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Letter to the Editor

LETTER TO THE EDITOR

The 2021 European Society of Cardiology Cardiovascular Disease Prevention Guidelines: adding albuminuria to the SCORE scale increases the prevalence of very high/high cardiovascular risk among patients with chronic kidney disease

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Chronic kidney disease (CKD) is a common condition worldwide [1]; however, it is vastly underdiagnosed as it frequently remains asymptomatic until reaching advanced stages [2]. Thus, in Spain, the prevalence of diagnosed CKD among adults is only 5%, far lower than in nationwide, population-based studies [3]. The CKD prevalence is expected to increase in the future, as the population becomes older and the prevalence of hypertension and diabetes, the leading causes of CKD, grows [2]. The 2019 European Society of Cardiology (ESC) guidelines of dyslipidemia classify severe CKD [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2], and moderate CKD (eGFR 30–59 mL/min/1.73 m^2) as having very high and high cardiovascular (CV) risk, respectively, without requiring Systematic COronary Risk Estimation (SCORE) [4]. However, CV risk is increased by both decreased renal function and albuminuria [3]. Thus, the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines include both parameters in the stratification of CV disease risk [5]. The 2021 ESC guidelines on CV disease prevention have added albuminuria to renal function for CV risk stratification [6]. As a result, it would be of great interest to analyze the impact of this new classification on CKD patients. For this purpose, we analyzed the impact on CV risk stratification of CKD patients, adopting the 2021 ESC guidelines by using BIG-PAC®, a database with information from 1.8 million non-selected persons of primary health care centers and referral hospitals within the Spanish national health system [1]. Adult patients, with one or more diagnostic code of CKD or having laboratory results meeting the definition of CKD, were included. CKD stages were defined according to eGFR (CKD Epidemiology Collaboration) and urine albumin-to-creatinine ratio (UACR) criteria: CKD stage 1: eGFR ≥90 mL/min/1.73 m^2 and UACR ≥30 mg/g; CKD stage 2: eGFR 60–89 mL/min/1.73 m^2 and UACR ≥30 mg/g; CKD stage 3a: eGFR 45–59 mL/min/1.73 m^2; CKD stage 3b: eGFR 30–44 mL/min/1.73 m^2; CKD stage 4: eGFR 15–29 mL/min/1.73 m^2;

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Table 1. CV risk stratification according to 2019 ESC lipid guidelines and 2021 ESC CVD prevention guidelines

	2019 ESC lipids	2021 ESC CVD prevention
Very high risk	• Documented ASCVD • T2DM with TOD (microalbuminuria, retinopathy, or neuropathy) or ≥3 major risk factors, or T1DM of long duration (>20 years) • Severe CKD (eGFR <30 mL/min/1.73 m^2) • SCORE ≥10% • FH with ASCVD or another major risk factor	• Documented ASCVD • T2DM with established ASCVD and/or severe TOD [eGFR <45 mL/min/1.73 m^2 irrespective of albuminuria, eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g), proteinuria (UACR >300 mg/g), presence of microvascular disease in ≥3 sites (e.g. microalbuminuria plus retinopathy plus neuropathy)] • CKD without diabetes or ASCVD: eGFR <30 mL/min/1.73 m^2 or eGFR 30–44 mL/min/1.73 m^2 and UACR >30 mg/g • Apparently healthy persons but SCORE2: <50 years ≥7.5%; 50–69 years ≥10% • Apparently healthy persons but SCORE2-OP: ≥70 years ≥15%
High risk	• Markedly elevated single risk factors (TC >310 mg/dL, LDL-C >190 mg/dL or BP ≥180/110 mmHg) • Patients with FH without other major risk factors • Patients with DM without TOD (microalbuminuria, retinopathy or neuropathy), with DM duration ≥10 years or another additional risk factor • Moderate CKD (eGFR 30–59 mL/min/1.73 m^2) • SCORE ≥5% and <10%	• CKD without diabetes or ASCVD: eGFR 30–44 mL/min/1.73 m^2 and UACR <30 mg/g or eGFR 45–59 mL/min/1.73 m^2 and UACR 30–300 mg/g or eGFR ≥60 mL/min/1.73 m^2 and UACR >300 mg/g) • T2DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria[a] • FH associated with markedly elevated cholesterol levels • Apparently healthy persons but SCORE2: <50 years 2.5–<7.5%; 50–69 years 5–<10% • Apparently healthy persons but SCORE2-OP: ≥70 years 7.5–<15%
Moderate risk	• SCORE ≥1% and <5% • Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors	• Moderate risk: ◦ Well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors ◦ CKD without diabetes or ASCVD: eGFR >60 mL/min/1.73 m^2 and UACR 30–300 mg/g[b]
Low risk	• SCORE <1%	• Low to moderate risk: ◦ Apparently healthy persons but SCORE2: <50 years <2.5%; 50–69 years <5% ◦ Apparently healthy persons but SCORE2-OP: ≥70 years <7.5%

