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LAZIO

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E PROSPETTIVE TERAPEUTICHE



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UNIVERSITÀ CAMPUS BIO-MEDICO DI ROMA

NOVITÀ FLASH DAGLI STUDI CLINICI

RIACE

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- **RIACE** is a multicentre observational, prospective cohort study that was conducted in 19 hospital diabetes centers in Italy
- **OBJECTIVES:**
 - eGFR as independent predictor of CVD morbidity and mortality in T2DM
 - The prevalence of eGFR reduction and its association with cardiovascular risk factors and albuminuria
- The RIACE **population** consists of 15,933 Caucasian patients with type 2 diabetes recruited in years 2007–2008
 - Exclusion criteria were dialysis or renal transplantation
 - 160 subjects were excluded due to missing or implausible values

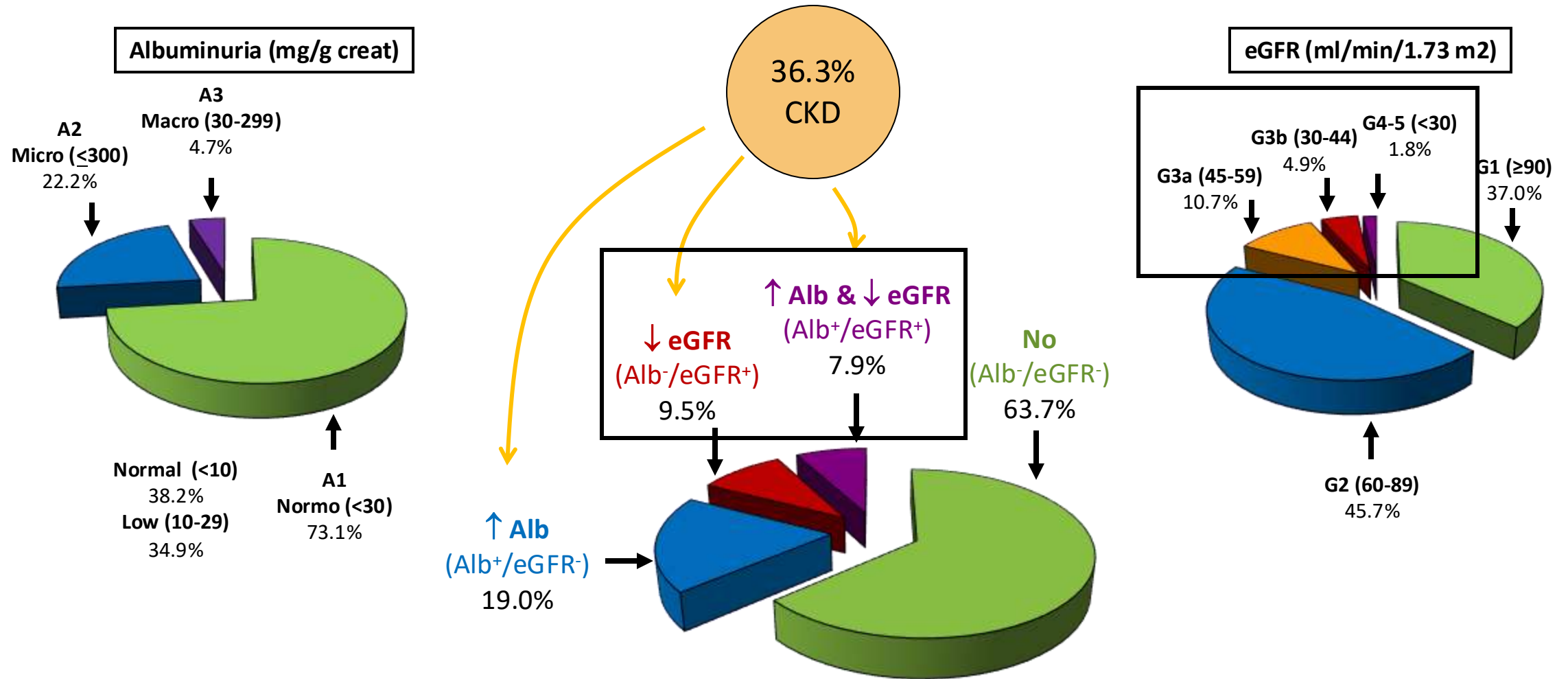
Data from the remaining 15,773 patients were analyzed



Age: 66.0 ± 10.3 years (median 67 years)
Sex: 56.8% male and 43.2% female
Diabetes duration: 13.2 ± 10.2 years (median 11 years)

The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

Clinical significance of nonalbuminuric renal impairment in type 2 diabetes



The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

Clinical significance of nonalbuminuric renal impairment in type 2 diabetes

Variable	Overall	No	↑ Alb	↓ eGFR	↑ Alb & ↓ eGFR	<i>p</i>
		Alb ⁻ /eGFR ⁻	Alb ⁺ /eGFR ⁻	Alb ⁻ /eGFR ⁺	Alb ⁺ /eGFR ⁺	
<i>n</i> (%)	15,656 (100)	9984 (63.77)	2966 (18.94)	1476 (9.43)	1230 (7.86)	
Age, years	66.6 ± 10.3	64.8 ± 10.0	66.0 ± 10.1	74.4 ± 8.1	73.2 ± 9.1	<0.0001
Sex, <i>n</i> (%)						<0.0001
Female	6754 (43.14)	4510 (45.17)	891 (30.04)	889 (60.23)	464 (37.72)	
Male	8902 (56.86)	5474 (54.83)	2075 (69.96)	587 (39.77)	766 (62.28)	
Smoking status, <i>n</i> (%)						<0.0001
Never	8849 (56.52)	5810 (58.19)	1449 (48.85)	935 (63.35)	655 (53.25)	
Former	4407 (28.15)	2644 (26.48)	926 (31.22)	417 (28.25)	420 (34.15)	
Current	2400 (15.33)	1530 (15.32)	591 (19.93)	124 (8.40)	155 (12.60)	
Diabetes duration, years	13.2 ± 10.2	11.9 ± 9.6	13.8 ± 10.0	16.4 ± 11.3	18.3 ± 10.9	<0.0001
HbA _{1c} , mmol/mol	59.0 ± 16.4	57.4 ± 15.4	62.6 ± 18.3	59.4 ± 15.8	62.3 ± 18.8	<0.0001
HbA _{1c} , %	7.55 ± 1.50	7.40 ± 1.41	7.88 ± 1.68	7.58 ± 1.45	7.85 ± 1.65	

