Kidney Dysfunction and Long-Term Outcome in Post-PCI Acute Coronary Syndrome Patients Treated by High-Dose Tirofiban: The Role of Creatinine Clearance

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Authors' contributions

ABSTRACT

Aims: Few data exist on kidney dysfunction (KD) and glycoprotein IIb/IIIa inhibitors (GPI) in acute coronary syndrome (ACS) patients treated by percutaneous coronary intervention (PCI) and whether they impact on long-term outcome since most frequently patients with various degrees of KD are excluded.
Study Design: Comparison of independent but concomitant arms of a randomized investigation on GPI.
Place and Duration of Study: The Sant'ANna TIrofiban Safety study (SANTISS www.clinicaltrials.gov Identifier: NCT00566891) was an open-label investigator-initiated single centre registry at Sant'Anna Hospital, Catanzaro, during a 5-year enrollment period.

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Methodology: We considered 726 ACS patients with PCI under either triple (aspirin, clopidogrel including high-dose tirofiban) or double (aspirin and clopidogrel) anti-aggregating drugs (AAD). Serum creatinine levels, creatinine clearance (CrCl, using the Cockcroft-Gault formula) and estimated glomerular filtration rate (eGFR, using both MDRD and CKD_EPI formulas) were used as continuous co-variables. Cox's proportional hazards model tested the multivariable contribution of covariates all fitted simultaneously (forced method) in order to predict the incidence of 1-year cumulative ischemic events (CIE).

Results: There were 69 (9.5%) 1-year CIE. Incidences were 5.4, 9.8 and 13.4% (P=0.012) in CrCl tertiles 1 (96-216 ml/min), 2 (73-95 ml/min) and 3 (15-72 ml/min), respectively. Compared to CrCl, the percentile distributions of eGFR, by MDRD or CKD_EPI formulas were similar: all were comparable and significant predictors multivariately (p<0.001) of long-term CIE. The presence of diabetes (hazard ratios, HRs 1.84-1.91), intra aortic balloon pump (HRs 3.59-4.03), and thrombolysis (a protective factor) by tenecteplase (HRs 0.30-0.30) were further significant risk factors. With high-dose tirofiban there was a 20% lower but not statistically different incidence of 1-year CIE.

Conclusion: KD assessed by CrCl or eGFR in ACS patients treated by PCI equally predicted and similarly impacted on 1-year CIE, independent of the formula adopted for eGFR calculation and the presence of GPI with high-dose tirofiban.

ACRONYMS

ACS: acute coronary syndrome; CKD: chronic kidney disease; CIE: composite ischemic event; KD: kidney dysfunction; NSTEMI: non ST elevation myocardial infarction; PCI: percutaneous coronary intervention; STEMI: ST elevation myocardial infarction.

1. INTRODUCTION

Early percutaneous coronary intervention (PCI) for high-risk patients with non–ST-elevation myocardial infarction (NSTEMI) is now recommended [1,2]. However, when there is also kidney dysfunction (KD), measured by creatinine and creatinine clearance, patients have poorer prognosis [3-5]. Similarly, after ST-segment elevation myocardial infarction (STEMI) there is a relation between KD and cardiovascular outcomes including mortality [6,7] whereas only 41% of patients on dialysis are alive 1 year post-STEMI [8]. Thus most randomized investigations in STEMI exclude patients with KD since they have worse prognosis [9], although chronic kidney disease (CKD) and NSTEMI were liable to be considered reasonably for "an invasive strategy" [1].

There is a lack of studies in patients with mixed acute coronary syndromes (ACS), including both STEMI and NSTEMI, whereby KD or CKD as continuous parameters were used to assess the benefits of early revascularization and/or the impact on long-term outcome. Recently Szummer et al. analyzed a large series of NSTEMI patients and showed that KD may reduce the benefits of an early invasive therapy [10]. On the other hand, in STEMI patients undergoing primary PCI [11] it was concluded that baseline KD was associated with markedly increased risk of mortality, bleeding and restenosis. The efficacy and safety of

short- and long-term dual antiplatelet therapy in patients with mild or moderate CKD were not the same than in patients with normal renal function, but this was not associated with a greater relative risk of bleeding based on renal function [12].

Targeted on the long-term cumulative incidence of ischemic events, the aim of this investigation was twofold: a) to assess comparatively the predictive roles of different parameters (serum creatinine levels, creatinine clearance and estimated glomerular filtration rate) used to define KD, using them as continuous co-variables; b) to evaluate the association of the glycoprotein IIb/IIIa inhibitor (GPI) tirofiban at high dose, with clinical risk beyond KD, a clinical relevant question since the safety profile of antithrombotic regimen [13] might be modified. We used ACS patients treated by PCI entering a study where CKD, assessed just by clinical judgement, was previously reported as a significant risk factor [13,14].

2. MATERIALS AND METHODS

2.1 Population

The Sant'ANna TIrofiban Safety study (SANTISS www.clinicaltrials.gov Identifier: NCT00566891) was an open-label investigator-initiated single centre registry enrolling an overall 2205 consecutive ACS patients treated by PCI. The primary objective was to assess the combination of bleeding and in-hospital access site complications after oral single anti-aggregating drug (AAD), two oral AADs (double AAD) and two oral AADs plus high-dose off-label tirofiban (triple AAD) [13]. Interventions were performed by 6-F or 7-F guiding catheter by femoral approach only. Operators were free to choose the most appropriate catheter curves, guidewires and stents. A bolus of heparin (70 UI/kg) was given before starting the procedure in order to maintain an activated clotting time (ACT) of 250s; further doses of heparin were given to adjust ACT when necessary.

