CYSTATIN C AS A RISK FACTOR OF THROMBOTIC AND BLEEDING EVENTS AFTER ELECTIVE PCI IN PATIENTS WITHOUT SEVERELY DECREASED KIDNEY FUNCTION: THE RESULTS OF 3 YEARS FOLLOW-UP

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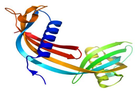


Cystatin C and cardiovascular risk

High serum level

1. Established marker of renal dysfunction
2. May be associated with:
   - inflammation (CRP, proinflammatory cytokins)
   - heart failure
   - vascular risk factors (obesity, ageing, hypertension, dyslipidemia, metabolic syndrome)

Low tissue expression/serum level ?

- Low inhibition activity of tissue cysteine proteases
- Increased vascular wall remodelling

❑ **The role of cystatin C as an early marker of adverse prognosis in pts with preserved kidney function (as assessed by creatinine) has not been clearly determined**

1

Aim of the study: to investigate the role of cystatin C as a predictor of adverse prognosis after elective percutaneous coronary intervention in patients without severely decreased kidney function

STUDY DESIGN

Study population
- Pts with stable CAD and recent elective PCI (< 7 days)
- Preserved kidney function (GFR_{MDRD} > 30ml/min/1.73m^2)
- Severe heart failure (NYHA functional class III-IV and/or LVEF < 30%) excluded
- Optimal medical treatment: DAPT within 6-12 months, ASA and Statins indefinitely, β-blockers and ACE inhibitors / AR blockers (if needed)

Methods
- Blood samples were taken 3-7 days after PCI and stored at -70^0 C until analyzed
- Serum cystatin C was measured by ELISA method
- Kidney function was calculated by MDRD (GFR_{MDRD}) and creatinine and cystatin - based ($GFR_{Cre-Cys}$) formulas

End points (follow-up 3-7 years)
- **Thrombotic events**: ACS (STEMI, NSTEMI, UA), ischemic stroke/TIA
- **Any bleeding events**: TIMI major and minor

2

Study population (risk factors profile)

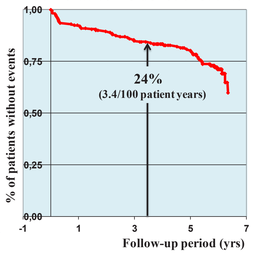
Gender (male/female), n	254 (205/49)
Age, yrs (M ±SD) *	**58.3 ± 9.7**
Heart failure, n (%) *	**12 (4.7%)**
Diabetes mellitus, n (%) *	**47 (18.5%)**
Arterial hypertension, n (%) *	**219 (86.2%)**
History of myocardial infarction, n (%) *	**132 (52.0%)**
History of unstable angina, n (%) *	**56 (22.0%)**
Peripheral vascular disease, n (%)	17 (6.7%)
History of stroke, n (%)	10 (3.9%)
Total cholesterol, mmol/L (M±SD)	4.8 ± 1.2
Smoking history (%):	
- past, n (%)	99 (39.9%)
- current, n (%)	57 (22.4%)

*** -** Clinical factors with potential impact on kidney function

3

Thrombotic and bleeding events after elective PCI
(mean follow-up period – 3.2 years)

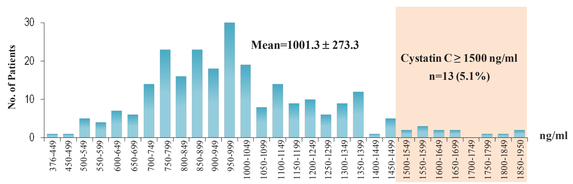
End point	Number of events
Thrombotic events	
• ACS (STEMI, NSTEMI, UA), n	33
• Ischemic stroke, n	4
• Transient ischemic attack, n	6
Subtotal, n	**43 (16.9%)**
Bleeding events	
• Major, n	2
• Minor, n	23
Subtotal, n	**25 (9.8%)**
Thrombotic and bleeding events (total)	**62 (24%)**



❑ **The composite end point of thrombotic and bleeding events occurred in 24% of pts during a mean follow-up of 3.2 years**

4

Cystatin C and prognosis after elective PCI



Events	Frequency in groups		RR (95%CI)	RR (95%CI)
	Cys ≥ 1500 ng/ml	Cys < 1500 ng/ml	Age and sex adjust	Age, sex, clinical adjust
Thrombotic	30.8%	16.2%	3.8 (1.3-11.7) p=0.02	2.9 (1.0-9.1) p=0.05
Thrombotic and bleeding	38.5%	23.7%	2.8 (1.1-7.5) p=0.03	2.3 (0.9-6.3) p=0.07

❑ **The risk of thrombotic and bleeding events was increased with cystatin C level ≥ 1500 ng/ml which was observed in 5.1% of patients**

5

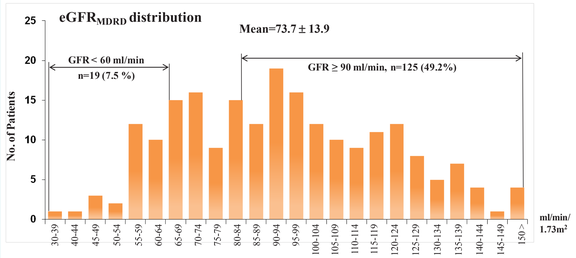
Factors associated with high serum cystatin C level
(regression model)

Factor	F value	p
Elderly age	3.3	0.07
Arterial hypertension	2.2	0.14
Low social support	**6.7**	**0.01**
History of unstable angina (>1 month)	**3.9**	**0.05**
History of CABG (>1 month)	**4.0**	**0.04**
Left bundle branch block on ECG	**4.4**	**0.04**
Aortic stenosis	3.3	0.07
Multivessel CAD	3.1	0.08
Left ventricular ejection fraction 30- 40%	2.1	0.1
History of bleeding events	3.2	0.1