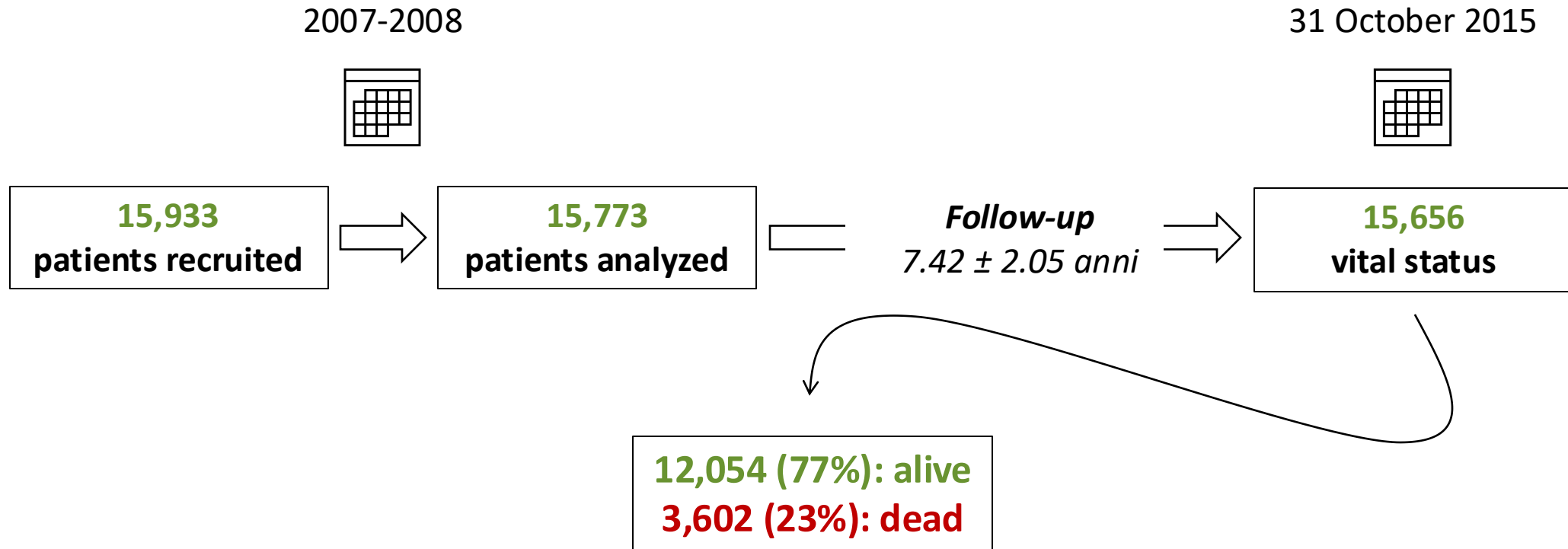
The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

Clinical significance of nonalbuminuric renal impairment in type 2 diabetes

Variable	Overall	No	↑ Alb	↓ eGFR	↑ Alb & ↓ eGFR	<i>p</i>
		Alb ⁻ /eGFR ⁻	Alb ⁺ /eGFR ⁻	Alb ⁻ /eGFR ⁺	Alb ⁺ /eGFR ⁺	
Anti-hypertensive therapy, n (%)	11,072 (70.72)	6347 (63.57)	2339 (78.86)	1270 (86.04)	1116 (90.73)	<0.0001
RAS blockers, n (%)	9340 (59.66)	5258 (52.66)	2051 (69.15)	1072 (72.63)	959 (77.97)	<0.0001
Hypertension, n (%)	13,096 (83.65)	7906 (79.19)	2650 (89.35)	1371 (92.89)	1169 (95.04)	<0.0001
Diabetic retinopathy, n (%)						<0.0001
No	12,189 (77.86)	8273 (82.86)	2072 (69.86)	1129 (76.49)	715 (58.13)	
Non-advanced	1947 (12.44)	1065 (10.67)	447 (15.07)	195 (13.21)	240 (19.51)	
Advanced	1520 (9.71)	646 (6.47)	447 (15.07)	152 (10.30)	275 (22.36)	
CVD, n (%)						
Any	3620 (23.12)	1770 (17.73)	793 (26.74)	495 (33.54)	562 (45.69)	<0.0001
Acute myocardial infarction	1742 (11.13)	880 (8.81)	344 (11.60)	258 (17.48)	260 (21.14)	<0.0001
Coronary revascularisation	1579 (10.09)	809 (8.10)	320 (10.79)	230 (15.58)	220 (17.89)	<0.0001
Any coronary event	2396 (15.30)	1218 (12.20)	478 (16.12)	351 (23.78)	349 (28.37)	<0.0001
Stroke	513 (3.28)	231 (2.31)	123 (4.15)	70 (4.74)	89 (7.24)	<0.0001
Carotid revascularisation	856 (5.47)	370 (3.71)	191 (6.44)	129 (8.74)	166 (13.50)	<0.0001
Any cerebrovascular event	1292 (8.25)	573 (5.74)	296 (9.98)	187 (12.67)	236 (19.19)	<0.0001
Ulcer/gangrene/amputation	556 (3.55)	197 (1.97)	164 (5.53)	70 (4.74)	125 (10.16)	<0.0001
Lower limb revascularisation	450 (2.87)	178 (1.78)	102 (3.44)	68 (4.61)	102 (8.29)	<0.0001

The Renal Insufficiency And Cardiovascular Events (**RIACE**) Italian Multicentre Study

Non-albuminuric renal impairment is a **strong predictor of mortality** in individuals with T2D



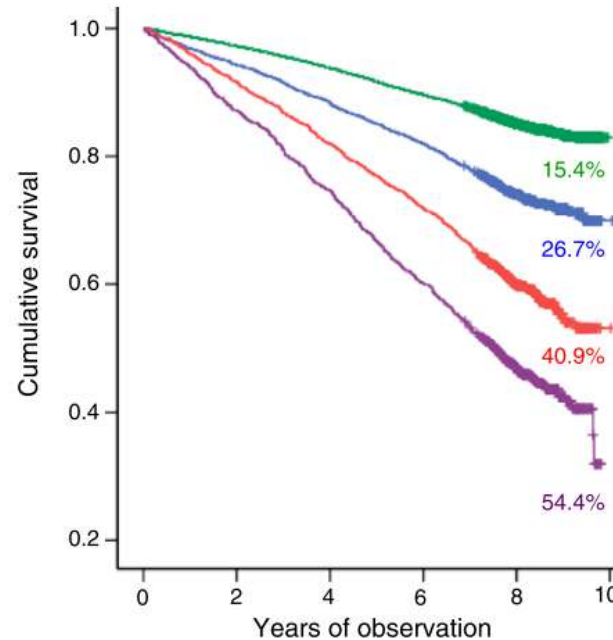
Death rate 31.0 per 1000 person-years

The Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

Non-albuminuric renal impairment is a **strong predictor of mortality** in individuals with T2D

Table 2 Mortality rates according to DKD phenotype and KDIGO risk category and subcategory