2.2 PCI Procedures

All patients underwent pre- and post-PCI standard electrocardiograms (ECG). CK-MB was routinely measured at admission in hospital as well as 6 and 12 h after the procedure and before discharge. STEMI was diagnosed when new Q waves appeared at least in two leads with an increase in CK-MB at least twice upper the normal limit (core laboratory upper limit: 15 U/l) was observed. NSTEMI was diagnosed when an increase in CK-MB at least three-fold upper the normal limit was observed without Q-waves. Red blood cell and platelet counts and hemoglobin and serum creatinine levels (SCr) were measured before the intervention, 24h later and before discharge.

2.3 Study Cohort

During the performance of SANTISS, there were 675 consecutive patients block-randomized to either tirofiban or eptifibatide (3.5:1) and a head-to-head comparison was performed to assess whether the incidence of composite ischemic events during 1-year was modified [14]. After excluding the very few lost to follow-up, there were 519 ACS patients undergoing PCI by triple AAD including high-dose tirofiban (25 mg/kg bolus followed by 0.15 mg/kg/min 18-h infusion) [14]. Concomitantly, an overall 207 ACS patients were treated by double AAD only. Thus, the present study involves 726 ACS patients with PCI under either triple (aspirin,

clopidogrel including high-dose tirofiban) [14] or double (aspirin and clopidogrel) [13] AAD. The time frame of data collection was from hospitalisation to 1 year later.

2.4 Clinical Outcomes

The primary end-point for the study consisted in the combination of ischemic events such as cardiac death, acute myocardial infarction, angina, acute stent thrombosis or the need for repeat PCI or coronary bypass surgery. All events were associated with a date but, when they occurred in a series, they had identical rank order, although only the first one was considered. An independent reviewer (PEP), unaware of treatment assignment, coded all events. Patients referred to perform a rescue-PCI few hours after thrombolysis failure were included.

2.5 Definition of Kidney dysfunction

Baseline SCr was obtained before PCI. Estimated creatinine clearance (CrCl) was calculated using the Cockcroft-Gault formula: CrCl (ml/min)=[(140-age)*weight(kg)]/[SCr (mg/dL) * 72], corrected in women [16] by a factor of 0.85. Estimated glomerular filtration rate (eGFR) was calculated using the abbreviated equation of the Modification of Diet in Renal Disease (MDRD) Study [17,18] where eGFR (mL/min per 1.73 m^2) = [186 * SCr $^{-1.154}$] * [Age $^{-0.203}$ (-0.742 if female)]. Since no African-American people were present, there was no correction for this [17].

There are (see: Appendix Table 1 available at www.annals.org) SCr ranges of values corresponding to eGFR of 60 ml/min per 1.73 m^2, depending on age, sex, and race, thus indicating clearly that minor elevations of SCr may be consistent with a substantial reduction of eGFR [17]. The MDRD study equation has reportedly [17] many advantages being more accurate and precise than the Cockcroft–Gault equation for persons with eGFR less than around 90 ml/min per 1.73 m^2. It estimates GFR measured using an accepted method (urinary clearance of 125I-iothalamate) and the database wherefrom it has been developed was large (n >1000), with people presenting various kidney diseases also having been validated on a database containing more than 500 additional patients. However, eGFR was more recently considered to be better expressed using the CKD_EPI formula [19]. Of note, that a comparative performance analysis among CrCl [16], eGFR_MDRD [17,18] and eGFR_CKD_EPI [19], all used as continuous covariates, has not been performed in ACS patients treated by PCI, neither were the variables derived by these formulas compared as to their potential predictive power on the occurrence of different events, including deaths, during 1-year follow-up.

2.6 Statistical Analysis

Continuous variables were summarized as mean value ± SD whereas discrete variables were given as proportions. Inter-group differences were assessed by analysis of variance (F values). Log-rank test was used to test CrCl [16] inter-tertile significance in the incidence (Kaplan-Meier curves) of the primary end-point of composite ischemic events during 1-year follow-up by an univariate test. Bland and Altman and mountain plots were used (by MedCalc software; see www.medcalcsoftware.com) to assess comparatively 2 (SCr vs CrCl [16]) and 3 (CrCl [16] vs eGFR_MDRD [17,18] and eGFR_CKD_EPI [19]) KD variables, respectively.

