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Reduced glomerular filtration rate and prior cardiovascular event entail similar risk for coronary atherosclerotic burden

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Abstract. – OBJECTIVE: Prior cardiovascular event and kidney dysfunction are both strong risk factors for coronary artery disease. The aim of this study is to assess coronary atherosclerotic burden in a large population of patients undergoing coronary angiography, according to prior cardiovascular event or chronic kidney disease.

PATIENTS AND METHODS: We evaluated 700 consecutive patients who underwent coronary angiography (CA). Serum creatinine to estimate glomerular filtration rate (eGFR) was measured. Clinically significant coronary artery disease (CAD) was defined by the presence of a coronary lesion resulting in a luminal stenosis >50%. For the purpose of the study, the whole population was divided into 4 subgroups according to the presence/absence of eGFR <60 ml/min/1.73 m2 or prior cardiovascular event: eGFR≥60/no event (Group A), eGFR≥60/yes event (Group B), eGFR<60/no event (Group C), eGFR<60/yes event (Group D).

PATIENTS: As expected, patients in group D had the worst clinical and biochemical profile. These patients also presented the highest values of urinary albumin creatinine ratio (ACR, p<0.001) and the lowest values of eGFR (p<0.01). One-hundred-ninety-six patients had three-vessel disease. Patients who had undergone PCI procedure showed a lower eGFR as compared to patients who had not (p=0.009). Considering group A as reference, the risk of having three-vessel disease was increased in group B (OR= 2.09; 95% CI 1.37-3.19), in group C, (OR= 1.80; 95% CI 1.04-3.14), and finally in group D (OR= 3.35; 95% CI 2.01-5.58). The risk carried by group C was not significantly different from that carried by Group B: OR= 0.86; 95% CI 0.5-1.5.

CONCLUSIONS: In our study, low eGFR seems to have the same excess risk of prior CV event.

Key Words:
Atherosclerosis, Chronic kidney disease, coronary angiography, previous CV event.

Abbreviations

CAD: Atherosclerotic coronary artery disease; CKD: Chronic kidney disease; eGFR: estimated glomerular filtration rate; CHD: coronary heart disease; CA: coronary angiography; PCI: percutaneous coronary intervention; BMI: Body mass index; BP: blood pressure; DBP: diastolic blood pressure; SBP: systolic BP; IDMS: isotope dilution mass spectrometry; ACR: urinary albumin creatinine ratio; HbA1c: Glycated haemoglobin; SVD: single vessel disease; 2 VD: two vessels disease; 3 VD: three vessels disease; T2DM: type 2 diabetes mellitus; ESKD: end stage kidney disease.

Introduction

Cardiovascular disease is the leading cause of death worldwide, as well as in the developed countries[1]. It is responsible for over 4 million deaths per year, close to half of all deaths in Europe; coronary heart disease, when considered separately, accounts for almost 1.8 million

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deaths, or 20% of all deaths in Europe annually[2].

Mortality from coronary heart disease greatly increases among patients with established coronary heart disease[3]. Prior myocardial infarction significantly rises the risk of coronary and cardiovascular disease mortality[4].

Chronic kidney disease (CKD), which is diagnosed by the presence of persistent increased urine albumin excretion and/or decreased estimated glomerular filtration rate (eGFR) (i.e., eGFR<60 ml/min/1.73 m^2), affects up to 17% of the general population in the European countries[5]. Decreased renal function is strongly associated with increased risk of cardiovascular events, including cardiovascular mortality[6-8]. The latter is the most frequent cause of death in patients with chronic kidney disease stage ≤3 (i.e., GFR <60 ml/min/1.73 m^2) and CAD is the most frequent cause of cardiovascular death in these patients[9]. Impaired eGFR and the presence of albuminuria associate with occurrence and severity of coronary atherosclerosis and, among patients with CAD, with major adverse cardiovascular outcome[10,11].