Characteristic	<i>n</i>	Events	Per cent events	Events per 1000 person-years (95% CI), unadjusted	<i>p</i>
DKD phenotype					<0.0001
No Alb ⁻ /eGFR ⁻	9984	1536	15.38	19.87 (18.87, 20.86)	
↑ Alb Alb ⁺ /eGFR ⁻	2966	793	26.74	36.79 (34.23, 39.35)	
↓ eGFR Alb ⁻ /eGFR ⁺	1476	604	40.92	61.49 (56.59, 66.40)	
↑ Alb & ↓ eGFR Alb ⁺ /eGFR ⁺	1230	669	54.39	90.25 (83.41, 97.08)	



ORIGINAL ARTICLE

Haemoglobin A1c variability is a strong, independent predictor of all-cause mortality in patients with type 2 diabetes

Orsi E et al. Diabetes Obes Metab 2018

ORIGINAL INVESTIGATION

Open Access

Independent association of atherogenic dyslipidaemia with all-cause mortality in individuals with type 2 diabetes and modifying effect of gender: a prospective cohort study



Orsi E et al. Cardiovasc Diabetol 2021

RESEARCH ARTICLE

Open Access

Is resistant hypertension an independent predictor of all-cause mortality in individuals with type 2 diabetes? A prospective cohort study



Solini A et al. BMC Medicine 2019

RESEARCH

Open Access

Body mass index versus surrogate measures of central adiposity as independent predictors of mortality in type 2 diabetes



Orsi E et al. Cardiovasc Diabetol 2022

Open access

Original research

BMJ Open
Diabetes
Research
& Care

Renal hyperfiltration is independently associated with increased all-cause mortality in individuals with type 2 diabetes: a prospective cohort study

Penno G et al. BMJ Open Diab Res Care 2020

ORIGINAL ARTICLE

Risk of all-cause mortality according to the European Society of Cardiology risk categories in individuals with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study



Orsi E et al. Acta Diabetol 2022

RESEARCH ARTICLE

Open Access

Insulin resistance, diabetic kidney disease, and all-cause mortality in individuals with type 2 diabetes: a prospective cohort study



Penno G et al. BMC Medicine 2021

Original article

Retinopathy as an independent predictor of all-cause mortality in individuals with type 2 diabetes



Orsi E et al. Diabetes Metab 2023

RESEARCH

Open Access



Independent association of history of diabetic foot with all-cause mortality in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study

Martina Vitale¹, Emanuela Orsi², Anna Solini³, Monia Garofolo⁴, Veronica Resi², Enzo Bonora⁵, Cecilia Fondelli⁶, Roberto Trevisan⁷, Monica Vedovato⁸, Giuseppe Penno⁴ and Giuseppe Pugliese^{1*}

Independent association of **history of diabetic foot** with all-cause mortality in patients with type 2 diabetes

Table 1 Baseline clinical features of study participants by history of diabetic foot

Variables	History of diabetic foot	
	No	Yes
N (%)	14,878 (94.3)	895 (5.7)
Ulcer/gangrene	–	532 (59.4)
Amputation	–	153 (17.1)
Minor	–	129 (14.4)
Major	–	24 (2.7)
Ulcer/gangrene/amputation	–	565 (63.1)
Lower limb revascularization	–	456 (50.9)
Endovascular	–	192 (21.5)
Surgical	–	245 (27.4)
Both	–	19 (2.1)

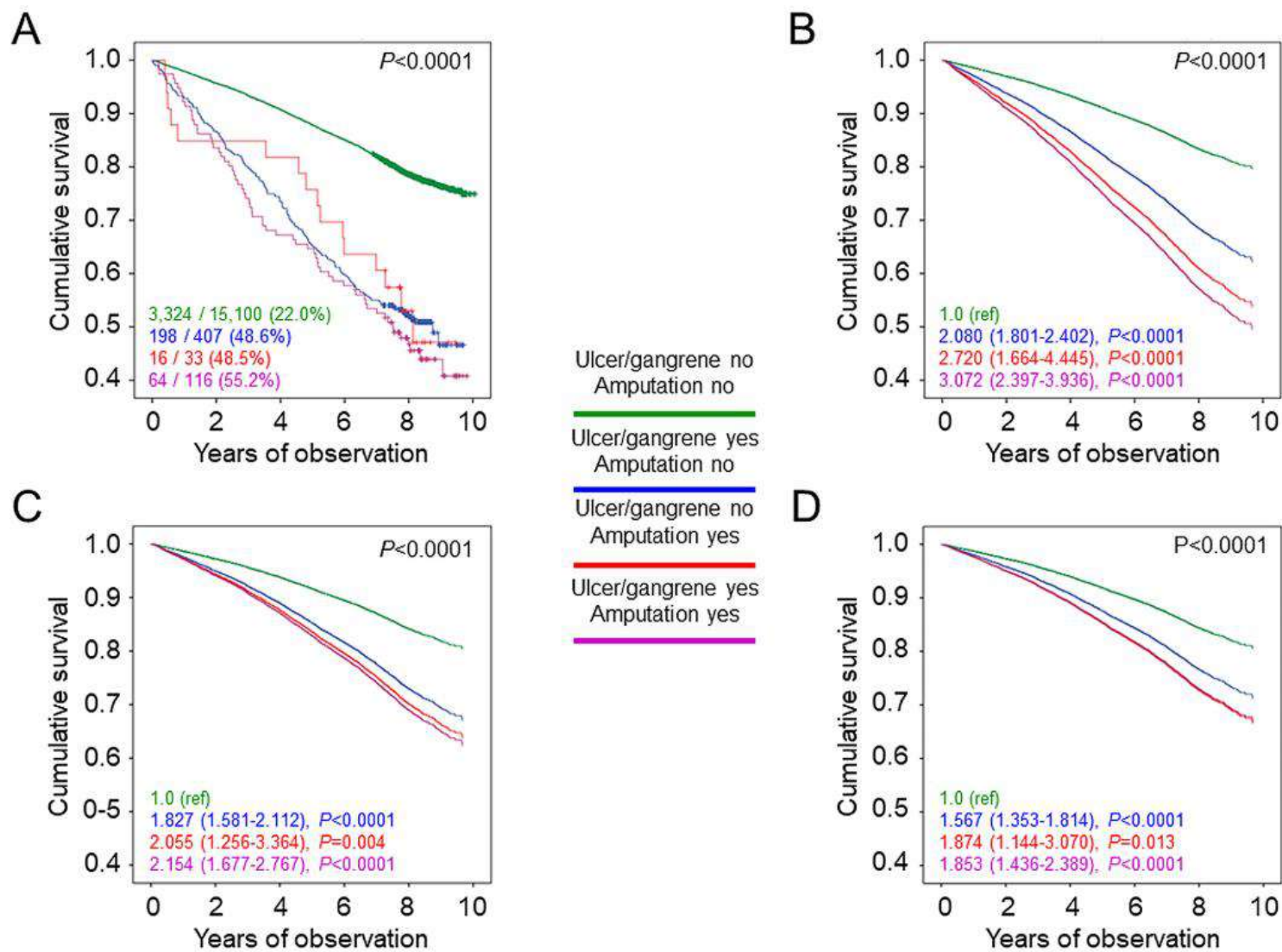
Independent association of **history of diabetic foot** with all-cause mortality in patients with type 2 diabetes

