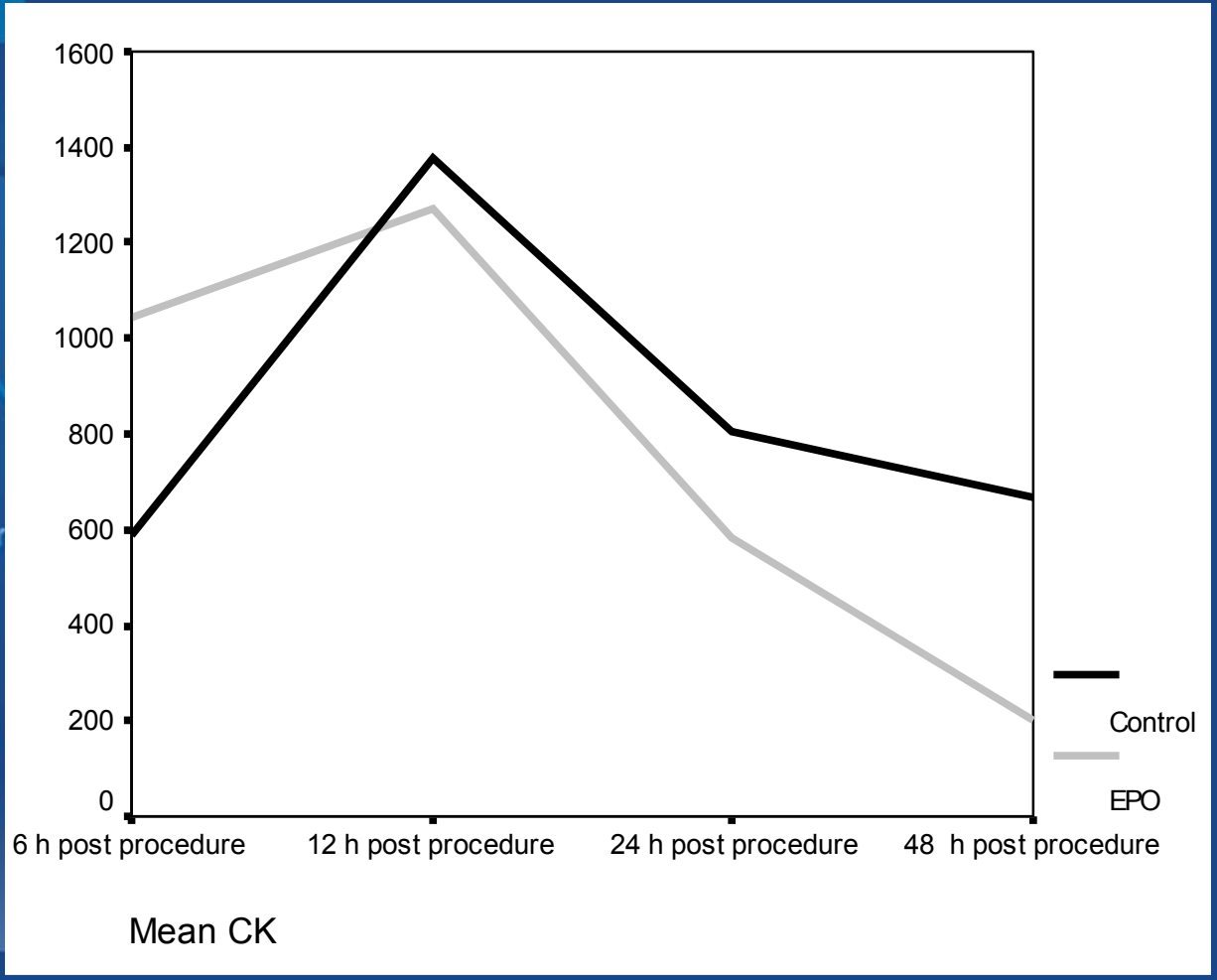
The effect of EPO on infarct size in STEMI with PPCI



The effect of EPO on infarct size in STEMI with PPCI

CK	Control		EPO		P.V*
	N	Mean±SD	N	Mean±SD	
6h post procedure	8	588.79±800.71	10	1043.10±980.5	0.52
12h post procedure	8	1378.25±2321.8	9	1273.88±904.7	0.48
24h post procedure	9	804.22±1190.7	9	583.77±467.7	0.93
48h post procedure	8	670.0±975.9	10	203.40±122.4	0.24

The effect of EPO on infarct size in STEMI with PPCI



Conclusions (1)

- The observed incidence of CIN in our study was much lower than the expected, and reduced the statistical power of the study.
- The administration of EPO prior to angiography resulted in a non-statistically significant reduction in CIN (as defined by commonly used criteria).
- There is a trend (p=0.11) that defines Cystatin C as an earlier marker for development of CIN.

Conclusions (2)

- There is a trend in reduction in CIN in patients undergoing PPCI.
- The administration of a single bolus of EPO prior to reperfusion may reduce infarct size as determined by biomarkers values.
- Further research and an increase in number of patients are needed to elucidate the effect of EPO on prevention of CIN and as an adjunct to reperfusion.