[a]No CKD patient is eligible for moderate risk, i.e. patients with CKD and T2DM not fulfilling very high risk criteria should be included directly as high risk patients.
[b]This criterion has not been included in 2021 ESC guidelines, but was added to classify all CKD patients.
ASCVD: atherosclerotic cardiovascular disease; BP: blood pressure; CKD: chronic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; ESC: European Society of Cardiology; FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol; SCORE: Systematic COronary Risk Estimation; SCORE2: Systemic COronary Risk Estimation 2; SCORE2-OP: Systematic COronary Risk Estimation 2-older persons (table used is for low-risk countries, as data are from Spain); T1DM: type 1 DM; T2DM: type 2 DM; TC: total cholesterol; TOD: target organ damage; UACR: urine albumin-to-creatinine ratio.
Table adapted from reference numbers [4] and [6].

and CKD stage 5: eGFR <15 mL/min/1.73 m^2 [1]. CV risk was classified according to 2021 ESC guidelines versus 2019 ESC guidelines (Table 1) [4, 6]. Categorical variables were described by their absolute and relative frequencies and were compared with the Chi-squared test or the Fisher exact test, when appropriate.

Of 56 435 (4.91%) patients with CKD, 26 955 (47.8%) were women. According to 2019 ESC guidelines, 34.7%, 45.3%, 16.3% and 3.7% of patients had very high, high, moderate and low CV risk, respectively (80.0% very high/high CV risk). With the 2021 risk stratification, these numbers were 36.7%, 53.6%, 7.2% and 0%, respectively; $P < 0.001$ in all cases (90.3% very high/high CV risk). Therefore, ESC 2021 criteria increased the prevalence of very high and high CV risk CKD patients as compared with the 2019 ESC guidelines (absolute difference: +2.0% and +8.3%; relative difference: +5.8% and +18.3%, respectively; both $P < 0.001$), both in women and in men (Table 2).

These data suggest that although with some limitations, adding albuminuria, as ESC 2021 guidelines on CV prevention did, could improve the risk stratification accuracy. Of note, preventing the development and progression of CKD (renal function and albuminuria) with renin–angiotensin system inhibitors, and more recently, with sodium–glucose cotransporter-2 inhibitors, with also a positive impact on CV disease, is mandatory [7–10]. Therefore, an improved CV risk stratification may be helpful to better identify those patients that would benefit more from these therapies.

CONFLICT OF INTEREST STATEMENT

None declared.

Table 2. CV risk stratification of CKD patients according to 2019 ESC lipid guidelines and 2021 ESC CVD prevention guidelines

	Total (n = 56 435)			Women (26 955)			Men (29 480)		
	2019 ESC	2021 ESC	P	2019 ESC	2021 ESC	P	2019 ESC	2021 ESC	P
Very high risk, n (%)	19 572 (34.7)	20 702 (36.7)	<0.001	7 682 (28.5)	8 289 (30.8)	<0.001	11 890 (40.3)	12 413 (42.1)	<0.001
(2019/2021) Documented ASCVD	16 425 (29.1)	16 425 (29.1)		6095 (22.6)	6095 (22.6)		10 330 (35.0)	10 330 (35.0)	
(2019) T2DM with TOD or ≥3 risk factors, or T1DM of long duration (>20 years)	11 380 (20.2)	–		4620 (17.1)	–		6760 (22.9)	–	
(2019) Severe CKD (eGFR <30)	4008 (7.1)	–		2295 (8.5)	–		1713 (5.8)	–	
(2019) SCORE ≥10%	NA	–		NA	–		NA	–	
(2019) FH with ASCVD or another major risk factor	581 (1.0)	–		292 (1.1)	–		289 (1.0)	–	
(2021) T2DM with established ASCVD and/or severe TOD[a]	–	10 952 (19.4)		–	4448 (16.5)		–	6504 (22.1)	
(2021) CKD without DM or ASCVD: eGFR <30 or eGFR 30–44 and UACR >30	–	3268 (5.8)		–	1876 (7.0)		–	1392 (4.7)	
(2021) SCORE2: <50 years ≥7.5%; 50–69 years ≥10%; SCORE2-OP: ≥70 years ≥15%[b]	–	NA		–	NA		–	NA	
High risk, n (%)	25 565 (45.3)	30 244 (53.6)	<0.001	13 316 (49.4)	16 191 (60.1)	<0.001	12 249 (41.6)	14 053 (47.7)	<0.001
(2019) Markedly elevated single risk factors	6147 (10.9)	–		3254 (12.1)	–		2893 (9.8)	–	
(2019) FH without other major risk factors	12 728 (22.6)	–		6384 (23.7)	–		6344 (21.5)	–	
(2019) DM without TOD, with DM duration ≥10 years or another additional risk factor	17 042 (30.2)	–		8436 (31.3)	–		8606 (29.2)	–	
(2019) Moderate CKD ESC 2019 (eGFR 30–59)	12 364 (21.9)	–		6852 (25.4)	–		5512 (18.7)	–	
(2019) SCORE ≥5% and <10%	NA	–		NA	–		NA	–	
(2021) T2DM without ASCVD and/or severe TOD and not fulfilling the moderate risk criteria	–	19 866 (35.2)		–	10 557 (39.2)		–	9309 (31.6)	
(2021) CKD without diabetes or ASCVD: eGFR 30–44 and UACR <30 or eGFR 45–59 and UACR 30–300 or eGFR ≥60 and UACR >300	–	10 378 (18.4)		–	5634 (20.9)		–	4744 (16.1)	
(2021) FH	–	NA[d]		–	NA[d]		–	NA[d]	
(2021) SCORE2: <50 years 2.5–<7.5%; 50–69 years 5–<10%; SCORE2-OP: ≥70 years 7.5–<15%[b]	–	NA		–	NA		–	NA	