Table 2 Mortality rates in study participants by history of diabetic foot, ulcer/gangrene and/or amputation, and ulcer/gangrene/ amputation and/or lower limb revascularization

	N	Events	Percent events	Events per 1,000 patient-years (95% CI), unadjusted	P	Events per 1,000 patient-years (95% CI), age- & sex-adjusted	p
History of diabetic foot no	14,773	3,186	21.6	28.78 (27.80–29.80)	Ref.	12.50 (11.10–14.09)	Ref.
History of diabetic foot yes	883	416	47.1	76.83 (69.79–84.58)	<0.0001	25.51 (21.84–29.79)	<0.0001
Ulcer/gangrene no – Amputation no	15,100	3,324	22.0	29.47 (28.49–30.49)	Ref.	12.53 (11.12–14.12)	Ref.
Ulcer/gangrene yes – Amputation no	407	198	48.6	81.27 (70.70–93.42)	<0.0001	25.05 (20.87–30.07)	<0.0001
Ulcer/gangrene no – Amputation yes	33	16	48.5	77.46 (47.45–126.43)	0.013	32.48 (19.59–53.84)	0.014
Ulcer/gangrene yes – Amputation yes	116	64	55.2	94.01 (73.58–120.11)	<0.0001	36.89 (27.96–486.7)	<0.0001
Ulcer/gangrene/amput no – Revasc no	14,773	3,186	21.6	28.78 (2780–29.80)	Ref.	12.50 (11.10–14.09)	Ref.
Ulcer/gangrene/amput yes – Revasc no	433	203	46.9	76.23 (66.43–87.47)	<0.0001	26.31 (21.95–31.54)	<0.0001
Ulcer/gangrene/amput no – Revasc yes	327	138	42.2	66.01 (55.87–78.00)	<0.0001	21.74 (17.65–26.78)	<0.0001
Ulcer/gangrene/amput yes – Revasc yes	123	75	61.0	113.50 (90.51–142.33)	<0.0001	33.46 (25.80–43.39)	<0.0001

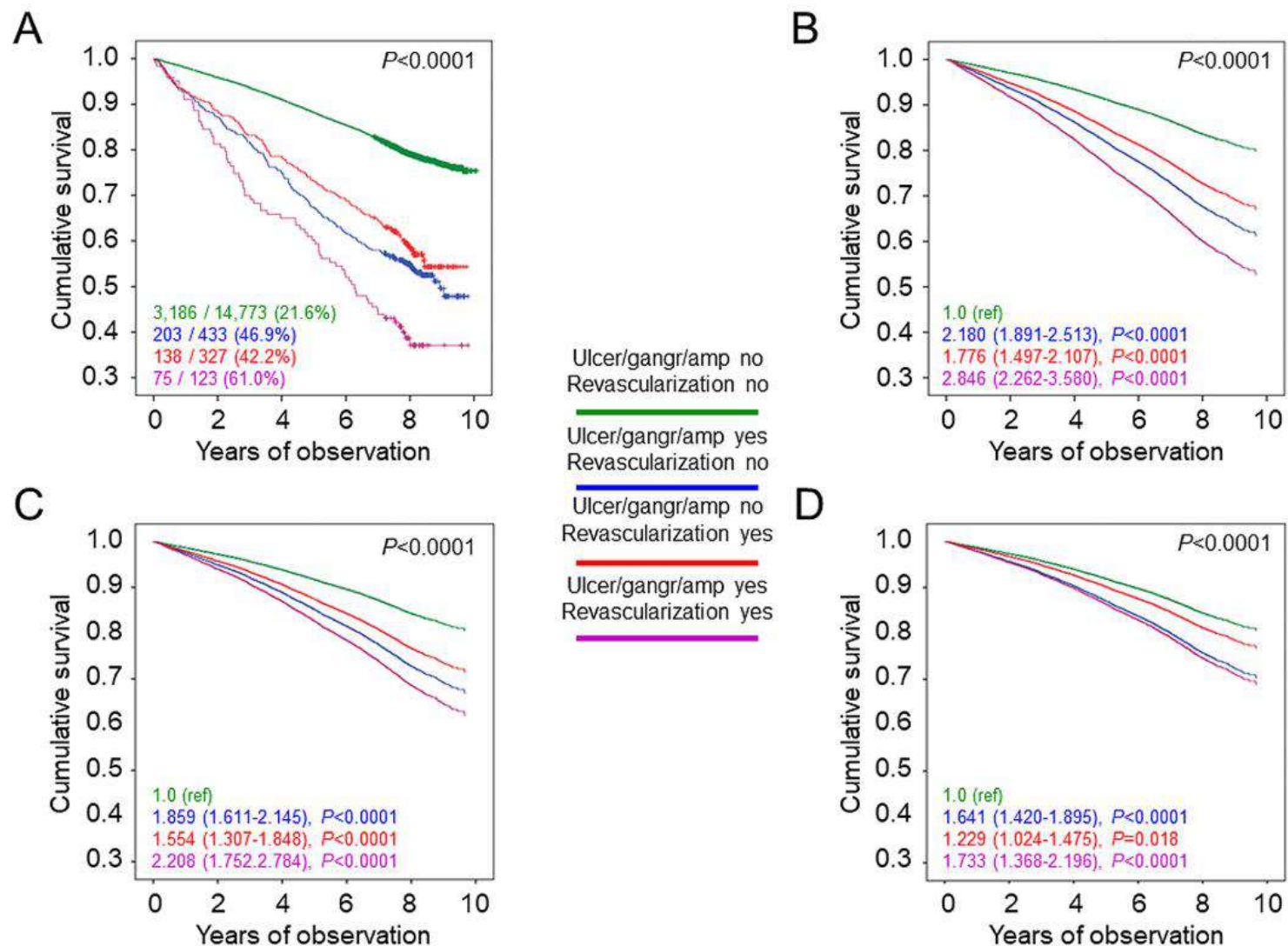
CI=confidence interval

Independent association of **history of diabetic foot** with all-cause mortality in patients with type 2 diabetes



Kaplan-Meier analysis (A) and Cox proportional hazards regression, adjusted for age and sex (B), plus cardiovascular risk factors (C), plus complications and comorbidities (D)

Independent association of **history of diabetic foot** with all-cause mortality in patients with type 2 diabetes



Kaplan-Meier analysis (A) and Cox proportional hazards regression, adjusted for age and sex (B), plus cardiovascular risk factors (C), plus complications and comorbidities (D)

RESEARCH

Open Access

Independent association of history of diabetic foot with all-cause mortality in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study