Cox's proportional hazards model was used to test the multivariable contribution of a selected series of covariates [14]. All covariates were fitted concomitantly in the Cox's model at step zero (forced method) in order to compute their individual relative contribution. There were 3 different solutions: one for CrCl [16], the other for eGFR_MDRD [17,18] and the last one for eGFR_CKD_EPI [19]. Further details are given elsewhere [20]. In order to fit CrCl [16], eGFR_MDRD [17,18] and eGFR_CKD_EPI [19] we run each respective Cox's model entering age, sex, weight, SCr and clinically coded CKD, separately or in conjunction with the other covariates. However, since it was observed (data not reported in detail) that presence of age and sex among the forced covariates did not modify the overall results whereas entering weight, SCr and clinically coded CKD, induced errors due to co-linearities, the abovementioned variables were omitted. There were also models run to include, for each solution, CK-MB, red blood cell and platelet counts and haemoglobin. These latter solutions are not reported in detail. NCSS software version 2007 (released August 14, 2007 by J Hintze, Kaysville, Utah; see www.ncss.com) was used, by the Efron's method, and Wald's t values and probability level, along with hazard ratios (HR) and $\pm$95% confidence intervals (CI) were computed using standard formulas[14]. A value of $p < 0.05$ was considered statistically significant.

3. RESULTS AND DISCUSSION

Baseline SCr was obtained before PCI in 723 of 726 (99.6%) patients enrolled in the study and an overall 69 (9.5%) composite ischemic events were observed 1-year following PCI. There was a non significant (P=0.07) univariate difference in the incidence of 1-year composite ischemic events among tertiles of baseline SCr levels, although a higher proportion was observed in tertile 3 (1.03-7.70 mg/dl) as compared to both tertile 1 (0.43-0.87 mg/dl) and 2 (0.88-1.02 mg/dl) showing similar incidences (Fig. 1). In contrast, when CrCl was calculated, respective incidences were 5.4, 9.8 and 13.4% in tertiles 1 (96-216 ml/min), 2 (73-95 ml/min) and 3 (15-72 ml/min), which was highly significantly different (P=0.012) univariately (Fig. 2).
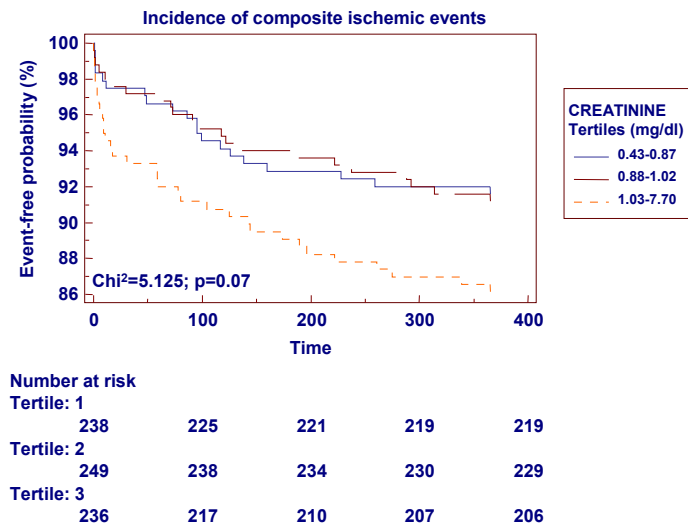
Fig. 1. Composite ischemic events distributed according to tertile distribution of creatinine (mg/dl) in 723 patients with acute coronary syndrome treated by percutaneous coronary intervention
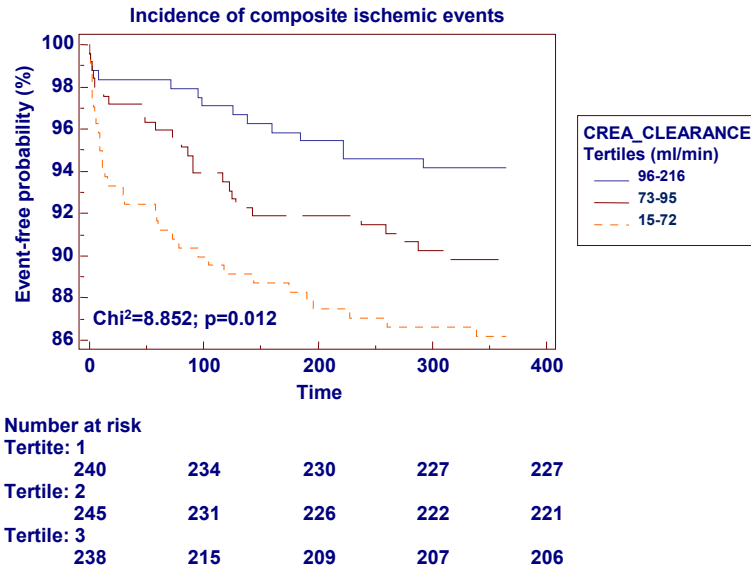
Fig. 2. Composite ischemic events distributed according to tertile distribution of creatinine clearance (ml/min) in 723 patients with acute coronary syndrome treated by percutaneous coronary intervention

Table 1 summarizes demographic and clinical variables, risk factors, procedural and treatment variables, renal function parameters and events occurred during 1 year after inclusion into the study in ACS patients submitted to PCI distributed according to CrCl [16] tertiles. As expected, there were highly significant inter-tertiles differences in age, gender, weight and height. Patients in the upper tertile had more risk factors, more treated coronary vessels and a tendency to receive less frequently high-dose tirofiban. All events (hemorrhagic, composite ischemic, multiple, namely the former 2 categories and deaths) were more frequent in the upper tertile, significantly so only for composite ischemic and multiple events and deaths. Finally, there was a close relation among renal function parameters either explored clinically, or by SCr, eGFR_MDRD [17,18] or eGFR-CKD-EPI [19] and CrCl [16] tertiles, whose average values were respectively 116±0.87, 84±0.87 and 56±0.88 ml/min.