Table 2. Continued

	Total ($n = 56\,435$)			Women (26 955)			Men (29 480)		
	2019 ESC	2021 ESC	P	2019 ESC	2021 ESC	P	2019 ESC	2021 ESC	P
Moderate risk, *n* (%)	9183 (16.3)	4076 (7.2)	<0.001	4829 (17.9)	1901 (7.1)	<0.001	4354 (14.8)	2175 (7.4)	<0.001
(2019) SCORE ≥1% and <5%	6069 (10.8)	–		3223 (12.0)	–		2846 (9.7)	–	
(2019) Young patients with DM duration <10 years, without other risk factors.	5215 (9.2)	–		2532 (9.4)	–		2683 (9.1)	–	
(2019) eGFR ≥60 with UACR 30–300	NA	–		NA	–		NA	–	
(2021) Well controlled short-standing DM (e.g. <10 years), no evidence of TOD and no additional ASCVD risk factors	–	0		–	0		–	0	
(2021) eGFR >60 and UACR 30–300[c]	–	4076 (7.2)		–	1901 (7.1)		–	2175 (7.4)	
(2021) SCORE2: <50 years <2.5%; 50–69 years < 5%; SCORE2-OP: ≥70 years <7.5%[b]	–	NA		–	NA		–	NA	
Low risk, *n* (%)	2115 (3.7)	0	<0.001	1128 (4.2)	0	<0.001	987 (3.3)	0	<0.001
(2019) SCORE <1%	2115 (3.7)	–		1128 (4.2)	–		987 (3.3)	–	
(2019) eGFR >60 with UACR <30	NA	–		NA	–		NA	–	
(2021) SCORE2: <50 years <2.5%; 50–69 years <5%; SCORE2-OP: ≥70 years <7.5%[b]	–	NA		–	NA		–	NA	
CKD patients not fitting categories above[e]	0	1 413 (2.5)	<0.001	0	574 (2.1)	<0.001	0	839 (2.8)	<0.001

ASCVD: atherosclerotic cardiovascular disease; CKD: chronic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; ESC: European Society of Cardiology; FH: familial hypercholesterolemia; SCORE: Systematic COronary Risk Estimation; SCORE2: Systemic COronary Risk Estimation 2; SCORE2-OP: Systematic COronary Risk Estimation 2-older persons; T1DM: type 1 DM; T2DM: type 2 DM; TOD: target organ damage; UACR: urine albumin-to-creatinine ratio.

[a]TOD: eGFR < 45 mL/min/1.73 m^2 irrespective of albuminuria, eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (UACR 30–300 mg/g), proteinuria (UACR >300 mg/g) or presence of microvascular disease in at least three different sites (e.g. microalbuminuria plus retinopathy plus neuropathy).

[b]SCORE2 and SCORE2-OP were not calculated, as all patients had CKD.

[c]This criterion has not been included in 2021 ESC guidelines, but was added to classify all CKD patients.

[d]Already included in the other subgroups.

[e]These patients had the diagnosis of CKD, but data about eGFR were not available. UACR: mg/g; eGFR: mL/min/1.73 m^2.

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