Martina Vitale¹, Emanuela Orsi², Anna Solini³, Monia Garofolo⁴, Veronica Resi², Enzo Bonora⁵, Cecilia Fondelli⁶, Roberto Trevisan⁷, Monica Vedovato⁸, Giuseppe Penno⁴ and Giuseppe Pugliese^{1*}

TAKE HOME MESSAGES - 1

- In patients with type 2 diabetes from the RIACE cohort, an **history of diabetic foot event**, including ulcer/gangrene, amputation, and lower limb revascularization, was associated with a **~ 50% increased risk** of subsequent death from any cause, **independent** of CVD risk factors, other complications and severe comorbidities
- The association with mortality was greatest for **amputation**
- The impact of **revascularization** alone was relatively modest

OXFORD



QJM: An International Journal of Medicine, 2024, **117(7)**, 495–502

<https://doi.org/10.1093/qjmed/hcae012>

Advance Access Publication Date: 10 January 2024

Original Article

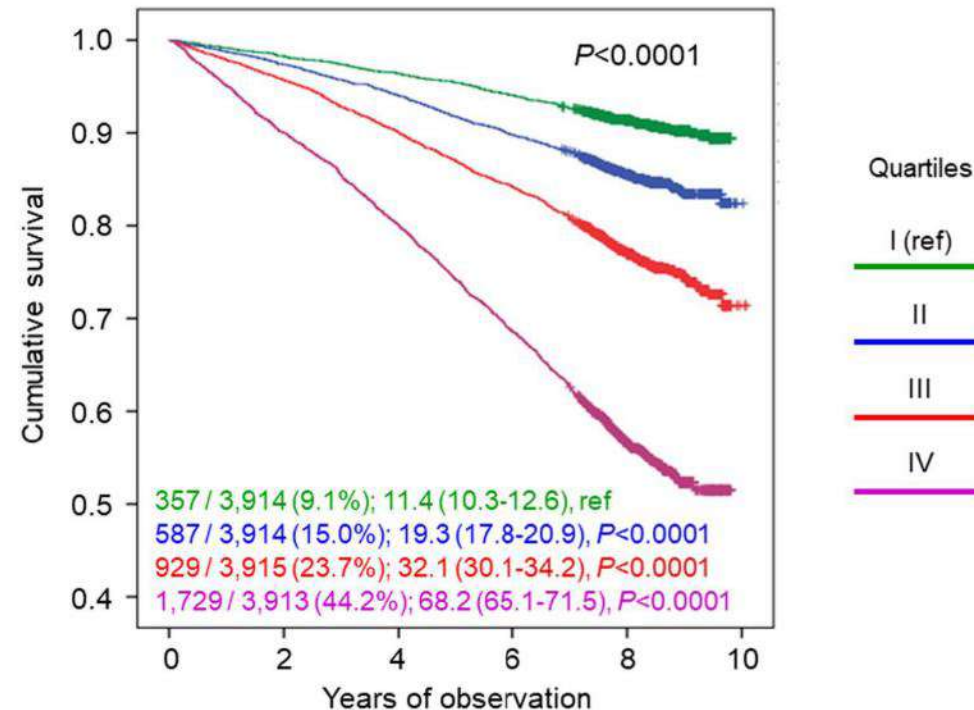
Independent association of estimated pulse-wave velocity with all-cause mortality in individuals with type 2 diabetes

A. Solini ¹, E. Orsi², M. Vitale³, M. Garofolo⁴, V. Resi², E. Bonora⁵, C. Fondelli⁶, R. Trevisan⁷, M. Vedovato⁸, A. Nicolucci⁹, G. Penno⁴ and G. Pugliese ^{3,*}, for the Renal Insufficiency And Cardiovascular Events (RIACE) Study Group[†]

Independent association of **estimated pulse-wave velocity** with all-cause mortality in individuals with type 2 diabetes

Table 1. Baseline clinical features of study participants by ePWV quartiles

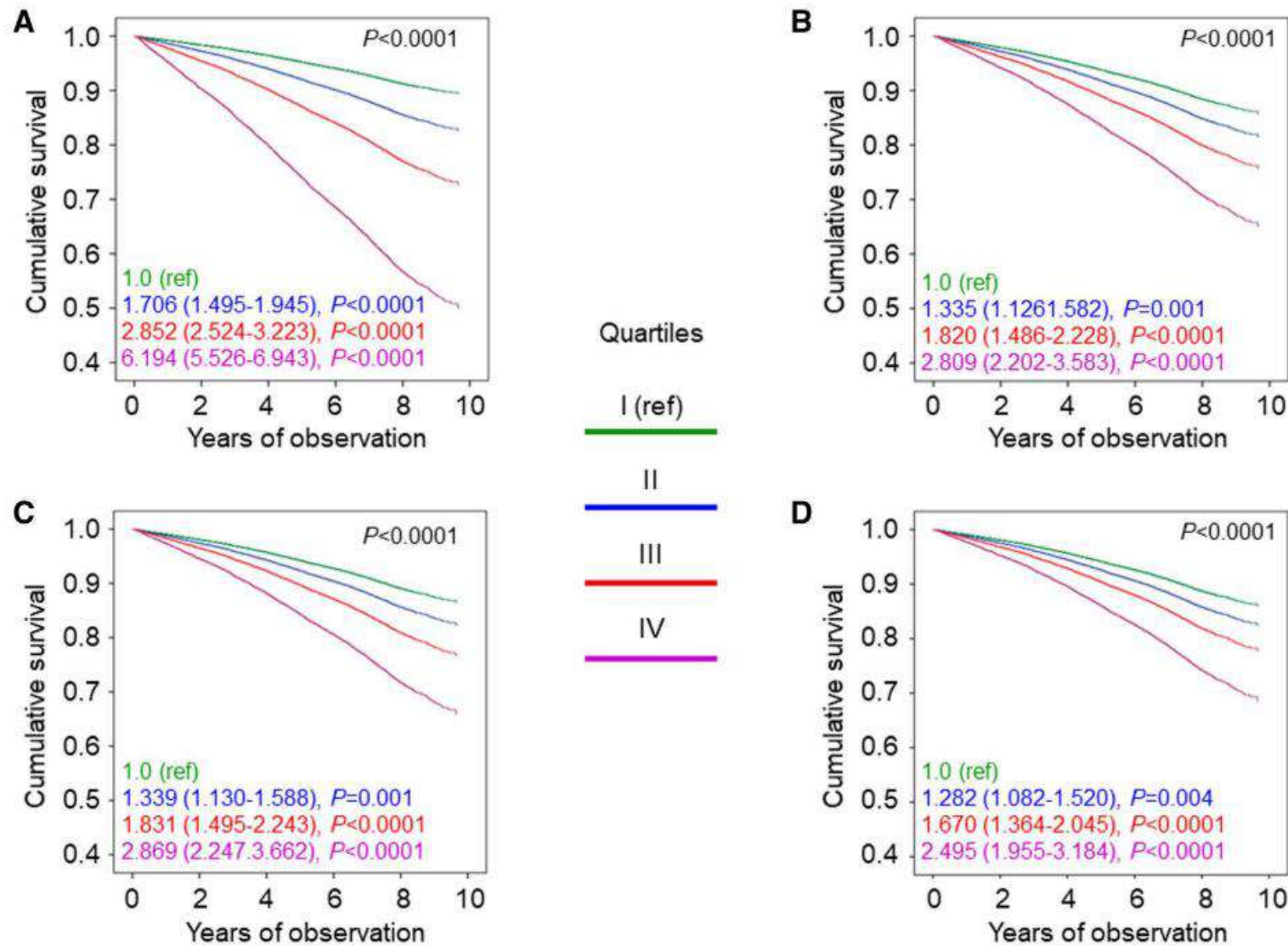
Variables	I	II	III	IV	P
N (%)	3914	3914	3915	3913	
ePWV, m·s ⁻¹ (range)	8.37 ± 0.81 (4.89–9.45)	10.12 ± 0.37 (9.46–10.74)	11.40 ± 0.40 (10.74–12.13)	13.33 ± 0.98 (12.13–19.74)	
Deaths, n (%)	357 (9.1)	587 (15.0)	929 (23.7)	1729 (44.2)	<0.0001