Taking into account these data, the American College of Cardiology/American Heart Association task force and the National Kidney Foundation in 2003 recommended that chronic kidney disease should be considered a coronary heart disease (CHD) risk equivalent[8]. However, whether kidney dysfunction carries a coronary atherosclerotic burden similar to that carried by patients with prior cardiovascular event is yet unknown.

Therefore, the aim of our work was to assess coronary atherosclerotic burden in a large population of patients undergoing CA, according to the prior cardiovascular event or chronic kidney disease.

Patients and Methods

Study Cohort and Baseline Measurements

In an ongoing observational study aiming to investigate the role of kidney dysfunction in modulating the risk of cardiovascular motility and mortality, we evaluated 700 consecutive patients who underwent coronary angiography (CA) from May 2016 to July 2017 at Coronary Unit of Scientific Institute "Casa Sollievo della Sofferenza". All procedures were in accordance with the Ethical Standards of the Responsible Committee on Human Experimentation. The study was approved by local Ethical Committee of Scientific Institute "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Foggia. Informed consent was obtained in written format from each subject before starting the study. As already reported[11], all patients underwent diagnostic CA as part of the clinical work-up of their symptoms or signs of CAD. CA has been performed with Judkins technique in all patients. In the whole sample, 400 patients had a percutaneous coronary intervention (PCI) procedure. Each patient, in the morning of CA, was interviewed for collecting demographic characteristics, such as age, gender, height and weight, and smoking habits (no smoker, current smoker or ex-smoker). For each patient, we collected pathological and remote history, highlighting prior cardiovascular events, such as stroke, myocardial infarction, angina, prior myocardial revascularization, significant carotid stenosis, prior carotid revascularization, peripheral obliterative arteriopathy and prior peripheral revascularization. The same day all patients had blood pressure (BP) measured. Fasting venous blood was also sampled from an antecubital vein from all patients for the measurement of standardized serum creatinine by using the modified kinetic Jaffè reaction (Hitachi 737 Autoanalyzer), calibrated to be traceable to an isotope dilution mass spectrometry (IDMS), total serum cholesterol (enzymatic method, Cobas; Roche Diagnostics, Welwin Garden City, UK), HDL-cholesterol (HDL-c), serum triglycerides (enzymatic method, Cobas). Serum lipids including triglycerides, HDL-c and LDL-cholesterol (LDL-c) were measured by enzymatic methods.

Urinary albumin and creatinine concentration were determined by the nephelometric method (Behring Nephelometer Analyzer; Behring, Marburg, Germany) and the Jaffè reaction rate method, respectively. Urinary albumin excretion was calculated and reported as urinary albumin creatinine ratio (ACR). We defined: normoalbuminuria if ACR ≤2.5 mg/mmol in men and ≤3.5 mg/mmol in women; microalbuminuria if ACR was >2.5 mg/mmol in men and >3.5 mg/mmol in women and ≤30 mg/mmol in both gender; macroalbuminuria if ACR was >30 mg/mmol in both gender. In the data analysis we have considered both microalbuminuria and macroalbuminuria as named albuminuria. GFR was estimated using the Chronic Kidney Disease Epidemiology Collaboration formula derived by standardized serum creatinine values[12]. CKD was defined by

the presence of albuminuria or eGFR <60 ml/min/1.73 m^2 (i.e., low eGFR), or both. Patients were classified as having T2DM if they reported a prior diagnosis or were receiving antidiabetic treatment. Glycated haemoglobin (HbA1c) was measured by HPLC (Diamat Analyzer; Bio-Rad, Richmond, CA, USA) in patients affected by diabetes. Antihypertensive, lipid-lowering and antihyperglycemic treatments were also recorded. As already reported[11], clinically significant CAD was defined as the presence of a coronary lesion with a lumen diameter stenosis ≥ 50% in a major epicardial artery. Patients were then classified according to the number of involved vessels as follows: single vessel disease (S VD), two vessels disease (2 VD) and three vessels disease (3 VD).

