European Journal of Internal Medicine xxx (xxxx) xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Relationship between degree of risk factor control and all-cause mortality in individuals with type 2 diabetes: A prospective cohort study

Monia Garofolo [a], Giuseppe Penno [a], Anna Solini [b], Emanuela Orsi [c], Martina Vitale [d], Veronica Resi [c], Enzo Bonora [e], Cecilia Fondelli [f], Roberto Trevisan [g], Monica Vedovato [h], Antonio Nicolucci [i], Giuseppe Pugliese [d,1,*], for the Renal Insufficiency And Cardiovascular Events (RIACE) Study Group [1]

[a] Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[b] Department of Surgical, Medical, Molecular and Critical Area Pathology, University of Pisa, Pisa, Italy
[c] Diabetes Unit, Fondazione IRCCS "Cà Granda - Ospedale Maggiore Policlinico", Milan, Italy
[d] Department of Clinical and Molecular Medicine, "La Sapienza" University, Rome, Italy
[e] Division of Endocrinology, Diabetes and Metabolism, University and Hospital Trust of Verona, Verona, Italy
[f] Diabetes Unit, University of Siena, Siena, Italy
[g] Endocrinology and Diabetes Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy
[h] Department of Clinical and Experimental Medicine, University of Padua, Padua, Italy
[i] Centre for Outcomes Research and Clinical Epidemiology (CORESEARCH), Pescara, Italy

ARTICLE INFO

Key words:
Type 2 diabetes
All-cause mortality
Treatment
Cardiovascular risk factors
Cardiovascular disease

ABSTRACT

Aims: To assess whether and to what extent excess risk of all-cause death is reduced in individuals with type 2 diabetes by achieving optimal control of traditional cardiovascular risk factors.
Methods: This observational, prospective, cohort study enrolled 15,773 Caucasian patients in 19 Italian centres in 2006–2008. Participants were stratified according to the number of the following risk factors outside target: haemoglobin A_{1c}, blood pressure, micro/macroalbuminuria, current smoking, LDL cholesterol, and triglycerides. All-cause mortality was retrieved for 15,656 patients (99.3 %) on 31 October 2015.
Results: Age-adjusted mortality rates and hazard ratios were significantly higher in the whole RIACE cohort (by ~20 %) and in patients with (by ~100 %) but not in those without prior cardiovascular disease (CVD), as compared with the coeval Italian general population. In all patients and in those without prior CVD, the relationship with mortality according to the number of risk factors outside target was J-shaped, an effect that was attenuated after either excluding "overtreated " patients, i.e., those with haemoglobin A_{1c} ≤6.0 % on anti-hyperglycaemic agents causing hypoglycaemia and/or systolic blood pressure ≤120 mmHg on anti-hypertensive agents, or adjusting for "overtreatment". Conversely, in patients with prior CVD, mortality remained higher than in the general population in all categories and increased progressively from +70 % to +314 %, without J-effect.
Conclusions: In patients with type 2 diabetes, optimal treatment of traditional cardiovascular risk factors completely eliminated the excess mortality risk versus the general population, provided that they were not "overtreated". However, this effect was observed only in participants without history of CVD.
Trial registration: ClinicalTrials.gov, NCT00715481, retrospectively registered 15 July 2008.

Abbreviations: BMI, body mass index; BP, blood pressure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CPRD, Clinical Practice Research Datalink; CVD, cardiovascular disease; DKD, diabetic kidney disease; DR, diabetic retinopathy; eGDR, estimated glucose disposal rate; GLP-1, glucagon-like peptide-1; HbA_{1c}, haemoglobin A_{1c}; HR, hazard ratio; RIACE, Renal Insufficiency And Cardiovascular Events; SGLT-2, sodium-glucose cotransporter-2; SNDR, Swedish National Diabetes Register.

* Corresponding author at: Department of Clinical and Molecular Medicine, "La Sapienza" University, Via di Grottarossa, 1035-1039 - 00189 Rome, Italy.
E-mail address: giuseppe.pugliese@uniroma1.it (G. Pugliese).

[1] See Supplementary Material for the list of RIACE Investigators.

https://doi.org/10.1016/j.ejim.2024.05.034
Received 9 December 2023; Received in revised form 28 April 2024; Accepted 29 May 2024

1. Introduction

Risk of death is approximately twice higher in people with diabetes than in those without, mainly though not exclusively due to an increased risk of cardiovascular disease (CVD) [1]. However, death rates, both absolute and relative to non-diabetic individuals, have decreased over time during the last decades [2-5], a phenomenon attributed to improved control of CVD risk factors including not only hyperglycaemia, but also dyslipidaemia and hypertension clustering with impaired glucose metabolism in the context of the metabolic syndrome, especially in people with type 2 diabetes [6]. Intensive glycaemic control was in fact shown to significantly reduce all-cause mortality in patients with type 2 diabetes from the United Kingdom Prospective Diabetes Study followed for further 10 years after trial completion [7]. Moreover, targeting multiple risk factors by lifestyle and pharmacological intervention was found to be successful in reducing mortality in patients with type 2 diabetes from the Steno-2 Study followed for additional 5.5 years post-trial [8].

These observations have prompted the concept of treat-to-target, i.e., treating patients for achieving pre-defined individualized targets for blood glucose and other CVD risk factors, as an effective approach for reducing morbidity and mortality from CVD and other causes in people with type 2 diabetes [9]. The results of cardiovascular and renal outcome trials showing that glucagon-like peptide-1 (GLP-1) receptor agonists [10] and sodium-glucose cotransporter-2 (SGLT-2) inhibitors [11] provide cardiorenal protection beyond their glucose-, but also blood pressure (BP)-, and body weight-lowering action, stimulated a paradigm shift from treat-to-target to treat-to-benefit [12], though these two concepts are not alternative, as achieving targets is also beneficial, regardless the class of drug used.

However, it is still unclear to what extent control of multiple CVD risk factors is able to reduce excess mortality risk in type 2 diabetes. A cohort study in individuals with type 2 diabetes from the Swedish National Diabetes Register (SNDR) and matched controls showed that mortality risk was only marginally increased in diabetic patients on-target for five risk factors versus controls (hazard ratio [HR] 1.06 (95 % confidence interval [CI] 1.00–1.12), whereas no difference was observed for acute myocardial infarction and stroke, but risk of hospitalization for heart failure was still 45 % higher [13]. More recently, a retrospective cohort study using data from the UK Clinical Practice Research Datalink (CPRD) GOLD showed that people with type 2 diabetes with optimal control of five CVD risk factors, partly different from those considered in the SNDR study, still had a 21 % higher risk of CVD events compared with controls [14].

This analysis of the large cohort of patients with type 2 diabetes from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study was aimed at assessing (a) whether and to what extent excess risk of all-cause death is reduced in these individuals by achieving optimal control of traditional CVD risk factors; and (b) whether risk factor control has differential effects in participants with and without prior CVD.

2. Methods

2.1. Design

The RIACE Italian Multicentre Study is an observational, prospective, cohort study on the impact of eGFR on morbidity and mortality in individuals with type 2 diabetes [15].

2.2. Patients

The RIACE study enrolled 15,933 Caucasian patients, consecutively attending 19 hospital-based, tertiary referral, outpatients diabetes clinics of the National Health Service throughout Italy in the years 2006–2008. Exclusion criteria were dialysis or renal transplantation. As 160 patients were excluded due to missing or implausible values, the study population consisted of the remaining 15,773 individuals.

2.3. Baseline data

Baseline data were collected using a standardized protocol across participating centres [15].

Participants underwent a structured interview to collect the following information: age at the time of the interview, smoking status, known diabetes duration, comorbidities, and current glucose-, lipid-, and BP-lowering treatments. Comorbidities included chronic obstructive pulmonary disease (COPD), chronic liver disease, and cancer.

Body mass index (BMI) was calculated from weight and height, whereas waist circumference was estimated from log-transformed BMI values, as previously reported [16]; BP was measured with a sphygmomanometer with the patients seated with the arm at the heart level.

Haemoglobin A_{1c} (HbA_{1c}) was measured by HPLC using DCCT-aligned methods, whereas estimated glucose disposal rate (eGDR), a surrogate measure of insulin resistance, was calculated using the following formula, which was validated against the euglycaemic-hyperinsulinaemic clamp technique also in individuals type 2 diabetes [17]: eGDR (mg kg^{-1}/min) = 21.158 - (0.09 x waist circumference) - (3.407 x hypertension) - (0.551 x HbA_{1c}), where waist circumference is in cm, hypertension is 0 (no) or 1 (yes), and HbA_{1c} is in%. Triglycerides and total and HDL cholesterol were determined in fasting blood samples by standard colorimetric enzymatic methods, whereas non-HDL cholesterol was calculated by subtracting HDL cholesterol to total cholesterol and LDL cholesterol concentration was estimated using the Friedewald formula. As this formula is not applicable for triglyceride levels above 4.52 mmol/L, LDL cholesterol was calculable only in 15,386 participants.