Kaplan–Meier analysis according to ePWV quartiles.

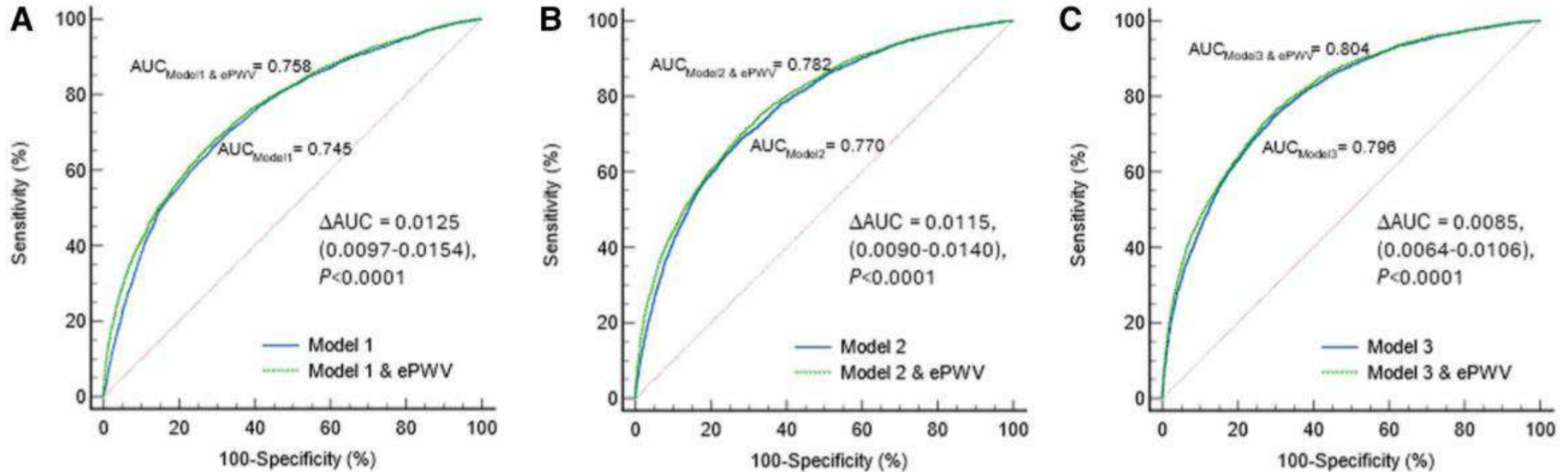
Number and percentage of deaths, death rates as events per 1000 patient-years (95% CI)

Independent association of **estimated pulse-wave velocity** with all-cause mortality in individuals with type 2 diabetes



Cox proportional hazards regression, unadjusted (A) adjusted for sex, age, BP (B), plus other CVD risk factors (C), plus complications and comorbidities (D)

Independent association of **estimated pulse-wave velocity** with all-cause mortality in individuals with type 2 diabetes



Marginal improvement provided by ePWV in the prediction of all-cause death over sex, age, BP (**A, Model 1**), plus other CVD risk factors (**B, Model 2**), plus complications and comorbidities (**C, Model 3**)



Independent association of estimated pulse-wave velocity with all-cause mortality in individuals with type 2 diabetes

A. Solini¹, E. Orsi², M. Vitale³, M. Garofolo⁴, V. Resi², E. Bonora⁵, C. Fondelli⁶, R. Trevisan⁷, M. Vedovato⁸, A. Nicolucci⁹, G. Penno⁴ and G. Pugliese^{3,*}, for the Renal Insufficiency And Cardiovascular Events (RIACE) Study Group[†]

TAKE HOME MESSAGES - 2

- This analysis of the RIACE cohort of individuals with type 2 diabetes shows that **ePWV** is **associated** with all-cause mortality **independently** of complications, comorbidities and traditional CVD risk factors
- ePWV improved **prediction** of mortality risk over CVD risk factors, complications and comorbidities, though the net difference was modest
- ePWV may represent a **simple and inexpensive tool** for risk stratification of diabetic patients and identification of those who deserve a more aggressive treatment

Acta Diabetologica

<https://doi.org/10.1007/s00592-024-02294-1>

ORIGINAL ARTICLE



Association between age at diagnosis and all-cause mortality in type 2 diabetes: the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study

Martina Vitale¹ · Emanuela Orsi² · Anna Solini³ · Monia Garofolo⁴ · Valeria Grancini² · Enzo Bonora⁵ · Cecilia Fondelli⁶ · Roberto Trevisan⁷ · Monica Vedovato⁸ · Giuseppe Penno⁴ · Antonio Nicolucci⁹ · Giuseppe Pugliese¹  · for the Renal Insufficiency And Cardiovascular Events (RIACE) Study Group*

Association between **age at diagnosis** and all-cause mortality in type 2 diabetes