According to the purpose of the study, all the population examined was divided into 4 subgroups according to the presence/absence of eGFR <60 ml/min/1.73 m^2 or prior cardiovascular event: eGFR≥60/no event (Group A), eGFR≥60/yes event (Group B), eGFR<60/no event (Group C), eGFR<60/yes event (Group D).

Statistical Analysis

Continuous variables are expressed as mean ± SD or median (range); categorical variables are described as frequencies and percentages. Mean differences were compared by unpaired Student's *t*-test or 1-way ANOVA tests, as appropriate. Differences between categorical variables were tested by x^2.

A multivariate logistic regression model was fitted to estimate the effect of kidney measures or prior CV event on the risk of having a three vessel disease. Two models of analysis were used. The first one, Group A, was the reference group for all others, in the second model (i.e., repeated analysis) the prior group was the one of reference for each following group (i.e., group B *vs.* group A, group C *vs.* group B and, finally, group D *vs.* group C). The results, adjusted for age and gender, are expressed as odds ratio and their 95% confidence interval. A *p*-value less than 0.05 was considered to be significant. All data analyses have been performed with the SPSS statistical program software (version 20 SPSS IBM Corp., Armonk, NY, USA).

Results

Clinical and biochemical characteristics of patients studied as whole sample or divided by presence/absence of renal impairment and/or prior cardiovascular event are reported in Table I. Overall, the mean age was 68.3±10.6 years, 74% were male, mean BMI 28.4±4.8 kg/m^2. At hospital admission BP was fairly controlled, mean systolic BP (SBP) was 133.8±15.9 mmHg and mean DBP 75.7±9.5 mmHg. It is worth to note that the vast majority of patients (i.e., 89%) were diagnosed as having arterial hypertension. As far as kidney function is concerned, the mean eGFR was 72.1±22.3 ml/min/1.73 m^2 with 29% of patients showing eGFR<60 ml/min/1.73 m^2, while median ACR was 1.4 mg/mmol (range 0.27-1471).

The subgroup of patients (n=400, M 323, F 77, age 68.0 ± 10.3 years), who underwent PCI procedure presented a lower eGFR as compared to patients who did not (71.1 ± 23 *vs.* 73.4 ± 21 PCI *vs.* no PCI, respectively; p=0.009).

One-hundred ninety-one patients (33%) exhibited an increased ACR [including patients with either microalbuminuria (25%) or macroalbuminuria (8%)]. Two-hundred ninety-two (42%) patients had T2DM.

According to the purpose of the study, the whole population was then divided into 4 subgroups according to the presence/absence of eGFR <60 ml/min/1.73 m^2 or prior CV event: eGFR≥60/no CV event (Group A), n=306 (43.7%), eGFR≥60/yes CV event (Group B), n=190 (27.1%), eGFR<60/no CV event (Group C), n=98 (14%), eGFR<60/yes CV event (Group D), n=106 (15.2%). Data reported in Table I show, as expected, some relevant differences among subgroups of patients. In fact, patients in group D had the worst clinical and biochemical profile. They were older, with higher prevalence of diabetes, dyslipidemia and arterial hypertension (p<0.01) for all. These patients also showed the highest values of ACR (p<0.001) and the lowest values of eGFR (p<0.01).

In **Supplementary Table I** and **Table II** we report clinical and biochemical features in further subgroups in which albuminuria or CKD replaced low eGFR. Here the total number of patients is not 700 due to the presence of baseline missing data: ACR in 114 patients and CKD in 83 patients.

Angiographic Data

In Table II we report coronary angiographic data in the whole population and according to presence/absence of prior cardiovascular event or low eGFR. While 223 patients show no significant coronary lesions, 196 had three vessel disease. Figure 1 depicts the percentage of patients with 3VD distributed among the 4 subgroups of pa-

Table I. Characteristics of 700 patients studied who underwent to CA; whole population and subgroups divided according to the presence/absence of eGFR < 60 ml/min/1.73 m^2 and the presence/absence of previous cardiovascular event.