The presence of diabetic kidney disease (DKD) was assessed by measuring albuminuria and serum creatinine, as previously reported [15,18]. Albumin excretion rate was obtained from 24-hour urine collections or calculated from albumin-to-creatinine ratio in early-morning, first-voided urine samples; albumin concentration in urines was measured by immunonephelometry or immunoturbidimetry, in the absence of interfering clinical conditions. Serum (and urine) creatinine was measured by the modified Jaffe method, traceable to IDMS, and eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. Patients were then assigned to one of the following DKD phenotypes [19]: no DKD, albuminuria alone (albuminuric DKD with preserved eGFR), reduced eGFR alone (non-albuminuric DKD), or both albuminuria and reduced eGFR (albuminuric DKD with reduced eGFR).

The presence of diabetic retinopathy (DR) was assessed in each centre by an expert ophthalmologist by dilated fundoscopy, as previously detailed [20]. On the basis of the actual fundus appearance or the retinal disease condition that had eventually required previous photocoagulation or surgical treatment, patients were graded according to the Global Diabetic Retinopathy Project Group and then stratified into the following categories: no DR, non-advanced DR (mild or moderate non-proliferative DR) and advanced DR (severe non-proliferative DR, proliferative DR, or maculopathy).

Previous major acute CVD events, including myocardial infarction; stroke; foot ulcer/gangrene/amputation; and coronary, carotid, and lower limb revascularization, were adjudicated based on hospital discharge records by an *ad hoc* committee in each centre [21].

2.4. All-cause mortality

The vital status of study participants on 31 October 2015 was verified by interrogating the Italian Health Card database (http://sistemats1.sanita.finanze.it/wps/portal/), which provides updated and reliable information on all current Italian residents [22].

2.5. Categorization of patients

Patients were categorized according to the number of risk factors not on-target (from none to six) including those considered by Rawshani et al., i.e., HbA_{1c} ≥7.0 % (≥53 mmol/mol), systolic BP ≥140 mmHg and/or diastolic BP ≥80 mmHg, microalbuminuria or macroalbuminuria, current smoking, and LDL cholesterol ≥2.5 mmol/L (≥97 mg/dL) [13] plus triglycerides >1.7 mmol/L (>150 mg/dL), as in Wright et al. [14] (Supplementary Table 1). Patients with prior CVD were categorized also according to an LDL cholesterol target of 1.8 mmol/L (69.4 mg/dL), consistent with the higher CVD risk in these individuals versus those without prior CVD.

Then, patients were categorized as described above after stratification by prior CVD and after exclusion of "overtreated" patients, i.e., those with an HbA_{1c} ≤6.0 % on anti-hyperglycaemic agents causing hypoglycaemia (insulin and/or secretagogues) and/or a systolic BP ≤120 mmHg on anti-hypertensive agents, according to guidelines for the management of hyperglycaemia and hypertension [10,23] (Supplementary Table 1).

2.6. Statistical analysis

Data are expressed as mean±SD or median (interquartile range) for continuous variables, and number of cases and percentage for categorical variables. Comparisons among categories of risk factor control were performed by one-way ANOVA for continuous variables and Pearson's χ^2 test for categorical variables.

Crude mortality rates were described as events per 1000 patient-years, with 95 % exact Poisson CIs and adjusted for age by a Poisson regression model. Mortality among patients with type 2 diabetes from the RIACE cohort was then compared to that of coeval male and female individuals from the Italian general population, as derived from the Italian National Institute of Statistics (ISTAT) life tables during the same time period (2006–2015) [24]. Kaplan-Meier survival probabilities for all-cause mortality were estimated according to categories of risk factor control and differences were analysed using the log-rank statistic. The HRs and their 95 % CIs were estimated by Cox proportional hazards regression and adjusted for age, using data from the general population as reference. Then, the analyses were repeated using category 1 (i.e., patients with one risk factor outside range) as reference and were unadjusted (model 1) or sequentially adjusted for age and sex (Model 2), plus diabetes duration, BMI, HDL cholesterol, lipid-lowering and anti-hypertensive treatment, DR grade, eGFR categories, any CVD, COPD, chronic liver disease, and cancer (Model 3), and plus treatment with anti-hyperglycaemic agents causing hypoglycaemia (yes/no) (Model 4) or "overtreatment" as defined above (yes/no) (Model 5). Finally, the HRs and 95 % CIs were calculated for 0.5 % HbA_{1c} and 10 mmHg systolic BP categories using the 6.1–6–5 % and the 111–120 mmHg categories as reference and adjusted for treatment with anti-hyperglycaemic agents causing hypoglycaemia (yes/no) and anti-hypertensive drugs (yes/no), respectively.

Additional Cox proportional hazards regression analyses were run to assess the individual impact of each risk factor outside target on mortality risk, unadjusted (Model 1) and adjusted as in Models 3 and 5.

All p values were two-sided, and a $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA).

3. Results

Valid information on vital status was retrieved for 15,656 participants (99.3 % of the cohort). At the time of the census, 3602 (23.0 %) individuals had died; death rate was 31.0 per 1000 person-years (95 % CI 30.0–32.0) over a follow-up of 7.4 ± 2.1 years [19,24].

The distribution and clinical features of the RIACE participants by categories of risk factor control are shown in Table 1. Only a few patients fell in category 0 (i.e., patients with all risk factors on-target; $n = 354$, 2.3 %) and particularly in category 6 (i.e., patients with all risk factors outside target; $n = 90$, 0.6 %), whereas the majority of participants were included in category 2 (i.e., patients with two risk factors outside target; $n = 4429$, 28.8 %) or 3 (i.e., patients with three risk factors outside target; $n = 4857$, 31.6 %). Diabetes duration, BMI, and prevalence of complications (except CVD showing a J-shaped trend) increased, whereas age and eGDR decreased from category 0 to category 6.

Kaplan-Meier estimates, percent deaths, and age-adjusted mortality rates were significantly higher in the whole RIACE cohort and in patients with prior CVD, but not in those without, as compared with the coeval Italian general population (Table 2). Likewise, the age-adjusted HRs were 20 % higher in the whole RIACE cohort and twice higher in patients with prior CVD, as compared with the general population, with no difference between patients without prior CVD and controls (Table 3). In the whole RIACE cohort and in patients without prior CVD, age-adjusted death rates (Table 2) and HRs (Table 3) were not different from those of the general population when one or two and one-to-three risk factors were outside target, respectively, whereas they increased progressively for further increases in the number of risk factors outside target. Moreover, a J-shaped trend was observed, with patients on-target for all risk factors (category 0) showing higher percent deaths and age-adjusted death rates than those with only one risk factor outside range (category 1), with differences that were not significant for death rates (Table 2) and were significant only in the whole cohort for HRs (Table 3). The J-shaped trend in age-adjusted death rates (Table 4) and HRs (Table 5) was attenuated and/or differences between category 0 and category 1 became non-significant after excluding "overtreated" patients. The J-shaped relationship between HbA_{1c} or systolic BP and mortality is shown in Supplementary Figure 1. Conversely, in patients with prior CVD, the relationships of age-adjusted death rates (Table 2) and HRs (Table 3) with categories of risk factor control were linear, with no J-effect. Values were higher than in the general population in all categories of risk factor control. The HRs were only slightly lower when using a more stringent LDL cholesterol target, though the number of participants falling in category 0 was very small (not shown).

The Cox proportional hazards regression analyses using category 1 as reference confirmed the progressive increase in the unadjusted HRs for mortality according to the category of risk factor control, with a higher mortality risk in category 0 that was again observed only in the whole cohort and in patients without prior CVD (Model 1) (Table 6). Differences between category 0 and 1 remained significant only in patients without prior CVD when adjusting for age and sex (Model 2) and further adjusting for multiple confounders (Model 3), but not when including treatment with anti-hyperglycaemic agents causing hypoglycaemia (Model 4) or "overtreatment" (Model 5) as covariates (Table 6).