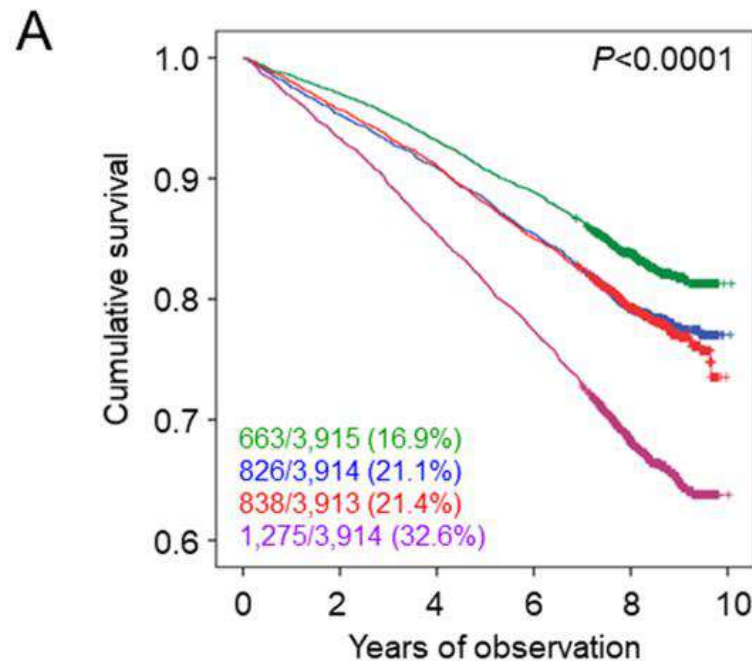
Table 1 Baseline clinical features of study participants by quartiles of age at type 2 diabetes diagnosis

Variables	I	II	III	IV	<i>P</i>
N (%)	3915	3914	3913	3914	
Age at type 2 diabetes diagnosis, years (range)	39.6±4.7 (20.5–45.9)	49.8±2.2 (45.9–53.5)	57.2±2.2 (53.5–61.2)	67.8±5.3 (61.2–93.5)	
Age, years	59.5±11.3	65.0±9.5	67.7±7.5	74.2±6.3	<0.0001
Diabetes duration, years	19.8±10.3	15.1±9.6	10.6±7.5	6.5±5.3	<0.0001

Association between **age at diagnosis** and all-cause mortality in type 2 diabetes

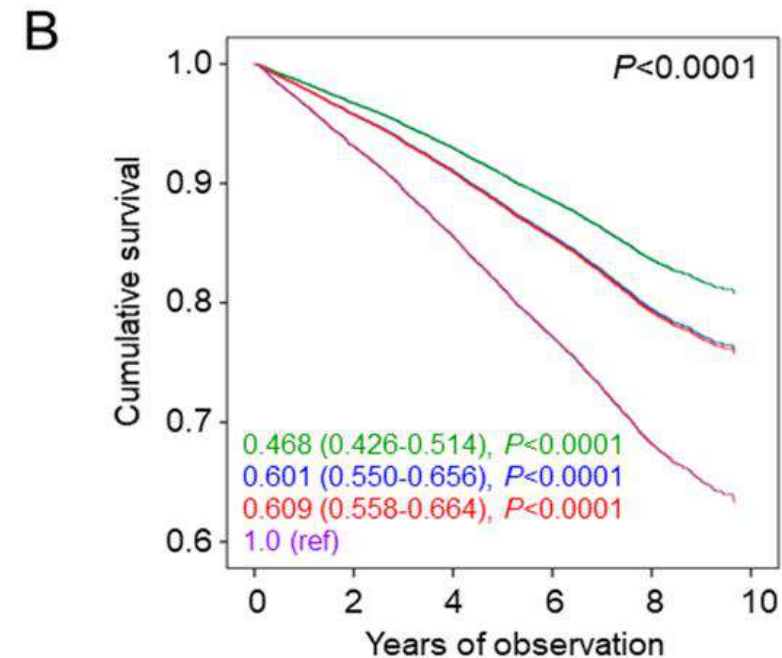
Table 3 Mortality rates in study participants by quartiles of age at type 2 diabetes diagnosis

Quartile	N	Events	Percent events	Events per 1,000 patient-years (95% CI), unadjusted	<i>P</i>
I	3,915	663	16.9	22.03 (20.41–23.77)	Ref
II	3,914	826	21.1	28.22 (26.36–30.21)	< 0.0001
III	3,913	838	21.4	28.57 (26.70–30.57)	< 0.0001
IV	3,914	1,275	32.6	46.54 (44.06–49.17)	< 0.0001



Quartiles

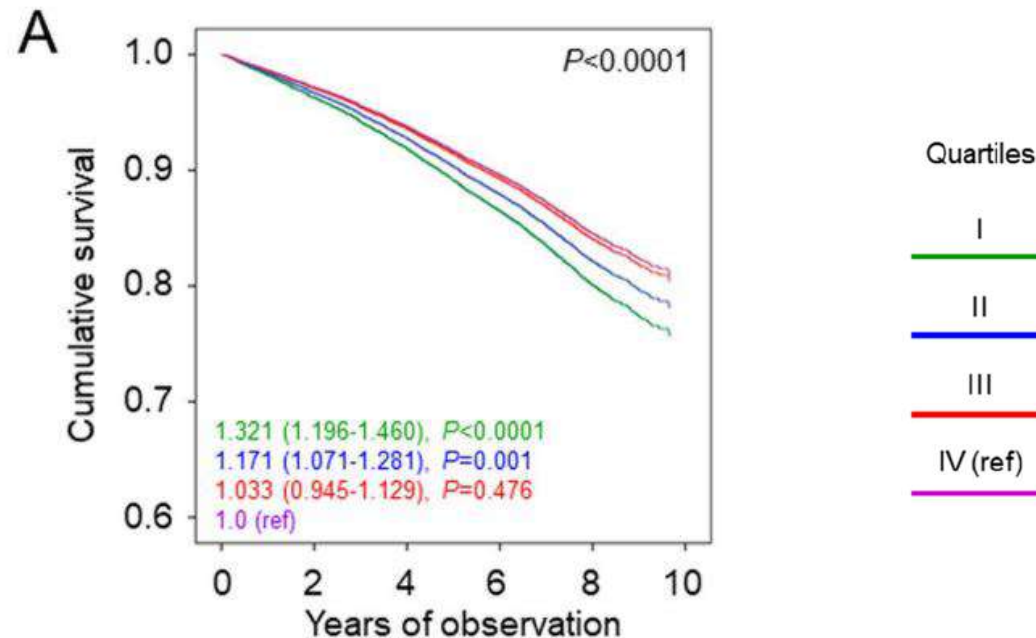
I
II
III
IV (ref)