Fig. 3 shows a Bland and Altman graph whereby it is clear that CrCl heavily depends on SCr, as expected by the direct straight-line relation implicit in applying the Cockcroft-Gault formula [16]. What is relatively more important is the mountain graph illustrated by Fig. 4 whereby it is evident that compared to CrCl the percentile distributions of eGFR, either by the MDRD [17,18] or the CKD_EPI [19] formulas, are both right-ward displaced but practically superimposed. Thus, by both formulas, although slightly differently, similar information should be expected as to index baseline renal function.

Table 1. Univariate analysis, use of high-dose tirofiban, eGFR and events among parameters grouped according to tertiles of creatinine clearance in 723 of 726 (99.6%) patients enrolled in the study

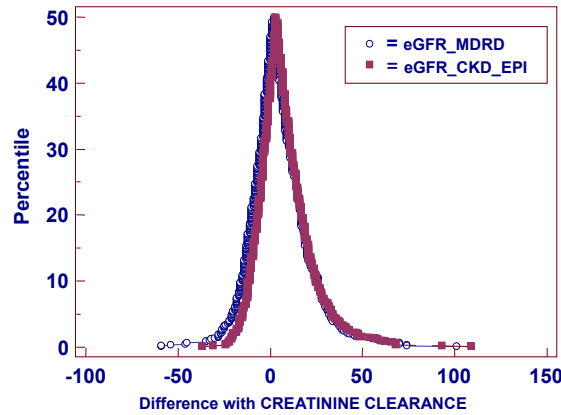|	Creatinine Clearance (ml/min)			F	p<
	96-216	**73-95**	**15-72**		
	(n=240)	**(n=245)**	**(n=238)**		
Demographic and Clinical					
Age (years)	54±0.54	62±0.53	72±0.54	289.07	0.00001
Gender (woman=1; man=0)	0.09	0.18	0.28	14.77	0.00001
Weight (kg)	84±0.65	75±0.64	71±0.65	115.40	0.00001
Height (cm)	170±0.57	166±0.56	163±0.56	38.11	0.00001
Unstable angina (no=0; yes=1)	0.33	0.30	0.36	1.12	0.32
Stable angina (no=0; yes=1)	0.12	0.13	0.10	0.51	0.59
Previous AMI (no=0; yes=1)	0.01	0.008	0.02	0.75	0.47
Shock (no=0; yes=1)	0.39	0.35	0.26	4.36	0.02
Risk factors					
Family History (no=0; yes=1)	0.39	0.35	0.26	4.36	0.02
Hypertension (no=0; yes=1)	0.62	0.64	0.75	5.21	0.01
Smoking habit (no=0; yes=1)	0.47	0.39	0.31	6.85	0.01
Diabetes (no=0; yes=1)	0.26	0.30	0.33	1.06	0.35
Diabetes insulin-dependent (no=0; yes=1)	0.07	0.06	0.10	1.64	0.19
Dyslipidemia (no=0; yes=1)	0.67	0.67	0.62	1.21	0.29
Procedural and Treatment					
Primary PCI (no=0; yes=1)	0.08	0.01	0.02	0.35	0.70
Rescue PCI (no=0; yes=1)	0.16	0.11	0.11	1.57	0.21
Thrombolysis by TEC (no=0; yes=1)	0.17	0.12	0.10	2.23	0.10
IABP (no=0; yes=1)	0.06	0.06	0.08	0.73	0.48
Number of vessels treated (N)	1.07±0.02	1.15±0.02	1.20±0.002	7.11	0.001
ICUS (no=0; yes=1)	0.12	0.06	0.09	2.19	0.11
Platelet count (x1000/dl)	235±5	222±5	223±5	2.07	0.13
High-dose tirofiban (no=0; yes=1)	0.75	0.73	0.66	3.25	0.04
Renal function parametrs					
Chronic renal failure (no=0; yes=1)[#]	0	0.004	0.12	29.89	0.00001
Creatinine (mg/dl)	79±3	86±3	111±3	41.55	0.00001
Creatinine Clearance (ml/min) [16]	116±0.87	84±0.87	56±0.88	1154.00	0.00001
eGFR-MDRD (ml/min per 1.73 m^2) [17,18]	98±0.97	84±0.96	64±0.97	303.00	0.00001
eGFR-CKD_EPI (ml/min per 1.73 m^2) [19]	95±0.79	82±0.78	61±0.79	471.00	0.00001
Events during 1 year after inclusion					
Hemorrhagic (no=0; yes=1)	0.02	0.02	0.04	1.27	0.28
Composite ischemic (no=0; yes=1)	0.06	0.10	0.14	4.34	0.02
Multiple (no=0; yes=1)	0.08	0.12	0.18	4.16	0.02
Death (no=0; yes=1)	0.008	0.02	0.06	36.20	0.002