	Whole population n = 700	eGFR ≥ 60 no event (Group A) n = 306	eGFR ≥ 60 yes event (Group B) n = 190	eGFR < 60 no event (Group C) n = 98	eGFR < 60 yes event (Group D) n = 106	*p*-value
Male n (%)	521 (74%)	231 (75.5%)	163 (85.8%)	58 (59.2%)	69 (65.1%)	< 0.01
Age (years)	68.3 ± 10.6	65.1 ± 10.6	66.9 ± 9.2	74.2 ± 10.2	74.5 ± 7.9	< 0.01
BMI (kg/m^2)	28.4 ± 4.8	28.2 ± 4.8	28.3 ± 4.2	28.5 ± 4.9	28.9 ± 5.9	0.652
SBP (mmHg)	133.8 ± 15.9	133.1 ± 15.4	134.5 ± 15.5	134.6 ± 17.5	133.9 ± 16.8	0.773
DBP (mmHg)	75.7 ± 9.5	75.8 ± 9.4	75.3 ± 8.8	77 ± 10.9	75.3 ± 9.9	0.545
Triglycerides (mg/dL)	142 (33-855)	134 (33-855)	146 (52-788)	127 (40-440)	156 (51-485)	0.029
HDL-c (mg/dL)	46.2 ± 13.3	47.4 ± 12.9	45.7 ± 12.7	46.6 ± 15	43.4 ± 13.5	0.073
LDL-c (mg/dL)	95.5 ± 35.1	110.4 ± 35.5	86.7 ± 30.5	93.2 ± 34.5	91.7 ± 32.3	< 0.01
eGFR (mL/min/1.73° m^2)	72.1 ± 22.3	84.5 ± 13.9	81.8 ± 13.3	45.8 ± 12.7	42.9 ± 13	< 0.01
ACR (mg/mmol)	1.4 (0.27-1471)	1.2 (0.34-141.4)	1.2 (0.36-831.01)	1.9 (0.41-780.9)	3.3 (0.27-1471)	< 0.001
Normoalbuminuria n (%)	392 (67%)	189 (77.1%)	116 (69%)	45 (56.3%)	42 (45.2%)	-
Microalbuminuria n (%)	149 (25%)	49 (20%)	44 (26.2%)	26 (32.5%)	30 (32.3%)	-
Macroalbuminuria n (%)	45 (8%)	7 (2.9%)	8 (4.8%)	9 (11.3%)	21 (22.6%)	< 0.01
Smokers n (%)	152 (22%)	78 (25.5%)	49 (25.8%)	14 (14.3%)	11 (10.4%)	0.012
Dyslipidemia n (%)	515 (74%)	190 (62.1%)	166 (87.4%)	64 (65.3%)	95 (89.6%)	< 0.01
Lipid-lowering treatment with Statins/fibrates n (%)	492 (70%)	178 (58.2%)	160 (84.2%)	60 (61.2%)	94 (88.7%)	< 0.01
Arterial hypertension n (%)	626 (89%)	251 (82%)	174 (91.6%)	95 (96.9%)	106 (100%)	< 0.01
Use of ACE-Is/ARBs n (%)	498 (71%)	204 (66.7%)	136 (71.6%)	74 (75.5%)	84 (79.2%)	0.063
T2DM n (%)	292 (41.7%)	97 (31.7%)	81 (42.6%)	50 (51.0%)	64 (60.4%)	< 0.01

Mean ± SD, absolute frequency (*percentage*) and °median (*range*). BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; ACR, urinary albumin-to-creatinine ratio; ACE-Is, angiotensin converting enzyme-inhibitors; ARBs, angiotensin II receptor antagonists; T2DM, type 2 diabetes mellitus. Patient's baseline missing data: ACR in 114 patients; CKD in 83 patients.

tients. Considering group A as reference, the risk of having 3VD, increased in group B (OR=2.09; 95% CI 1.37-3.19), in group C, (OR=1.80; 95% CI 1.04-3.14) and, finally in group D (OR=3.35; 95% CI 2.01-5.58) (Table IIIA). The risk carried by group C was not significantly different from the one carried by Group B: OR=0.86; 95% CI 0.5-1.5 (Table IIIB), showing a similar 3VD among these two groups of patients.