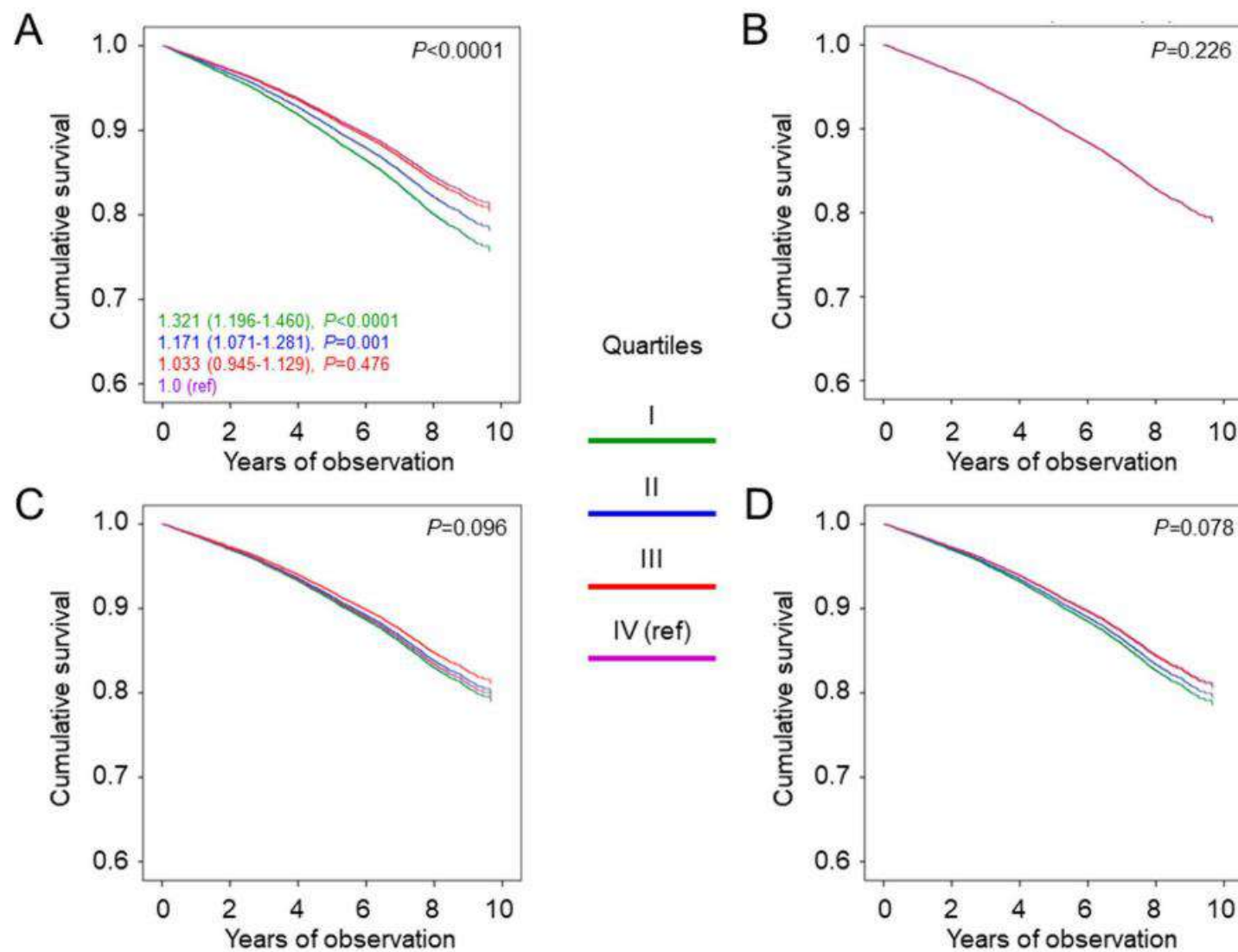
Association between **age at diagnosis** and all-cause mortality in type 2 diabetes

Table 3 Mortality rates in study participants by quartiles of age at type 2 diabetes diagnosis

Quartile	N	Events	Percent events	Events per 1,000 patient-years (95% CI), unadjusted	<i>P</i>	Events per 1,000 patient-years (95% CI), age- & sex-adjusted	<i>P</i>
I	3,915	663	16.9	22.03 (20.41–23.77)	Ref	14.98 (13.07–17.18)	Ref
II	3,914	826	21.1	28.22 (26.36–30.21)	<0.0001	13.28 (11.64–15.15)	0.023
III	3,913	838	21.4	28.57 (26.70–30.57)	<0.0001	11.74 (10.29–13.40)	<0.0001
IV	3,914	1,275	32.6	46.54 (44.06–49.17)	<0.0001	11.40 (9.99–13.00)	<0.0001



Association between age at diagnosis and all-cause mortality in type 2 diabetes



Cox proportional hazards regression, adjusted for sex, age (A), plus diabetes duration (B), plus other risk factors (C), plus complications and comorbidities (D)



Association between age at diagnosis and all-cause mortality in type 2 diabetes: the Renal Insufficiency and Cardiovascular Events (RIACE) Italian Multicenter Study

Martina Vitale¹ · Emanuela Orsi² · Anna Solini³ · Monia Garofolo⁴ · Valeria Grancini² · Enzo Bonora⁵ · Cecilia Fondelli⁶ · Roberto Trevisan⁷ · Monica Vedovato⁸ · Giuseppe Penno⁴ · Antonio Nicolucci⁹ · Giuseppe Pugliese¹  · for the Renal Insufficiency And Cardiovascular Events (RIACE) Study Group*

TAKE HOME MESSAGES - 3

- This analysis of the RIACE cohort showed that type 2 diabetes diagnosed in **early adulthood** was **associated with higher age- and sex-adjusted risk** of all-cause death than that occurring later in life
- However, **no difference** was observed when further **adjusting for diabetes duration** or complications/comorbidities
- These data point to the need for **public health policies and tailored guidelines** for **preventing and treating** early-onset type 2 diabetes to avoid premature morbidity and mortality from complications.

The RIACE Study Group



The RIACE Steering Committee

Coordinator: Giuseppe Pugliese

Secretary: Giuseppe Penno

Scientific committee: Anna Solini, Enzo Bonora, Emanuela Orsi, Roberto Trevisan, Luigi Laviola, Antonio Nicolucci

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3. Ospedale San Luigi Gonzaga, Orbassano: Franco Cavalot, Mariella Trovati, Leonardo Di Martino, and Fabio Mazzaglia.
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6. Ospedale San Paolo, Milano: Antonio Pontiroli, Annamaria Veronelli, and Barbara Zecchini.
7. Ospedale San Giuseppe, Milano: Maura Arosio, Laura Montefusco, and Guido Adda.
8. ASST - Ospedale Papa Giovanni XXIII, Bergamo: Roberto Trevisan, Anna Corsi, and Mascia Albizzi.
9. Ospedale Maggiore, Verona: Enzo Bonora, and Giacomo Zoppini.
10. Policlinico Universitario, Padova: Angelo Avogaro, and Monica Vedovato.
11. Ospedale Cisanello, Azienda Ospedaliero-Universitaria Pisana, Pisa: Giuseppe Penno, Laura Pucci, Daniela Lucchesi, Eleonora Russo, and Monia Garofolo.
12. Ospedale Santa Chiara, Azienda Ospedaliero-Universitaria Pisana, Pisa: Anna Solini.
13. Ospedale Le Scotte, Siena: Francesco Dotta, Cecilia Fondelli, and Laura Nigi.
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19. Policlinico Monserrato, Cagliari: Marco Giorgio Baroni, Giuseppina Frau, and Alessandra Boi.