Continuous variables are mean ± standard errors; categorical are proportions.
[#]: a clinical definition used in previous studies whereby indications came that this was a risk factor [13,14,42].
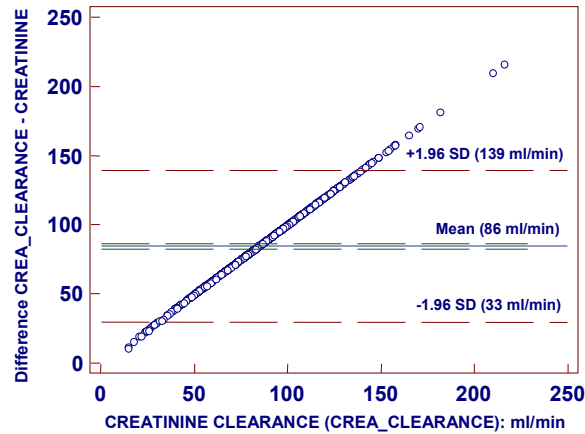
Fig. 3. Bland and Altman plot to show the heavy dependance of creatinine clearance on creatinine due to the adoption of the calculation formula [16].

Fig. 4. Mountain graphs showing that compared to creatinine clearance the percentile distributions of eGFR, either by the MDRD [17,18] or the CKD_EPI [19] formulas, are both right-ward displaced but practically superimposable

Table 2 summarises the results of the forced Cox's models run to assess the predictive roles of renal function parameters (SCr [16], eGFR_MDRD [17,18] and eGFR_CKD_EPI [19]) to predict 1-year composite ischemic events and the interaction of high-dose tirofiban (72% of the overall study group) versus double AAD including clopidogrel (28%). It is impressive that all 3 continuous parameters of baseline renal function are highly significantly predictive (t between –3.28 and –3.34) of long-term composite ischemic events in these ACS patients submitted to PCI, although none was clearly superior. Hazard ratios were 0.98 for all 3 parameters and 95% CI were superimposed. Thus, the lower the renal function parameter (either by CrCl or eGFR, independently of the adopted formula), the higher the incidence of composite ischemic events within 1 year after PCI. The presence of diabetes (t between 2.06 and 2.19) and of intra aortic balloon pump (t between 3.10 and 3.34) were concomitant multivariable risk factors whereas thrombolysis by tenecteplase was a significant protector (t between –2.13 and –2.18). None among the remaining 13 co-variables contributed significantly. Of note that age and sex were not included to enable a direct comparability among the 3 renal function parameters.

Table 2. Proportional hazards models predicting 1-year composite ischemic events according to 3 parameters of renal function

	Creatinine clearance (bold) **by Cockcroft-Gault equation** [16]				Estimate (Estimated) glomerular filtration rate by MDRD equation [17,18]				Estimated glomerular filtration rate by CKD_EPI formula [19]			
	Mean	β	t	HR(±95%CI)	Mean	β	t	HR(±95%CI)	Mean	β	t	HR(±95%CI)
Clinical												
Unstable angina	0.33	0.80	1.80	2.22(0.93-5.30)	0.33	0.83	1.88	2.30(0.96-5.48)	0.33	0.83	1.88	2.29(0.97-5.45)
Stable angina	0.12	0.53	0.95	1.69(0.57-5.00)	0.12	0.61	1.10	1.84(0.62-5.42)	0.12	0.56	1.02	1.75(0.60-5.17)
Previous AMI	0.44	0.27	0.67	1.31(0.59-2.92)	0.44	0.32	0.79	1.38(0.62-3.08)	0.44	0.32	0.79	1.38(0.62-3.06)
Shock	0.01	0.73	1.18	2.08(0.61-7.07)	0.01	0.65	1.04	1.92(0.56-6.57)	0.01	0.64	1.02	1.90(0.55-6.49)
Risk factors												
Family history	0.34	0.12	0.45	1.13(0.67-1.92)	0.34	0.07	0.25	1.07(0.63-1.81)	0.34	0.09	0.34	1.10(0.65-1.86)
Hypertension	0.67	-0.49	-1.85	0.61(0.36-1.03)	0.67	-0.51	-1.91	0.60(0.35-1.01)	0.67	-0.52	-1.92	0.60(0.35-1.01)
Smoking habit	0.39	0.15	0.55	1.16(0.68-1.97)	0.39	0.12	0.46	1.13(0.67-1.91)	0.39	0.16	1.02	1.17(0.69-1.98)
Diabetes	0.30	0.65	2.19	1.91(1.07-3.43)	0.30	0.61	2.07	1.85(1.03-3.31)	0.30	0.61	2.06	1.84(1.03-3.29)
Diabetes insulin-dependent	0.08	0.06	0.16	1.07(0.48-2.39)	0.08	0.02	0.05	1.02(0.45-2.29)	0.08	-0.004	-0.01	1.00(0.44-2.24)
Dyslipidemia	0.66	-0.41	-1.60	0.66(0.40-1.10)	0.66	-0.46	-1.77	0.63(0.38-1.05)	0.66	-0.45	-1.72	0.64(0.39-1.06)
Renal function parameter[#]	85.9	-0.02	-3.34	0.98(0.97-0.99)	82.3	-0.02	-3.28	0.98(0.97-0.99)	79.9	-0.02	-3.30	0.98(0.97-0.99)
Procedural												
Primary PCI	0.01	0.75	0.70	2.13(0.26-17.47)	0.01	0.79	0.74	2.21(0.27-18.15)	0.01	0.80	0.74	2.22(0.27-18.37)
Rescue PCI	0.13	0.92	1.45	2.52(0.72-8.78)	0.13	0.96	1.52	2.62(0.75-9.06)	0.13	0.99	0.74	2.68(0.77-9.27)
Thrombolysis by TEC	0.13	-1.20	-2.13	0.30(0.10-0.91)	0.13	-1.21	-2.18	0.30(0.10-0.89)	0.13	-1.22	-2.18	0.30(0.10-0.88)
IABP	0.07	1.39	3.34	4.03(1.78-9.14)	0.07	1.28	3.10	3.59(1.60-8.07)	0.07	1.29	3.12	3.63(1.61-8.15)
Number of vessels treated	1.15	0.02	0.06	1.02(0.55-1.88)	1.15	0.04	0.14	1.04(0.57-1.92)	1.15	0.04	0.13	1.04(0.57-1.91)
ICUS	0.10	-0.12	-0.26	0.89(0.38-2.10)	0.10	-0.12	-0.27	0.89(0.38-2.08)	0.10	-0.12	-0.27	0.89(0.38-2.08)
Outcome for composite ischemic events within one year												
Tirofiban versus double AAD	0.72	-0.22	-0.83	0.80(0.48-1.35)	0.72	-0.19	-0.72	0.82(0.49-1.39)	0.72	-0.19	-0.70	0.83(0.49-1.40)