When assessing the individual impact of each risk factor outside target (Supplementary Table 2), microalbuminuria or macroalbuminuria and HbA_{1c} ≥7.0 %, were significantly associated with mortality in both the unadjusted and adjusted analyses, and this was the case in the whole cohort as well as in patients with or without prior CVD. In the whole cohort and in patients without prior CVD, current smoking was negatively associated with mortality in the unadjusted analysis, but the relationship became positive when adjusting for confounding and particularly age, as smokers were much younger than non-smokers. Moreover, systolic BP ≥140 mmHg and/or diastolic BP ≥80 mmHg were not associated with death in the unadjusted and negatively associated with death in the adjusted analyses; LDL cholesterol ≥2.5 mmol/L (≥97 mg/dL) was inversely associated with mortality in both the unadjusted and adjusted analyses; and triglycerides >1.7 mmol/L (>150 mg/dL) were not associated with mortality in both the unadjusted and adjusted analyses.

4. Discussion

This analysis of patients with type 2 diabetes from the RIACE cohort

Table 1
Baseline clinical features of the RIACE participants stratified according to the number of CVD risk factors outside target.

	Number of CVD risk factors outside target							*P*
	0	1	2	3	4	5	6	
N (%)	354 (2.3)	2087 (13.6)	4429 (28.8)	4857 (31.6)	2726 (17.7)	843 (5.5)	90 (0.6)	
Age, years	67.06±10.65	66.26±10.15	66.64±10.15	67.14±10.34	66.78±10.45	65.08±10.43	62.19±10.27	<0.0001
Sex, n (%)								<0.0001
Female	140 (39.5)	887 (42.5)	1995 (45.0)	2163 (44.5)	1141 (41.9)	316 (37.5)	23 (25.6)	
Male	214 (60.5)	1200 (57.5)	2434 (55.0)	2694 (55.5)	1585 (58.1)	527 (62.5)	67 (74.4)	
Smoking status, n (%)								<0.0001
Never	239 (67.5)	1371 (65.7)	2752 (62.1)	2796 (57.6)	1287 (47.2)	276 (32.7)	0 (0)	
Former	115 (32.5)	651 (31.2)	1368 (30.9)	1362 (28.0)	669 (24.5)	163 (19.3)	0 (0)	
Current	0 (0)	65 (3.1)	309 (7.0)	699 (14.4)	770 (28.2)	404 (47.9)	90 (100)	
Diabetes Duration, years	11.14±8.89	11.62±10.06	12.49±10.13	13.83±10.24	14.39±10.20	14.32±10.05	13.20±8.98	<0.0001
HbA_{1c},%	6.20±0.55	6.69±1.11	7.12±1.30	7.76±1.42	8.21±1.49	8.68±1.66	8.91±1.50	<0.0001
(mmol/mol)	(44.2 ± 6.)0	(49.6 ± 12.2)	(54.4 ± 14.2)	(61.3 ± 15.5)	(66.2 ± 16.3)	(71.3 ± 18.2)	(73.9 ± 16.4)	
eGDR, mg kg^{-1}/min	6.50±2.02	5.90±1.94	5.31±1.81	4.69±1.76	4.25±1.71	3.77±1.68	3.69±1.67	<0.0001
BMI, kg/m^2	27.39±4.97	28.00±4.98	28.52±5.02	29.14±5.16	29.70±5.18	30.47±5.38	30.37±5.96	<0.0001
Waist circumference, cm	99.3 ± 10.1	100.5 ± 10.0	101.5 ± 10.1	102.8 ± 10.5	104.0 ± 10.4	105.7 ± 10.9	105.9 ± 12.4	<0.0001
Triglycerides, mmol/L	0.98	1.07	1.15	1.35	1.82	2.13	2.12	<0.0001
	(0.77–1.30)	(0.82–1.36-)	(0.88–1.49)	(1.00–1.86)	(1.28–2.33)	(1.81–2.59)	(1.93–2.59)	
Total cholesterol, mmol/L	3.79±0.57	4.17±0.81	4.56±0.90	4.87±0.90	5.20±0.96	5.44±0.90	5.65±0.88	<0.0001
HDL-cholesterol, mmol/L	1.35±0.38	1.36±0.39	1.34±0.36	1.29±0.34	1.22±0.31	1.16±0.28	1.09±0.28	<0.0001
Non-HDL cholesterol, mmol/L	2.44±0.43	2.81±0.73	3.22±0.81	3.59±0.82	3.99±0.90	4.28±0.83	4.57±0.85	<0.0001
LDL cholesterol, mmol/L	1.97±0.40	2.29±0.70	2.65±0.80	2.89±0.80	3.12±0.85	3.26±0.77	3.49±0.78	<0.0001
Dyslipidaemia, n (%)	192 (54.2)	1365 (65.4)	3458 (78.1)	4187 (86.2)	2503 (91.8)	794 (94.2)	87 (96.7)	<0.0001
Systolic BP, mmHg	120.7 ± 10.1	130.1 ± 16.4	136.6 ± 17.6	140.2 ± 17.7	142.7 ± 17.8	144.7 ± 16.7	144.8 ± 16.4	<0.0001
Diastolic BP, mmHg	68.4 ± 5.8	74.4 ± 9.2	78.1 ± 9.2	80.0 ± 9.0	81.1 ± 8.9	82.3 ± 8.7	83.6 ± 8.4	<0.0001
Pulse pressure, mmHg	52.31±10.18	55.78±13.72	58.50±15.39	60.20±16.05	61.55±16.48	62.45±16.35	61.21±16.67	<0.0001
Hypertension, n (%)	239 (67.5)	1549 (74.2)	3619 (81.7)	4186 (86.2)	2423 (88.9)	764 (90.6)	80 (88.9)	<0.0001
Anti-hyperglycaemic treatment, n (%)								
Lifestyle	74 (20.9)	376 (18.0)	735 (16.6)	584 (12.0)	237 (8.7)	57 (6.8)	4 (4.4)	<0.0001
Non-insulin	210 (59.3)	1313 (62.9)	2765 (62.4)	3015 (62.1)	1649 (60.5)	484 (57.4)	50 (55.6)	
Insulin	70 (19.8)	398 (19.1)	929 (21.0)	1258 (25.9)	840 (30.8)	302 (35.8)	36 (40.0)	<0.0001
Anti-hypertensive treatment, n (%)	239 (67.5)	1393 (66.7)	3069 (69.3)	3458 (71.2)	2009 (73.7)	638 (75.7)	66 (73.3)	<0.0001
Lipid-lowering treatment, n (%)	192 (54.2)	1050 (50.3)	2043 (46.1)	2121 (43.7)	1208 (44.3)	408 (48.4)	39 (43.3)	<0.0001
AER, mg/24h	8.12	9.00	10.80	13.59	31.20	66.96	97.50	<0.0001
	(4.59–14.10)	(4.67–15.98)	(5.70–18.63)	(6.91–31.40)	(11.00–83.47)	(34.29–185.96)	(50.07–350.31)	
eGFR, mL/min/1.73 m^2	81.60±19.27	83.42±18.72	81.60±19.55	79.78±20.58	77.55±22.67	76.88±25.26	82.57±26.01	<0.0001
DKD phenotypes, n (%)								<0.0001
$Alb^-/eGFR^-$	304 (85.9)	1775 (85.1)	3405 (76.9)	3121 (64.3)	1117 (41.0)	148 (17.6)	0 (0.0)	
$Alb^+/eGFR^-$	0 (0)	62 (3.0)	387 (8.7)	884 (18.2)	994 (36.5)	477 (56.6)	72 (80.0)	
$Alb^-/eGFR^+$	50 (14.1)	218 (10.4)	483 (10.9)	488 (10.0)	204 (7.5)	11 (1.3)	0 (0.0)	
$Alb^+/eGFR^+$	0 (0)	32 (1.5)	154 (3.5)	364 (7.5)	411 (15.1)	207 (24.6)	18 (20.0)	
DR, n (%)								<0.0001
No	300 (84.7)	1760 (84.3)	3581 (80.9)	3722 (76.6)	1982 (72.7)	580 (68.8)	64 (71.1)	
Non-advanced	34 (9.6)	196 (9.4)	501 (11.3)	631 (13.0)	411 (15.1)	131 (15.5)	17 (18.9)	
Advanced,	20 (5.6)	131 (6.3)	347 (7.8)	504 (10.4)	333 (12.2)	132 (15.7)	9 (10.0)	
CVD, n (%)								
Any	94 (26.6)	481 (23.0)	965 (21.8)	1096 (22.6)	680 (24.9)	202 (24.0)	27 (30.0)	0.017
Myocardial infarction	52 (14.7)	265 (12.7)	483 (10.9)	533 (11.0)	289 (10.6)	69 (8.2)	13 (14.4)	0.004
Coronary revascularization	56 (15.8)	252 (12.1)	442 (10.0)	444 (9.1)	261 (9.6)	85 (10.1)	13 (14.4)	<0.0001
Any coronary event	75 (21.2)	357 (17.1)	659 (14.9)	720 (14.8)	408 (15.0)	112 (13.3)	18 (20.0)	0.002
Stroke	75 (21.2)	357 (17.1)	659 (14.9)	720 (14.8)	408 (15.0)	112 (13.3)	18 (20.0)	0.002
Carotid revascularization	14 (4.0)	61 (2.9)	138 (3.1)	151 (3.1)	98 (3.6)	29 (3.4)	8 (8.9)	0.060
Any cerebrovascular event	15 (4.2)	76 (3.6)	216 (4.9)	261 (5.4)	205 (7.5)	58 (6.9)	11 (12.2)	<0.0001
Ulcer/gangrene/amputation	27 (7.6)	130 (6.2)	332 (7.5)	389 (8.0)	288 (10.6)	83 (9.8)	17 (18.9)	<0.0001
Lower limb revascularization	8 (2.3)	47 (2.3)	124 (2.8)	162 (3.3)	124 (4.5)	48 (5.7)	3 (3.3)	<0.0001
Any peripheral event)	12 (3.4)	85 /4.1)	220 (5.0)	271 (5.6)	200 (7.3)	71 (8.4)	11 (12–2)	<0.0001
Comorbidities, n (%)								
Any	71 (20.1)	442 (21.2)	750 (16.9)	811 (16.7)	495 (18.2)	148 (17.6)	19 (21.1)	<0.0001
COPD	15 (4.2)	100 (4.8)	173 (3.9)	196 (4.0)	140 (5.1)	32 (3.8)	6 (6–7)	0.121
Chronic liver disease	42 (11.9)	221 (10.6)	371 (8.4)	387 (8.0)	237 (8.7)	67 (7.9)	10 (11.1)	0.004
Cancer	23 (6.5)	164 (7.9)	281 (6.3)	304 (6.3)	175 (6.4)	59 (7.0)	6 (6.7)	0.310
Follow-up, years	7.39±2.15	7.56±2.00	7.51±1.98	7.41±2.03	7.24±2.16	7.15±2.26	7.35±2.03	<0.0001