The results did not change when albuminuria or CKD replaced low eGFR in the different subgroups analyzed (**Supplementary Figure 1** and **2**, **Supplementary Table III** and **IV**).

Discussion

In our study involving 700 patients undergoing CA, patients with low eGFR and prior CV event carry the heaviest coronary atherosclerotic burden (i.e., percentage of patients affected by 3 VD). Low eGFR seems to give the same excess risk of prior CV event. According to our knowledge, this is the first study comparing coronary atherosclerotic burden in this peculiar setting of patients.

Three-vessel disease is the most severe form of coronary atherosclerosis. In fact, therapeutic

Table II. Angiographic reports of severity of coronary artery disease among patients with or without renal impairment and previous cardiovascular event.

CAD	Whole population	Group A	Group B	Group C	Group D
No-vessel disease (No-VD)	223 (32%)	133 (44%)	36 (19%)	35 (36%)	19 (18%)
Single-vessel disease (S-VD)	152 (22%)	67 (22%)	47 (25%)	19 (19%)	19 (18%)
Two-vessel disease (2-VD)	129 (18%)	50 (16%)	43 (22%)	15 (15%)	21 (20%)
Three-vessel disease (3-VD)	196 (28%)	56 (18%)	64 (34%)	29 (30%)	47 (44%)

*Adjusted by age and gender. $p < 0.01$. CAD, Atherosclerotic coronary artery disease; Group A, eGFR ≥ 60/no event; Group B, eGFR ≥ 60/yes event; Group C, eGFR < 60/no event; Group D, eGFR<60/yes event.

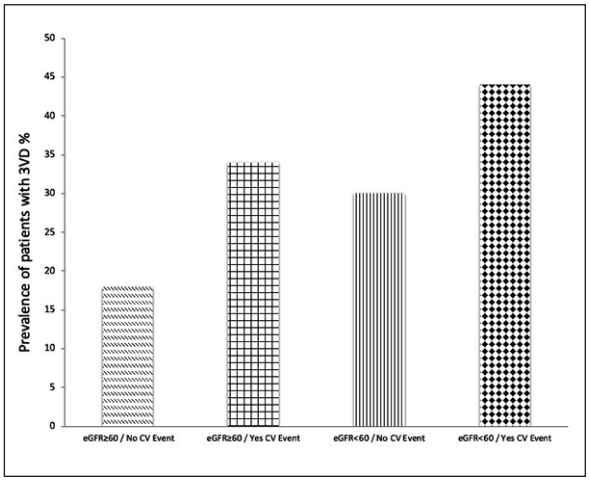

Figure 1. Percentage of patients with 3VD distribution in 4 subgroups of patients, according to the presence/absence of eGFR < 60 ml/min/1.73 m^2 or prior cardiovascular event.

guidelines indicate these patients being at very high CV risk[13-15].

CKD is also associated with high risk of CHD events and mortality either in the general population[16] or in high-risk subjects, such as those with known vascular disease[17,18], diabetes mellitus[19], hypertension[20], or CHD[21]. Natali et al[22] have clearly shown how mild reduction in GFR is associated with a more severe coronary artery disease.

The causative relationship between augmented atherosclerotic burden with unstable, calcified plaques in patients with end stage renal disease is well known; on the contrary, scant information is available on the relationship between atherosclerotic burden with initial stages 3 CKD. More than a decade ago, Buzzello et al[23] demonstrated in an animal model of atherosclerosis with advanced kidney disease, the presence of large atherosclerotic plaque with unstable morphology rather than onset of new ones. Recently, Sugiyama et al[24] have investigated coronary atherosclerotic plaque by optical coherence tomography. With this sophisticate methodology CKD was associated with the growth of lipidic plaques suggesting that the progression of CKD to more advanced stages might cause silent plaque rupture.