[#]: *Age, Gender and Weight, entering the formulas of the renal function parameters [16-19], were not considered, although, when present, the (they) did not contribute significantly and the overall results were similar. β = coefficient; t = t value of coefficient (when t>|1.96| p<0.05). The differences for hazards ratio are expressed as 0-1 for dichotomic variables, and as standard deviations for continuous variables. AAD = anti-aggregating drug; AMI = acute myocardial infarction; CI: confidence intervals of relative risk; HR= hazard ratio; IABP= intra aortic balloon pump; ICUS = intra coronary ultra sound; PCI= percutaneous coronary intervention; TEC= tenecteplase. Note that models are forced, meaning that all covariates stay in at step zero. The coding of the Grouping variable Tirofiban versus double AAD was Tirofiban = 1; double AAD = 0. Tirofiban patients' proportion was 72%, the multivariate risk of 1-year composite ischemic events was 17-20% lower than in those receiving AAD, depending on which parameter was used to define renal function continuously, a not significantly different effect, however.*

In presence of high-dose tirofiban, relative to double AAD including clopidogrel, there was a lower incidence of 1-year composite ischemic events in this study. However, the difference was not statistically significant: the hazard ratios were between 0.80 and 0.83 with 95% CI crossing the unit. As the Cox's models were forced, this means that GPI use in ACS patients treated by PCI did not modify *per se* the long-term risk of composite ischemic events related to KD as assessed by renal function parameters measured continuously.

Both creatinine clearance [16] and eGFR, independent of the formula used [17-19] adequately dissect the probability to manifest composite ischemic events within 1 year from PCI in ACS patients with an approximately unadjusted threefold relative risk between upper and lower tertiles. There was no multivariate advantage in measuring any specific renal function parameters since all 3 enabled comparable statistically significant predictivity. Creatinine levels alone were not useful. The role of the GPI tirofiban at off-label high-dose did not modify statistically the long-term risk provided by KD, although a lower and not a higher hazard ratio was seen. This is of interest since in patients with KD the safety profile of GPI might have been modified. Finally, diabetes and intra aortic balloon pump were significant predictors of long-term outcome whereas thrombolysis by tenecteplase was an independent protector.

The following questions might be raised: why should one use a relatively more complex parameter such as eGFR (independent of the formula adopted) [17-19,37] when the simpler parameter obtained by calculating CrCl [16] just provided the same information? Why should CrCl or even eGFR data be compressed to higher or lower than a given threahold (with an uncertain cut-off value) once the evidence presented shows that the risk is continuous? We try to reply in the following sections.

3.1 Cardiovascular Diseases and Renal Function

Although adequate hydration [21], minimization of contrast agents quantities [22] and using low-osmolarities [21,23] may prevent contrast nephropaty in AMI patients undergoing PCI, KD has an high incidence and prognosis are still bad with an hospital mortality ranging 21-34.5%, a roughly 10-fold increase as compared to that of patients with normal renal function [24]. The situation was unchanged by high-dose intravenous N-acetylcysteine to reduce oxidative stress in presence of moderate doses of contrast medium and optimal hydration [25] but there are some initial data to support high-dose statins [26].

ACS [27] and/or STEMI [9,11] patients had worse prognosis when renal function was abnormal. Addition of multiple biomarkers including eGFR (along with glucose and N-terminal pro-brain natriuretic peptide) to a model including established risk factors improved mortality prediction in STEMI patients undergoing PCI [28]. Moreover, an eGFR <60 ml/min per 1.73 m^2 in post-PCI patients with low platelet response to clopidogrel was associated with worse outcomes [29] whereas it increased mortality, in congestive heart failure candidates to resynchronization therapy [30] or in patients undergoing carotid endarterectomy and carotid angioplasty and stenting [31]. Finally, the incidence of atrial fibrillation during a median follow-up of 10.1 years in the ARIC study had Cox's multivariable hazard ratios of 1.3, 1.6 and 3.2 (P for trend <0.0001) in both genders with cystatin-based eGFR of 60 to 89, 30 to 59, and 15 to 29 ml/ min per 1.73 m^2, respectively [32].