Data are expressed as mean (SD) or median (interquartile range; IQR) for continuous variables, and number of cases (percentage) for categorical variables.
RIACE = Renal Insufficiency And Cardiovascular Events; CVD = cardiovascular disease; HbA_{1c} = haemoglobin A_{1c}; eGDR = estimated glucose disposal rate; BMI = body mass index; BP = blood pressure; AER = albumin excretion rate; eGFR = estimated glomerular filtration rate; $Alb^-/eGFR^-$ = no DKD, $Alb^+/eGFR^-$ = albuminuric DKD with preserved eGFR; $Alb^-/eGFR^+$ = non-albuminuric DKD; $Alb^+/eGFR^+$ = albuminuric DKD with reduced eGFR; DR = diabetic retinopathy; COPD = chronic obstructive pulmonary disease.

Table 2
Number and percentage of deaths, survival analysis by Kaplan-Meier, and age-adjusted death rates according to number of CVD risk factors outside target in the whole RIACE cohort versus the coeval Italian general population and in the RIACE participants without and with prior CVD.

	Deaths n/total (%)	Death rate, x1000 patients/year (95 % CI)		
		General population (n = 3625,975) vs RIACE cohort (n = 15,386)	RIACE participants without prior CVD (n = 11,841)	RIACE participants with prior CVD (n = 3545)
General population	711,903/3625,975 (19.64)	19.64 (19.59–19.69)	–	–
RIACE cohort	3542/15,386 (23.0)	23.47 (22.50–24.47)	19.27 (18.30–20.30)	39.55 (36–78–42.53)
Number of CVD risk factors outside target				
No risk factor	91/354 (25.7)	25.34 (20.59–31.17) *	23.25 (17.94–30.12) *	33.37 (23.62–47.15)
1 risk factor	415/2087 (19.9)	20.72 (18.77–22.88)	17.14 (15.12–19.43)	33.77 (28.72–39.72)
2 risk factors	905/4429 (20.4)	20.77 (19.37–22.27 (19.37–22.27)	17.35 (15.91–18.92)	34.64 (30.76–39.01)
3 risk factors	1113/4857 (22.9)	22.18 (20.77–23.68)	18.07 (16.65–19.61)	38.75 (34.74–43.22)
4 risk factors	724/2726 (26.6)	27.27 (25.23–29.47) **	21.65 (19.59–23.94) **	47.14 (41.62–53.41) *
5 risk factors	264/843 (31.3)	38.21 (33.81–43.19) ***	32.75 (28.10–38.16) ***	58.16 (47.41–71.34) **
6 risk factors	30/90 (33.3)	49.50 (34.60–70.81) ****	35.82 (21.21–60.48)	81.38 (49.79–133.01 ***
	Kaplan-Meier	Pairwise comparisons		
	Log Rank = 86.60	* $p < 0.0001$ vs 5; $p = 0.01$ vs 6	* $p < 0.02$ vs 5	* $p < 0.05$ vs 0, 3; $p \leq 0.001$ vs 1, 2
	($p < 0.0001$)	** $p < 0.0001$ vs 1–3, 5; $p < 0.05$ vs 6	** $p \leq 0.004$ vs 1–3; $p < 0.0001$ vs 5	** $p < 0.005$ vs 0, 3; $p < 0.0001$ vs 1, 2
		*** $p < 0.0001$ vs 0–4	*** $p < 0.02$ vs 0; $p < 0.0001$ vs 1–4	*** $p < 0.05$ vs 0–3
		**** $p < 0.02$ vs 1, 4; $p \leq 0.003$ vs 1–3		

CVD = cardiovascular disease; RIACE = Renal Insufficiency And Cardiovascular Events; CI = confidence interval.

Table 3
Survival analysis by Cox proportional hazard regression, adjusted for age, according to number of CVD risk factors outside target in the whole RIACE cohort versus the coeval Italian general population and in the RIACE participants without and with prior CVD. HRs (95 % CI) for mortality are shown.

	Whole RIACE cohort (n = 15,386)	RIACE participants without prior CVD (n = 11,841)	RIACE participants with prior CVD (n = 3545)
General population	Ref.	Ref.	Ref.
RIACE cohort	1.20 (1.16–1.23)	0.98 (0.94–1.02)	2.01 (1.93–2.10)
Number of CVD risk factors outside target			
No risk factor	1.29 (1.08–1.53)	1.18 (0.94–1.49)	1.72 (1.30–2.24)
1 risk factor	1.06 (0.97–1.15)	0.87 (0.78–0.98)	1.72 (1.51–1.95)
2 risk factors	1.06 (1.00–1.12)	0.88 (0.82–0.95)	1.76 (1.61–1.93)
3 risk factors	1.13 (1.07–1.20)	0.92 (0.86–0.98)	1.97 (1.83–2.13)
4 risk factors	1.39 (1.30–1.48)	1.10 (1.01–1.20)	2.40 (2.21–2.61)
5 risk factors	1.95 (1.76–2.15)	1.67 (1.46–1.90)	2.96 (2.56–3.42)
6 risk factors	2.52 (1.88–3.38)	1.82 (1.15–2.90)	4.14 (3.03–5.67)

CVD = cardiovascular disease; RIACE = Renal Insufficiency And Cardiovascular Events; HR = hazard ratio; CI = confidence interval.

showed that optimal treatment of six traditional CVD risk factors was effective in completely eliminating the excess risk of all-cause death versus the general population. However, this was observed in patients with one or two risk factors outside target, but not in those with all risk factors on-target, who showed higher mortality rates and HRs than controls, though such differences became non-significant after excluding "overtreated" patients or adjusting for "overtreatment". More importantly, the extent of reduction of excess risk of death with optimal risk factor control differed according to the history of CVD. In fact, in participants without prior CVD, risk of death was only 20 % higher than in controls and having only half of the risk factors (i.e., three out of six) on-target was sufficient for having a mortality risk similar to that of the general population, a finding that was again not observed if all risk factors were on-target. Conversely, in patients with prior CVD, risk of death was twice higher than in controls, increased linearly according to the number of risk factors outside target with no J-effect, and treating risk factors to target was not effective in eliminating the excess risk versus the general population, even when excluding "overtreated" patients or adjusting for "overtreatment". Finally, of the six risk factors considered, microalbuminuria or macroalbuminuria, HbA_{1c} ≥7.0 %, and current smoking appeared to have the greatest impact on mortality.