❑ **High serum cystatin C was associated with cardiovascular risk factors burden and severity of atherosclerotic disease**

6

Creatinine - based GFR* in patients after elective PCI

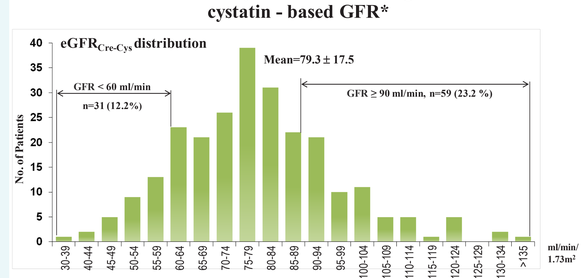


❑ **According to creatinine-based GFR, 49.2% of patients has normal or high kidney function. Moderately decreased kidney function (stage G3A/G3B) was observed in 7.5% of patients**

* - KDIGO 2012 Guideline for the Evaluation and Management of CKD, Kidney International, Suppl 2013; Vol 3, Issue 1

7

Reclassification on kidney function according to creatinine and cystatin - based GFR*

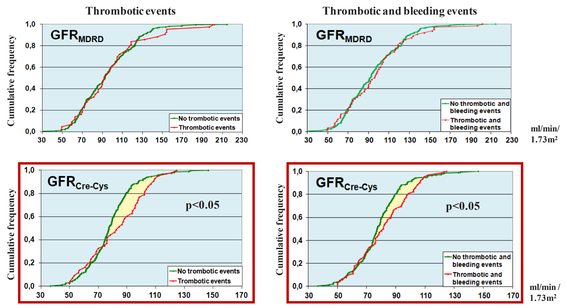


❑ **Reclassification of GFR revealed normal or high kidney function only in 23.2% of pts and moderately decreased kidney function in 12.2% of patients**

* - KDIGO 2012 Guideline for the Evaluation and Management of CKD, Kidney International, Suppl 2013; Vol 3, Issue 1

8

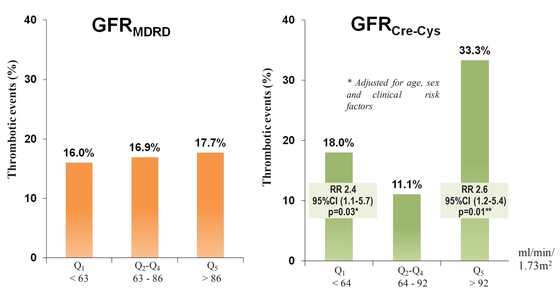
Cumulative frequency distribution curves for GFR_{MDRD} and $GFR_{Cre-Cys}$ in relation to clinical outcomes



❑ **Difference in distributions for events and non-events can be distinguished only when estimating GFR from creatinine and cystatin C**

9

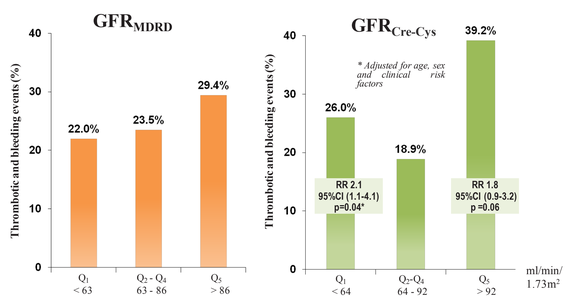
Frequency of thrombotic events according to quintiles of GFR_{MDRD} and $GFR_{Cre-Cys}$



❑ **Use of creatinine alone to assess kidney function could not predict the risk of thrombotic events. Use of creatinine in combination with cystatin C provided greater predictive value: thrombotic events were observed more frequently in lower (Q_1) and upper (Q_5) quintiles of $GFR_{Cre-Cys}$ distribution**

10

Frequency of thrombotic and bleeding events according to quintiles of GFR_{MDRD} and $GFR_{Cre-Cys}$



❑ **The total incidence of thrombotic and bleeding events was higher in lower (Q_1) and upper (Q_5) quintiles of $GFR_{Cre-Cys}$ distribution. Creatinine-based GFR_{MDRD} has no prognostic impact**

11

Conclusion

1. Our cohort study demonstrated that GFR_{MDRD} formula may not be sufficient for prediction of thrombotic and bleeding events in elective PCI patients without severe kidney dysfunction
2. High serum cystatin C (≥ 1500 ng/ml) was associated with cardiovascular risk factors burden and severity of atherosclerotic disease
3. Serum cystatin C (≥ 1500 ng/ml) was associated with thrombotic and bleeding events (age and sex adjusted RR=2.8; 95%CI 1.1-7.5, p=0.03)
4. Kidney function assessed by $GFR_{Cre-Cys}$ formula allowed us to reveal pts at high risk of thrombotic and bleeding events. Increased risk was observed in upper and lower quintiles of $GFR_{Cre-Cys}$ distribution:
   - adjusted RR for the lower quintile (Q_1 < 62 ml/min/1.73m^2) was 2.1 (95%CI 1.1-4.1), p=0.04. This result confirmed the sensitivity of $GFR_{Cre-Cys}$ formula for detection of preclinical kidney disease
   - adjusted RR for the upper quintile (Q_5 > 94 ml/min/1.73m^2) was 1.8 (95%CI 0.9-3.2), p=0.06. Possible explanation is the influence of non-kidney clinical determinants which may confound the associations between GFR and events

12