In 2763 postmenopausal women [33] with coronary artery disease, over a mean follow-up of 6.8 years, sudden coronary death comprised 136 of the 254 cardiac deaths with an annual event rate of 0.79%. Independently associated with sudden coronary were myocardial

infarction, heart failure, eGFR <40 ml/min per 1.73 m^2, atrial fibrillation, physical inactivity, and diabetes. The combination of clinical risk factors, including eGFR and LVEF (C-index, 0.681) were better predictors of sudden coronary death than LVEF alone (C-index, 0.600) and resulted in a net reclassification improvement of 0.20 (P<0.001).

A recent trial comparing bivalirudin monotherapy or heparin plus GPI during primary PCI in STEMI patients sought to investigate the impact of CKD (defined as CrCl <60 ml/min, present at baseline in 554 of 3397 patients, 16.3%) with different antithrombotic strategies [34]. GPIs were administered before PCI: either abciximab (a bolus of 0.25 mg/kg followed by an infusion of 0.125 microg/kg/min; maximum dose, 10 microg/min) or double-bolus eptifibatide (a bolus of 180 microg/kg followed by an infusion of 2.0 microg/kg/min, with a second bolus given 10 min after the first) was permitted at the discretion of the investigator and was continued for 12 h (abciximab) or 12 to 18 h (eptifibatide). In patients with a CrCl <50 ml/min, the infusion dose of eptifibatide was reduced to 1.0 microg/kg/min. Patients were followed for 3 years. Patients with CKD compared with patients without had higher rates of composite events (41.4% vs. 23.8%, P < 0.0001), death (18.7% vs. 4.4%, P < 0.0001), and major bleeding (19.3% vs. 6.7%, p < 0.0001). Multivariable analysis identified baseline creatinine as an independent predictor of death at 3 years (hazard ratio: 1.51, 95% confidence interval: 1.21 to 1.87, P < 0.001). Patients with CKD randomized to bivalirudin monotherapy versus heparin plus GPI had no significant difference in major bleeding (19.0% vs. 19.6%, P = 0.72) or death (19.0% vs. 18.4%, P = 0.88) at 3 years.

The global picture from the above investigations [9,11-14,21-34] may concurrently indicate that KD, assessed as a categorized variable with varying cut-off values to dissect normal versus abnormal kidney function, is a crucial cardiovascular risk factor, it variably interplays with chronic or acute myocardial ischemia and/or antithrombotic agents used in this context and at the end it increases the risk of composite events including death, thus becoming a necessary index to be ascertained in cardiovascular outcome-related investigations. What was not unanimously assessed however is by which method KD is best comparatively assessed (versus normal renal function), which are the most suitable cut-off values and whether continuous parameters defining renal function might provide more accurate information.

3.2 Non-Cardiovascular Diseases and Renal Function

Non-cardiovascular investigations may provide some insights to dissect among the different ways one should select to define KD. It was investigated whether combining creatinine, cystatin C, and urine albumin-to-creatinine ratio (ACR) would improve identification of risks associated with CKD compared with creatinine alone [35]. Participants were categorized into 8 groups defined by eGFR determined by creatinine (using CKD_EPI formula [19]) and by cystatin C of either <60 or ≥60 ml/min per 1.73 m^2 and ACR of either <30 or ≥30 mg/g. Participants had a mean age of 65 years, 40% were black, and 54% were women. Of 26643 participants, 1940 died and 177 developed end-stage renal disease. Among participants without CKD defined by creatinine, 24% did not have CKD by either ACR or cystatin C. Compared with those with CKD defined by creatinine alone, the hazard ratio for death in multivariable-adjusted models was 3.3 for participants defined by creatinine and ACR; 3.2 for those defined by creatinine and cystatin C, and 5.6 for those defined by all biomarkers. Compared with participants who did not have CKD by any measure, the HRs for mortality were 1.7 for participants defined by ACR alone, 2.2 for participants defined by cystatin C alone, and 3.0 for participants defined by both measures. The second highest end-stage renal disease rate was among persons missed by the creatinine measure but detected by

both ACR and cystatin C (rate per 1000 person-years, 6.4). Net reclassification improvement for death was 13.3% (P <0.001) and for end-stage renal disease was 6.4% (P <0.001) after adding eGFR cystatin C in fully adjusted models with eGFR, creatinine and ACR. Thus adding cystatin C to the combination of creatinine and ACR measures improved the predictive accuracy for all-cause mortality and end-stage renal disease.