The finding that optimal treatment of traditional risk factors in patients with type 2 diabetes was effective in matching mortality risk of these individuals to that of the general population is consistent with previous findings from the SNDR showing only a 6 % and 9 % increased risk of death in diabetic with no or only one of five risk factors outside target, respectively, versus non-diabetic people [13]. It also consistent with the SNDR data on myocardial infarction and stroke, showing that risk of these two major causes of CVD death in patients with type 2 diabetes was not different in those with optimal risk factor control compared with non-diabetic controls, though risk of heart failure remained markedly higher [13]. The minimal differences between our results and those of Rawshani et al. might depend on differences in the control group, which consisted of non-diabetic individuals for comparison with the SNDR cohort and the coeval general population for comparison with the RIACE cohort. Therefore, our control group included also patients with type 2 diabetes, who were ~4 % of the Italian general population at the time the study started, though percentage was higher among individuals in the same age range as the RIACE participants. This may have attenuated differences between the diabetic and control groups in our study, in addition to the effect of risk factor control. Conversely, our data seems at odds with those from the CPRD showing that treating five risk factors to target reduced, but did not eliminate the excess risk of individuals with type 2 diabetes, which remained 21 % higher than in controls, though these data refer to CVD events, not to all-cause mortality [14]. It is important to highlight the fact that, when our study as well as those of Rawshani et al. and Wright et al. were started, only a few therapeutic options were available (i.e., insulin, sulfonylureas, glinides, metformin, glitazones, and acarbose), whereas GLP-1 receptor agonists and SGLT-2 inhibitors were introduced only later and the percentages of patients on these cardio-nephroprotective drugs at the end of the follow-up periods were negligible. This allowed us to rule out an effect of treatment beyond glycaemia and other

Table 4
Number and percentage of deaths, survival analysis by Kaplan-Meier, and age-adjusted death rates according to number of CVD risk factors outside target in the whole RIACE cohort versus the coeval Italian general population and in the RIACE participants without and with prior CVD, after excluding "overtreated" patients.

	Deaths n/total (%)	Death rate, x1000 patients/year (95 % CI)		
		General population (n = 3625,975) vs RIACE cohort (n = 12,666)	RIACE participants without prior CVD (n = 9994)	RIACE participants with prior CVD (n = 2672)
General population	711,903/3625,975 (19.64)	19.64 (19.59–19.69)	–	–
RIACE cohort	2773/12,666 (21.9)	22.23 (21.20–23.31)	18.5 (17.54–19.67)	37.80 (34.72–41.16)
Number of CVD risk factors outside target				
No risk factor	34/187 (18.2)	19.68 (14.05–27.56)	19.35 (13.17–28.44)	22.62 (11.29–45.32)
1 risk factor	255/1478 (17.3)	18.25 (16.10–20.68)	15.25 (13.07–17.79)	31.34 (25.26–38.88)
2 risk factors	665/3517 (18.9)	19.34 (17.84–20.96)	16.70 (15.16–18.41)	31.55 (27.27–36.49)
3 risk factors	900/4154 (21.7)	20.73 (19.27–22.30)	17.27 (15.79–18.89)	35.97 (31.69–40.84)
4 risk factors	643/2453 (26.2)	26.44 (24.33–28.74) *	21.34 (19.19–23.72) *	45.59 (39.74–52.31) *
5 risk factors	250/793 (31.5)	37.95 (33.45–43.06) **	32.68 (27.93–38.25) **	57.52 (46.52–71.12) **
6 risk factors	26/84 (31.0)	45.25 (30.80–66.48) ****	31.87 (18.10–56.13)	76.80 (45.43–129.85) ***
	Kaplan-Meier *Log Rank = 113.46* *($p < 0.0001$)*	Pairwise comparisons * $p < 0.0001$ vs 1–3, 5; $p < 0.05$ vs 6 ** $p < 0.0001$ vs 0–4 *** $p = 0.007$ vs 1, 4; $p < 0.005$ vs 1–3; $p < 0.05$ vs 4	* $p < 0.0001$ vs 1, 5; $p < 0.002$ vs 2, 3 ** $p = 0.004$ vs 0; $p < 0.0001$ vs 1–4	* $p < 0.01$ vs 0, 3; $p \leq 0.001$ vs 1, 2; ** $p = 0.001$ vs 0, 3; $p < 0.0001$ vs 1, 2 *** $p < 0.05$ vs 0–3

CVD = cardiovascular disease; RIACE = Renal Insufficiency And Cardiovascular Events; CI = confidence interval.

Table 5
Survival analysis by Cox proportional hazard regression, adjusted for age, according to number of CVD risk factors outside target in the whole RIACE cohort versus the coeval Italian general population and in the RIACE participants without and with prior CVD, after excluding "overtreated" patients. HRs (95 % CI) for mortality are shown.

	Whole RIACE cohort (n = 12,666)	RIACE participants without prior CVD (n = 9994)	RIACE participants with prior CVD (n = 2672)
General population	Ref.	Ref.	Ref.
RIACE cohort	1.13 (1.10–1.17)	0.96 (0.92–1.04)	1.93 (1.83–2.02)
Number of CVD risk factors outside target			
No risk factor	1.00 (0.74–1.36)	0.99 (0.69–1.40)	1.52 (0.94–2.46)
1 risk factor	0.93 (0.83–1.04)	0.78 (0.67–0.89)	1.60 (1.34–1.90)
2 risk factors	0.99 (0.92–1.06)	0.87 (0.78–0.98)	1.61 (1.43–1.80)
3 risk factors	1.06 (1.02–1.12)	0.92 (0.82–0.98)	1.82 (1.67–2.01)
4 risk factors	1.35 (1.26–1.44)	1.12 (1.02–1.19)	2.32 (2.12–2.55)
5 risk factors	1.93 (1.74–2.14)	1.66 (1.46–1.90)	2.93 (2.52–3.40)
6 risk factors	2.30 (1.67–3.17)	1.62 (0.98–2.69)	3.91 (2.76–5.54)

CVD = cardiovascular disease; RIACE = Renal Insufficiency And Cardiovascular Events; HR = hazard ratio; CI = confidence interval.

risk factors, which would have hidden the role of risk factor control per se. Taken together, our results strongly support the importance of achieving targets for traditional CVD risk factors for aligning mortality of patients with type 2 diabetes to that of non-diabetic individuals.

The J-effect observed in the whole RIACE cohort and in patients without a history of CVD is at variance with data from the Steno-2 [8], SNDR [13] and CPRD [14] cohorts, but consistent with previous reports showing such a non-linear relationship between achieved HbA_{1c} [25-27] or BP [28-30] and mortality, with both higher and lower values associated with increased all-cause death. More importantly, the finding that the apparently higher increased risk of death in patients with no versus one risk factor outside target became non-significant when adjusting for "overtreatment" of hyperglycaemia and/or hypertension is in keeping with previous studies showing that the J-effect was related to the type of treatment rather than to the glucose and/or BP levels per se. In fact, reports form the RIACE Study [31] and the Fremantle Diabetes Study Phase II [32] showed that the increased mortality associated with lower HbA_{1c} levels in people with type 2 diabetes was observed only in those treated with sulfonylurea and/or insulin. Likewise, the increased mortality reported in hypertensive patients with low BP levels was found to be related to intensive anti-hypertensive treatment [33-35]. These observations prompted the American Diabetes Association to recommend variable HbA_{1c} target according to several potential risks associated with achievement of near-normoglycaemia with anti-hyperglycaemic treatment, including the risk of treatment-induced hypoglycaemia [9]. However, as the classes of anti-hyperglycaemic agents that have been made available during the last decades do not cause hypoglycaemia, the use of these drugs may likely allow to safely achieve more stringent HbA_{1c} goals even in high-risk patients. Similarly, the guidelines of the European Society of Cardiology for the treatment of hypertension in diabetic patients recommend not to achieve systolic BP levels <120 mmHg (<130 mmHg in older individuals) and diastolic BP levels <70 mmHg, implying the need of de-intensifying anti-hypertensive therapy if BP levels fell below these thresholds [23]. Our findings provide further support to guideline recommendations of avoiding overtreatment-induced hypoglycaemia and hypotension.

The differential impact of risk factor control on mortality risk in patients with type 2 diabetes with versus without prior CVD is attributable to the 5-fold higher excess risk of death in the former than in the latter group (+100 % versus +20 %) and is consistent with data on CVD events from the CPRD and the Scottish Care Information (SCI)-Diabetes dataset, showing that patients with cardio-renal disease and poor versus optimal control of all five CVD risk factors had only a 9 % increased risk, whereas risk was 96 % higher in those without cardio-renal disease who were not on-target for all risk factors [14]. Our data are also in keeping with previous studies showing no excess mortality risk versus controls in patients with type 2 diabetes falling in the lowest albuminuria or the highest eGFR category, though this was the case in older, but not in younger individuals [24,36]. This implies that a widespread use of GLP-1 receptor agonists and SGLT-2 inhibitors might help in reducing the risk of death close to that of non-diabetic individuals also in diabetic patients with prior CVD, in addition to allow achieving an optimal

Table 6
Survival analysis by Cox proportional hazard regression according to number of CVD risk factors outside target in the whole RIACE cohort and the RIACE participants without and with prior CVD, after excluding "overtreated" patients, unadjusted (Model 1) or adjusted for age and sex (Model 2), plus several confounders (Model 3) or further adjusted for anti-hyperglycaemic treatment (Model 4) or "overtreatments". HRs (95 % CI) for mortality are shown.