The American College of Cardiology/American Heart Association task force and the National Kidney Foundation fifteen years ago already recommended to consider CKD a coronary heart disease (CHD) risk equivalent[8]. The results of the Alberta Kidney Disease Network investigating a large population of more than one million of subjects confirmed the above indications stating that all-cause mortality is higher in patients with advanced CKD than those with a prior myocardial infarction[25]. Our results agree with American College of Cardiology/American Heart Association task force and the National Kidney Foundation indications.

On the contrary, Wattanakit et al[26] have investigated the same issue analyzing 12,243 non diabetic subjects from the ARIC (Atherosclerosis Risk in Communities) study. They stratified the whole population by the presence/absence of CKD and myocardial infarction. After adjustment for several confounders, the authors found that CHD incidence and CVD mortality rates per

Table IIIA. Risk for having three-vessel coronary disease according to presence/absence of eGFR <60 ml/min/1.73m^2 or prior cardiovascular events, considering group A as reference.

Group A	Group B	Group C	Group D
Reference	OR, 95% CI: 2.09 (1.37-3.19)	OR, 95% CI: 1.80 (1.04-3.14)	OR, 95% CI: 3.35 (2.01-5.58)

ORs are adjusted by age and gender.

Table IIIB. Risk for having three-vessel coronary disease according to presence/absence of eGFR <60 or prior cardiovascular events: comparison between groups.

Group A	Group B	Group C	Group D
Reference	OR, 95% CI: 2.09 (1.37-3.19)	OR, 95% CI: 0.86 (0.49-1.51)	OR, 95% CI: 1.85 (1.03-3.34)

ORs are adjusted by age and gender.

1,000 person-years were 4.1 and 1.0 among subjects with neither condition, 8.0 and 3.4 in CKD only, 18.8 and 7.0 in MI only, and 30.8 and 18.0 in CKD and MI, thus concluding that stage 3 CKD cannot be considered a CHD risk equivalent. Although in our study we do not have information on cardiovascular events, the difference with our finding can be explained, at least partially, by the differences in the features of patients studied. In fact, Wattanakit et al[26] have investigated patients with prior MI and stage 3 CKD while in our study we have enrolled patients with a broad figure of cardiovascular disease and stage ≥3 CKD. Moreover, Wattanakit et al[26] did not consider patients with diabetes.

Our study has some strength and weakness points: the main strength point is the uni-centric nature of the study. In fact, all CA were performed and read by the same two co-authors (CV and NM). When the opinion was discordant, the judgment of a third independent person was asked. A second point is the method used to measure serum creatinine, calibrated to be traceable to an isotope dilution mass spectrometry (IDMS) IDMS-traceable. Among the limitations: first: the lack of information on hard cardiovascular events is relevant. The second one: there is only one measurement of serum creatinine or albuminuria.

Conclusions

Our study states that patients with CKD and prior CV event have the worst atherosclerotic coronary burden. Patients with CKD carry a similar risk of coronary atherosclerotic burden of patients with prior CV event. Further larger prospective studies will clarify whether a similar coronary atherosclerotic burden will end up in similar cardiovascular outcomes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval and Consent to Participate

All procedures followed were in accordance with the Ethical Standards of the Responsible Committee on Human Experimentation. The study was approved by local Ethical Committee of Scientific Institute "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Foggia, Italy. Informed prior consent was obtained in written format by each subject.

Availability of Data and Materials

All data generated or analysed during this study are included on this published article [and its supplementary information files].

Authors' Contribution

Conception and design of total study, SD and PP; Acquisition of data, PP, AMa, NM, EVG, MMD, VM, AM, APP, GV, AR, CV; Analysis and interpretation of data, PP, SD, RP; Drafting of manuscript and critical revision, all authors. All authors have read and approved the manuscript.

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