3.3 Different Methods to Assess Kidney Dysfunction

It is not common practice to use cystatin C and although ACR might easily be used, eGFR based on serum creatinine remains the most popular method in Cardiology to assess KD-related investigations [9,11-14,21-34]. Accordingly, it is important to define by which formula, since eGFR_MDRD [17,18] and eGFR_CKD_EPI [19] were proposed and creatinine clearance may also be used [16,34]. The ARIC study involving 13905 middle-aged participants without a history of cardiovascular disease with median follow-up of 16.9 years aimed at investigating comparatively eGFR_CKD_EPI [19] and eGFR_MRD [17,18] equations and which one might improve risk prediction [36]. The association of eGFR was compared in categories (>or=120, 90-119, 60-89, 30-59, and <30 ml/min per 1.73 m^2) using the CKD_EPI [19] and MDRD [17,18] equations with risk of incident end-stage renal disease, all-cause mortality, coronary heart disease, and stroke. The median value for eGFR_CKD_EPI was higher than that for eGFR_MDRD (97.6 vs 88.8 ml/min per 1.73 m^2; P < 0.001). The CKD_EPI equation reclassified 44.9% (n = 3079) and 43.5% (n = 151) of participants with eGFR_MDRD of 60-89 and 30-59 ml/min per 1.73 m^2, respectively, upward to a higher GFR category, but reclassified no one with eGFR_MDRD of 90-119 or <30 ml/min per 1.73 m^2, decreasing the prevalence of CKD stages 3-5 from 2.7% to 1.6%. Participants with eGFR_MDRD of 30-59 ml/min per 1.73 m^2 who were reclassified upward had lower risk compared with those who were not reclassified. More frequent reclassification of younger, female, and white participants explained some of these trends. Thus, CKD_EPI equation [19] more appropriately categorized individuals with respect to long-term clinical risk compared with the MDRD Study equation [17,18], suggesting improved clinical usefulness in ARIC middle-aged population and confirming a previous conclusion [37] in development and validation cohorts from the National Health and Nutrition Examination Survey 1999 to 2006, considering CKD_EPI equation [19] more accurate than MDRD Study equation [17,18] for eGFR. However, the ARIC investigators did not assess reclassification in comparison with CrCl.

There are other parameters that should be assessed to define KD as a cardiovascular risk factor because they might cluster in different individuals. These include urinary albumin excretion [38], non-quantitative dipstick [39] or quantitative [40] proteinuria. We were unable to obtain these parameters in the present study.

3.4 Is there any Interaction between Renal Function and Antiplatelet Therapy?

When clopidogrel plus aspirin are on, there might be no advantage to add small molecules in ACS at large [41]. In STEMI patients treated by primary PCI, all 3 GPIs might provide comparable effects [41]. When PCI is elective for ACS, definite distinction among the 3 agents, both pharmacoeconomically and pharmacodynamically, might be invoked although there are still points open to debate [41]. However, there are few studies whereby the critical interaction was considered among KD (variously defined), the presence of GPIs and PCI in ACS [13,14,28,34,42]. Clopidogrel in general was not associated with a greater relative risk of bleeding based on renal function [12] although the presence of low platelet response to

clopidogrel (by vasodilator-stimulated phosphoprotein flow cytometry) was associated with worse outcome in patients with CKD (defined as eGFR <60 ml/min per 1.73m^2) [29]. A possible beneficial impact of more potent P2Y$_{12}$ inhibition by a higher dose of clopidogrel, prasugrel, or ticagrelor [43] needs further evaluation. On the other hand, all studies performed until now made categories of KD and no investigation was performed whereby eGFR (independent on the formula adopted) or CrCl were considered as continuous parameters and the results assessed multivariately.

Patients undergoing PCI have an approximately threefold increase in the risk of in-hospital mortality when renal function is compromised as compared with preserved renal function and radically different mortality predictors exist for varying levels of renal function [44]. Independent predictors of mortality included female gender and myocardial infarction within the past 72 hr in the end stage renal disease on dialysis group, versus left ventricular ejection fraction, peripheral vascular disease, congestive heart failure, emergency PCI, and absence of prior PCI in the moderate CKD group and age, prior bypass graft surgery, congestive heart failure, emergency PCI, and absence of prior myocardial infarction in patients with preserved renal function.

3.5 Study Limitations

Single time-point laboratory assessment represents a common limitations to most studies assessing prognostic implications of the variables explored here. Stent implantation (bare-metal versus drug-eluting stents) was not randomized. The cardiovascular events were not adjudicated by an independent Committee. The multivariable analysis should be interpreted cautiously since the number of composite ischemic events was relatively low. As with similar evaluations of registry data wherefrom SANTISS experience was obtained [13,14,41,42], there are inherent limitations in this type of study, mainly related to known or unknown factors [29].

4. CONCLUSION

The explored renal function parameters, CrCl [16] and eGFR by MDRD [17,18] and CKD-EPI [19] formulas, enabled comparable long-term prediction of composite ischemic events in ACS patients treated by PCI. However, only two of them were previously compared across a broad range of populations [36] and CKD_EPI equation classified fewer individuals as having CKD and more accurately categorized the risk for mortality and end-stage renal disease than did the MDRD Study equation [45]. In our study, KD did not modify significantly the long-term effects of GPI by the small molecule GPI tirofiban given at an off-label high-dose, an unexpected finding since if any there was a lower incidence of composite ischemic events, although confirmation by larger studies taking renal function into account are certainly needed.

CONSENT AND ETHICAL APPROVAL

All Authors declare that written informed consent was obtained from the patients to be enrolled in the present Study and that ethical approval was obtained.

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COMPETING INTERESTS

The Authors disclose no financial or personal relationships with other people or organizations that could inappropriately influence their work.

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