	Whole cohort (n = 15,386)			Patients without prior CVD (n = 11,841)			Patients with prior CVD (n = 3545)		
	HR	95 % CI	P	HR	95 % CI	P	HR	95 % CI	P
Model 1									
Number of CVD risk factors outside target			<0.0001			<0.0001			<0.0001
No risk factor	1.327	1.058–1.665	0.015	1.420	1.068–1.889	0.016	1.107	0.761–1.611	0.595
1 risk factor	1			1			1		
2 risk factors	1.034	0.921–1.162	0.570	1.056	0.912–1.222	0.470	1.042	0.861–1.260	0.673
3 risk factors	1.177	1.051–1.317	0.005	1.178	1.021–1.360	0.024	1.205	1.003–1.447	0.046
4 risk factors	1.399	1.240–1.579	<0.0001	1.334	1.142–1.557	<0.0001	1.483	1.223–1.798	<0.0001
5 risk factors	1.676	1.436–1.956	<0.0001	1.719	1.415–2.088	<0.0001	1.618	1.256–2.086	<0.0001
6 risk factors	1.731	1.195–2.507	0.004	1.375	0.803–2.355	0.246	2.035	1.217–3.404	0.007
Model 2									
Age	1.100	1.096–1.104	<0.0001	1.102	1.097–1.108	<0.0001	1.083	1.075–1.090	<0.0001
Male sex	1.478	1.380–1.582	<0.0001	1.412	1.297–1.537	<0.0001	1.313	1.168–1.477	<0.0001
Number of CVD risk factors outside target			<0.0001			<0.0001			<0.0001
No risk factor	1.208	0.963–1.515	0.103	1.373	1.032–1.826	0.029	0.954	0.655–1.389	0.805
1 risk factor	1			1			1		
2 risk factors	1.019	0.908–1.145	0.746	1.022	0.883–1.184	0.768	1.047	0.866–1.267	0.635
3 risk factors	1.089	0.973–1.220	0.137	1.061	0.920–1.225	0.414	1.185	0.986–1.424	0.071
4 risk factors	1.335	1.183–1.506	<0.0001	1.274	1.091–1.488	0.002	1.431	1.180–1.735	<0.0001
5 risk factors	1.896	1.625–2.213	<0.0001	1.948	1.603–2.366	<0.0001	1.803	1.398–2.324	<0.0001
6 risk factors	2.310	1.594–3.347	<0.0001	1.991	1.162–3.410	0.012	2.465	1.474–4.122	0.001
Model 3									
Age, year	1.084	1.079–1.090	<0.0001	1.089	1.083–1.096	<0.0001	1.074	1.066–1.083	<0.0001
Male sex	1.371	1.277–1.472	<0.0001	1.370	1.254–1.496	<0.0001	1.350	1.195–1.525	<0.0001
Diabetes duration, year	1.005	1.002–1.009	0.002	1.008	1.004–1.00912	<0.0001	–	–	–
BMI, kg/m^2	–	–	–	–	–	–	–	–	–
HDL cholesterol, x 5 mg/dL	0.965	0.953–0.978	<0.0001	0.971	0.956–0.987	0.001	0.959	0.938–0.980	<0.0001
Lipid-lowering treatment	0.783	0.731–0.840	<0.0001	0.798	0.730–0.872	<0.0001	0.746	0.666–0.836	<0.0001
Anti-hypertensive treatment	1.187	1.088–1.294	<0.0001	1.163	1.052–1.285	0.003	1.230	1.029–1.471	0.023
eGFR categories			<0.0001			<0.0001			<0.0001
G1 (≥90 mL•min^{-1}•1.73m^{-2})	1			1			1		
G2 (60–89 mL•min^{-1}•1.73m^{-2})	0.984	0.891–1.085	0.740	1.017	0.904–1.144	0.780	0.890	0.746–1.061	0.194
G3 (30–59 mL•min^{-1}•1.73m^{-2})	1.426	1.272–1.599	<0.0001	1.404	1.216–1.622	<0.0001	1.400	1.158–1.692	<0.0001
G4–5 (<30 mL•min^{-1}•1.73m^{-2})	2.512	2.101–3.003	<0.0001	2.718	2.136–3.460	<0.0001	2.321	1.769–3.046	<0.0001
DR grade			<0.0001			<0.0001			<0.0001
No	1			1			1		
Non-advanced	1.172	1.066–1.288	0.001	1.098	0.969–1.245	0.144	1.244	1.079–1.433	0.003
Advanced	1.407	1.273–1.555	<0.0001	1.453	1.272–1.660	<0.0001	1.327	1.141–1.543	<0.0001
Any CVD	1.593	1.481–1.714	<0.0001						
COPD	1.432	1.267–1.619	<0.0001	1.447	1.228–1.704	<0.0001	1.427	1.184–1.720	<0.0001
Chronic liver disease	1.515	1.369–1.675	<0.0001	1.826	1.608–2.074	<0.0001	1.172	0.993–1.384	0.061
Cancer	1.739	1.566–1.932	<0.0001	1.858	1.633–2.113	<0.0001	1.511	1.259–1.813	<0.0001
Number of CVD risk factors outside target			<0.0001			<0.0001			0.069
No risk factor	1.194	0.951–1.498	0.126	1.333	1.002–1.773	0.049	1.032	0.709–1.504	0.868
1 risk factor	1			1			1		
2 risk factors	1.004	0.894–1.128	0.943	1.012	0.873–1.172	0.877	1.005	0.830–1.218	0.957
3 risk factors	1.028	0.917–1.151	0.639	1.011	0.875–1.168	0.883	1.077	0.895–1.296	0.432
4 risk factors	1.115	0.987–1.261	0.081	1.090	0.931–1.276	0.285	1.193	0.981–1.451	0.077
5 risk factors	1.488	1.271–1.742	<0.0001	1.604	1.316–1.956	<0.0001	1.366	1.054–1.720	0.018
6 risk factors	1.543	1.062–2.240	0.023	1.716	1.000–2.944	0.050	1.527	0.906–2.573	0.112
Model 4									
Anti-hyperglycaemic treatment									
Drugs not causing hypoglycaemia	1			1			1		
Drugs causing hypoglycaemia	1.468	1.351–1.596	<0.0001	1.461	1.318–1.619	<0.0001	1.441	1.249–1.662	<0.0001
Number of CVD risk factors outside target			<0.0001			<0.0001			0.153
No risk factor	1.191	0.949–1.495	0.131	1.317	0.990–1.752	0.059	1.040	0.714–1.514	0.839
1 risk factor	1			1			1		
2 risk factors	0.993	0.884–1.116	0.905	0.997	0.861–1.155	0.971	0.994	0.821–1.204	0.950
3 risk factors	1.005	0.897–1.126	0.932	0.983	0.851–1.135	0.813	1.058	0.879–1.274	0.548
4 risk factors	1.076	0.952–1.217	0.241	1.042	0.889–1.220	0.613	1.160	0.953–1.411	0.139
5 risk factors	1.420	1.213–1.662	<0.0001	1.512	1.240–1.845	<0.0001	1.318	1.017–1.708	0.037
6 risk factors	1.441	0.993–2.093	0.055	1.543	0.899–2.648	0.116	1.442	0.856–2.430	0.169
Model 5									
HbA_{1c} ≤6.0 % on anti-hyperglycaemic agents causing hypoglycaemia									
No	1			1			1		
Yes	1.371	1.204–1.561	<0.0001	1.379	1.160–1.639	<0.0001	1.308	1.073–1.593	0.008
Systolic BP ≤120 mmHg on anti-hypertensive agents									
No	1			1			1		
Yes	1.167	1.060–1.284	0.002	1.119	0.982–1.275	0.091	1.226	1.063–1.412	0.005
Number of CVD risk factors outside target			<0.0001			<0.0001			0.005

(*continued on next page*)

Table 6 (*continued*)

	Whole cohort (n = 15,386)			Patients without prior CVD (n = 11,841)			Patients with prior CVD (n = 3545)		
Model 1	HR	95 % CI	*P*	HR	95 % CI	*P*	HR	95 % CI	*P*
No risk factor	1.109	0.882–1.394	0.377	1.246	9.934–1.661	0.135	0.954	0.654–1.393	0.809
1 risk factor	1			1			1		
2 risk factors	1.027	0.913–1.154	0.661	1.032	0.890–1.196	0.675	1.031	0.851–1.250	0.754
3 risk factors	1.077	0.959–1.208	0.209	1.052	0.909–1.217	0.496	1.141	0.945–1.377	0.170
4 risk factors	1.192	1.052–1.352	0.006	1.152	0.980–1.352	0.086	1.295	1.059–1.584	0.012
5 risk factors	1.610	1.371–1.890	<0.0001	1.706	1.394–2.086	<0.0001	1.517	1.163–1.979	0.002
6 risk factors	1.681	1.156–2.445	0.007	1.836	1.068–3.154	0.028	1.700	1.005–2.875	0.048

CVD = cardiovascular disease; RIACE = Renal Insufficiency And Cardiovascular Events; HR = hazard ratio; CI = confidence interval; BMI = body mass index; eGFR = estimated glomerular filtration rate; DR = diabetic retinopathy; COPD = chronic obstructive pulmonary disease; HbA_{1c} = haemoglobin $A_{1c;}$ BP = blood pressure; HR = hazard ratio; CI = confidence interval.

control of risk factors without causing hypoglycaemia. A recent study assessing the effect of a treat-to-benefit approach including prescription of these agents to patients with prior CVD showed a lower risk of all-cause and CVD mortality as well of major adverse CVD events and hospitalization for heart failure [37].

Finally, the strong association of HbA_{1c} ≥7.0 %, and current smoking with mortality, but not that of microalbuminuria or macroalbuminuria, is also in keeping with the SNDR data, showing that HbA_{1c} was the best predictor of myocardial infarction and stroke, whereas smoking was the best predictor of death [13]. Conversely, the paradox inverse association with mortality of BP and LDL cholesterol levels outside target is likely due to an indication effect, i.e., patients more complicated and, hence, at higher risk of death, were treated more (and more intensively) and, therefore, presented with lower BP and lipid levels.

Strength of our study include the large sample size, the completeness of baseline and follow-up data and the assessment of a wide range of clinical parameters which allowed stratifying patients by the number of risk factors on-target and also accounting for several confounding factors including complications and comorbidities. However, there are several limitations. First, the analysis is based on baseline risk factor profile, which has likely changed during the follow-up for several reasons, including disease progression, guideline change, and availability of new drugs, the use of which was however very limited at the time of the census, as discussed above. Second, the lack of information on the causes of death did not allow detecting differences in CVD versus non-CVD deaths. Third, results may have been affected by unmeasured confounders that can affect mortality, including education, socio-economic status, depression, and cognitive impairment. Fourth, the study findings may not be applicable to the general ambulatory population, as only part of the individuals with type 2 diabetes attend outpatients diabetes clinics in Italy; however, the RIACE cohort is representative of patients followed by diabetes specialists in these clinics [38]. Finally, the observational design makes causal interpretation impossible.

In conclusion in individuals with type 2 diabetes, optimal treatment of six traditional CVD risk factors completely eliminated the excess risk of death from any cause versus the general population, provided that patients were not “overtreated” for hyperglycaemia and/or hypertension. This effect was observed in patients without a history of CVD, in whom achieving targets was sufficient for reducing mortality risk to values similar to those observed in the coeval general population, whereas having all risk factor on-target was still associated with a 70 % excess risk of death in patients with prior CVD. These findings support the importance of a treat-to-benefit approach using GLP-1 receptor agonists and SGLT-2 inhibitors to reduce the excess risk of death also in patients with prior CVD, in addition to achieving an optimal control of traditional risk factors using a treat-to-target approach.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The research protocol was approved by the ethics committee of the coordinating centre (Sant’Andrea University Hospital, Rome Italy) (n. 4306) and subsequently by the ethics committee of each participating centre. Participants provided an informed consent.

Funding

This research was supported by the Research Foundation of the Italian Diabetes Society (Diabete Ricerca) and the Diabetes, Endocrinology and Metabolism (DEM) Foundation, and by unconditional grants from Eli-Lilly, Sigma-Tau, Takeda, Chiesi Farmaceutici, and Boehringer-Ingelheim. The funding sources had no role in the study’s design, conduct, and reporting.

CRediT authorship contribution statement

Monia Garofolo: Conceptualization, Data curation, Formal analysis, Investigation, Resources, Visualization, Writing – review & editing. **Giuseppe Penno:** Conceptualization, Data curation, Formal analysis, Investigation, Resources, Visualization, Writing – review & editing. **Anna Solini:** Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. **Emanuela Orsi:** Conceptualization, Data curation, Investigation, Resources, Writing – review & editing. **Martina Vitale:** Investigation, Resources, Writing – review & editing. **Veronica Resi:** Investigation, Resources, Writing – review & editing. **Enzo Bonora:** Investigation, Resources, Writing – review & editing. **Cecilia Fondelli:** Investigation, Resources, Writing – review & editing. **Roberto Trevisan:** Investigation, Resources, Writing – review & editing. **Monica Vedovato:** Investigation, Resources, Writing – review & editing. **Antonio Nicolucci:** Data curation, Formal analysis, Software, Writing – review & editing. **Giuseppe Pugliese:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Investigation, Resources, Supervision, Validation, Visualization, Writing – original draft.

Declaration of Competing Interest

Monia Garofolo: consultant fees from Eli Lilly, and lecture fees from Eli Lilly, Merck Sharp & Dohme, and Novo Nordisk. **Giuseppe Penno:** consultant fees from Bayer and Eli Lilly, and lecture fees from AstraZeneca, Boerhinger Ingelheim, Eli-Lilly, Merck Sharp & Dohme, Mundipharma, Novo Nordisk, and Takeda. **Anna Solini:** consultant fees from Axxam, Bayer, and Novo Nordisk, and lecture fees from Eli Lilly, Novo Nordisk, and Sanofi-Aventis. **Emanuela Orsi:** consultant fees from Eli Lilly and Novo Nordisk, and lecture fees from Astellas. **Martina Vitale:** lecture fees from MundiPharma and Novo Nordisk. **Veronica Resi:** lecture fees from Astra-Zeneca, Eli Lilly, and Sanofi-Aventis. **Enzo**

Bonora: consultant fees from Abbott, Bayer, Becton Dickinson, Boehringer Ingelheim, Daiichi-Sankyo, Eli Lilly, and Novo Nordisk. **Cecilia Fondelli:** lecture fees from Abbot, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, Merck Sharp & Dohme, Mundipharma, and Theras Lifetech. **Roberto Trevisan:** consultant fees from AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Novo Nordisk, and Sanofi-Aventis, and lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, and Novo Nordisk. **Monica Vedovato:** lecture fees from Lifescan and Novo Nordisk. **Antonio Nicolucci:** consultant fees from AstraZeneca, lecture fees from Eli Lilly, Medtronic, and Novo Nordisk, and grant support from AlfaSigma, Novo Nordisk, Pikdare, Sanofi, Shionogi, SOBI, and Theras. **Giuseppe Pugliese:** consultant fees from Abbot, Bayer, and Novo Nordisk, and lecture fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Mundipharma, and Novo Nordisk.

Acknowledgement

The Authors thank the patients and the RIACE Investigators (see Supplementary Material for the complete list) for participating in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejim.2024.05.034.

References

[1] Rao Kondapally Seshasai S, Kaptoge S, Thompson A, Di Angelantonio E, Gao P, Sarwar N, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–41. https://doi.org/10.1056/NEJMoa1008862.

[2] Preis SR, Hwang SJ, Coady S, Pencina MJ, Sr D'Agostino RB, Savage PJ, et al. Trends in all-cause and cardiovascular disease mortality among women and men with and without diabetes mellitus in the Framingham Heart Study, 1950 to 2005. Circulation 2009;119:1728–35. https://doi.org/10.1161/CIRCULATIONAHA.108.829176.

[3] Gregg EW, Cheng YJ, Saydah S, Cowie C, Garfield S, Geiss L, et al. Trends in death rates among U.S. adults with and without diabetes between 1997 and 2006: findings from the National Health Interview Survey. Diabetes Care 2012;35:1252–7. https://doi.org/10.2337/dc11-1162.

[4] Lind M, Garcia-Rodriguez LA, Booth GL, Cea-Soriano L, Shah BR, Ekeroth G, et al. Mortality trends in patients with and without diabetes in Ontario, Canada and the UK from 1996 to 2009: a population-based study. Diabetologia 2013;56:2601–8. https://doi.org/10.1007/s00125-013-3063-1.

[5] Anon, GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1736–88. https://doi.org/10.1016/S0140-6736(18)32203-7.

[6] Alexander CM, Landsman PB, Teutsch SM, Haffner SM. Third National Health and Nutrition Examination Survey (NHANES III); National Cholesterol Education Program (NCEP). NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes 2003;52:1210–4. https://doi.org/10.2337/diabetes.52.5.1210.

[7] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577–89. https://doi.org/10.1056/NEJMoa0806470.

[8] Gaede P, Lund-Andersen H, Parving HH, Pedersen O. Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med 2008;358:580–91. https://doi.org/10.1056/NEJMoa0706245.

[9] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–79. https://doi.org/10.2337/dc12-0413.

[10] Davies MJ, D'Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, Management of Hyperglycemia in Type 2 Diabetes. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2018;41:2669–701. https://doi.org/10.2337/dci18-0033.

[11] Sattar N, Lee MMY, Kristensen SL, Branch KRH, Del Prato S, Khurmi NS, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. Lancet Diabetes Endocrinol 2021;9:653–62. https://doi.org/10.1016/S2213-8587(21)00203-5.

[12] McGuire DK, Shih WJ, Cosentino F, Charbonnel B, Cherney DZI, Dagogo-Jack S, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. JAMA Cardiol 2021;6:148–58. https://doi.org/10.1001/jamacardio.2020.4511.

[13] Rawshani A, Rawshani A, Franzén S, Sattar N, Eliasson B, Svensson AM, et al. Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2018;379:633–44. https://doi.org/10.1056/NEJMoa1800256.

[14] Wright AK, Suarez-Ortegon MF, Read SH, Kontopantelis E, Buchan I, Emsley R, et al. Risk factor control and cardiovascular event risk in people with type 2 diabetes in primary and secondary prevention settings. Circulation 2020;142:1925–36. https://doi.org/10.1161/CIRCULATIONAHA.120.046783.

[15] Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, et al. Clinical significance of nonalbuminuric renal impairment in type 2 diabetes. J Hypertens 2011;29:1802–9. https://doi.org/10.1097/HJH.0b013e3283495cd6.

[16] Penno G, Solini A, Bonora E, Fondelli C, Orsi E, Zerbini G, et al. Gender differences in cardiovascular disease risk factors, treatments and complications in patients with type 2 diabetes: the RIACE Italian multicentre study. J Intern Med 2013;274:176–91. https://doi.org/10.1111/dom.13306.

[17] Penno G, Solini A, Orsi E, Bonora E, Fondelli C, Trevisan R, et al. Insulin resistance, diabetic kidney disease, and all-cause mortality in individuals with type 2 diabetes: a prospective cohort study. BMC Med 2021;19:66. https://doi.org/10.1111/joim.12073.

[18] Pugliese G, Solini A, Fondelli C, Trevisan R, Vedovato M, Nicolucci A, et al. Reproducibility of albuminuria in type 2 diabetic subjects. Findings from the Renal Insufficiency And Cardiovascular Events (RIACE) study. Nephrol Dial Transplant 2011;26:3950–4. https://doi.org/10.1186/s12916-021-01936-3.

[19] Penno G, Solini A, Orsi E, Bonora E, Fondelli C, Trevisan R, et al. Non-albuminuric renal impairment is a strong predictor of mortality in individuals with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicentre study. Diabetologia 2018;61:2277–89. https://doi.org/10.1093/ndt/gfr140.

[20] Penno G, Solini A, Zoppini G, Orsi E, Zerbini G, Trevisan R, et al. Rate and determinants of association between advanced retinopathy and chronic kidney disease in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. Diabetes Care 2012;35:2317–23. https://doi.org/10.1007/s00125-018-4691-2.

[21] Solini A, Penno G, Bonora E, Fondelli C, Orsi E, Arosio M, et al. Diverging association of reduced glomerular filtration rate and albuminuria with coronary and noncoronary events in patients with type 2 diabetes: the renal insufficiency and cardiovascular events (RIACE) Italian multicenter study. Diabetes Care 2012;35:143–9. https://doi.org/10.2337/dc12-0628.

[22] Orsi E, Solini A, Bonora E, Fondelli C, Trevisan R, Vedovato M, et al. Haemoglobin A1c variability is a strong, independent predictor of all-cause mortality in patients with type 2 diabetes. Diabetes Obes Metab 2018;20:1885–93. https://doi.org/10.2337/dc11-1380.

[23] Marx N, Federici M, Schütt K, Müller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J 2023;44:4043–140. https://doi.org/10.1093/eurheartj/ehad192.

[24] Penno G, Solini A, Bonora E, Orsi E, Fondelli C, Zerbini G, et al. Defining the contribution of chronic kidney disease to all-cause mortality in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study. Acta Diabetol 2018;55:603–12. https://doi.org/10.1007/s00592-018-1133-z.

[25] Currie CJ, Peters JR, Tynan A, Evans M, Heine RJ, Bracco OL, et al. Survival as a function of HbA(1c) in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–9. https://doi.org/10.1016/S0140-6736(09)61969-3.

[26] Nichols GA, Joshua-Gotlib S, Parasuraman S. Glycemic control and risk of cardiovascular disease hospitalization and all-cause mortality. J Am Coll Cardiol 2013;62:121–7. https://doi.org/10.1016/j.jacc.2013.04.031.

[27] Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. Diabetes Care 2011;34:1329–36. https://doi.org/10.2337/dc10-2377.

[28] Olsen E, Holzhauer B, Julius S, Kjeldsen SE, Larstorp ACK, Mancia G, et al. Cardiovascular outcomes at recommended blood pressure targets in middle-aged and elderly patients with type 2 diabetes mellitus and hypertension. Blood Press 2021;30:82–9. https://doi.org/10.1080/08037051.2020.1855968.

[29] Wu CY, Hu HY, Chou YJ, Huang N, Chou YC, Li CP. High Blood Pressure and All-Cause and Cardiovascular Disease Mortalities in Community-Dwelling Older Adults. Medicine (Baltimore) 2015;94:e2160. https://doi.org/10.1097/MD.0000000000002160.

[30] Vidal-Petiot E, Ford I, Greenlaw N, Ferrari R, Fox KM, Tardif JC, et al. Cardiovascular event rates and mortality according to achieved systolic and diastolic blood pressure in patients with stable coronary artery disease: an international cohort study. Lancet 2016;388:2142–52. https://doi.org/10.1016/S0140-6736(16)31326-5.

[31] Orsi E, Bonora E, Solini A, Fondelli C, Trevisan R, Vedovato M, et al. Association between on-treatment haemoglobin A_{1c} and all-cause mortality in individuals with type 2 diabetes: importance of personalized goals and type of anti-hyperglycaemic treatment. J Clin Med 2020;9:246. https://doi.org/10.3390/jcm9010246.

[32] Bruce DG, Davis WA, Davis TME. Glycaemic control and mortality in older people with type 2 diabetes: the Fremantle Diabetes Study Phase II. Diabetes Obes Metab 2018;20:2852–9. https://doi.org/10.1111/dom.13469.

[33] Sleight P, Redon J, Verdecchia P, Mancia G, Gao P, Fagard R, et al. Prognostic value of blood pressure in patients with high vascular risk in the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial study. J Hypertens 2009;27:1360–9. https://doi.org/10.1097/HJH.0b013e32832d7370.

[34] Bangalore S, Messerli FH, Wun CC, Zuckerman AL, DeMicco D, Kostis JB, et al. J-curve revisited: an analysis of blood pressure and cardiovascular events in the Treating to New Targets (TNT) Trial. Eur Heart J 2010;31:2897–908. https://doi.org/10.1093/eurheartj/ehq328.

[35] Solini A, Penno G, Orsi E, Bonora E, Fondelli C, Trevisan R, et al. Is resistant hypertension an independent predictor of all-cause mortality in individuals with type 2 diabetes? A prospective cohort study. BMC Med 2019;17:83. https://doi.org/10.1186/s12916-019-1313-x.

[36] Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjörnsdottir S, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med 2015;373:1720–32. https://doi.org/10.1056/NEJMoa1504347.

[37] Morieri ML, Longato E, Di Camillo B, Sparacino G, Avogaro A, Fadini GP. Management of type 2 diabetes with a treat-to-benefit approach improved long-term cardiovascular outcomes under routine care. Cardiovasc Diabetol 2022;21:274. https://doi.org/10.1186/s12933-022-01712-4.

[38] De Cosmo S, Rossi MC, Pellegrini F, Lucisano G, Bacci S, Gentile S, et al. Kidney dysfunction and related cardiovascular risk factors among patients with type 2 diabetes. Nephrol Dial Transplant 2014;29:657–62. https://doi.org/10.1093/ndt/gft506.