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Diabetes and cardiovascular events in high-risk patients: Insights from a multicenter registry in a middle-income country

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ABSTRACT

Aims: The aim of this study was to determine the rate of major clinical events and its determinants in patients with previous cardiovascular event or not, and with or without diabetes from a middle-income country.

Methods: REACT study is a multicenter registry conducted between July 2010 and May 2013 in Brazil. Patients were eligible if they were over 45 years old and high cardiovascular risk. Patients were followed for 12 months; data were collected regarding adherence to evidence-based therapies and occurrence of clinical events (all-cause mortality, non-fatal cardiac arrest, myocardial infarction, or stroke).

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Results: A total of 5006 subjects was included and analyzed in four groups: No diabetes and no previous cardiovascular event, $n = 430$; diabetes and no previous cardiovascular event, $n = 1138$; no diabetes and previous cardiovascular event, $n = 1747$; and diabetes and previous cardiovascular event, $n = 1691$. Major clinical events in one-year follow-up occurred in 332 patients. A previous cardiovascular event was associated with a higher risk of having another event in the follow-up (HR 2.31 95% CI 1.74–3.05, $p < 0.001$), as did the presence of diabetes (HR 1.28 95% CI 1.10–1.73, $p = 0.005$). In patients with diabetes, failure to reach HbA1c targets was related to poorer event-free survival compared to patients with good metabolic control (HR 1.70 95% CI 1.01–2.84, $p = 0.044$).

Conclusions: In Brazil, diabetes confers high risk for major clinical events, but this condition is not equivalent to having a previous cardiovascular event. Moreover, not so strict targets for HbA1c in patients with diabetes and previous cardiovascular events might be considered.

1. Introduction

Cardiovascular disease represents the main cause of morbidity and mortality in individuals with diabetes [1,2] and the largest contributor to the direct and indirect costs of the disease, in high [3] and middle-income countries [4]. Although a trend toward mortality reduction among people with diabetes was reported in the USA [1], this was not seen in middle-income countries [2,5]. The rising prevalence of obesity [5,6], and the high frequency of people not achieving recommended treatment goals [7] are probably involved in the increased burden of diabetes in such countries.

The term cardiovascular risk equivalence for individuals with diabetes has become popular and controversial following the report by Haffner et al. [8] of higher rates of cardiac events in these subjects. This term means that individuals with diabetes and non-diabetic individuals with a prior cardiovascular event are at similar risk of future cardiovascular events, meaning that both should be treated aggressively to prevent future outcomes. This concept prompted modifications of the guidelines, placing people with diabetes in a separate category of risk as requiring intensified cardiovascular risk factor management [9]. The recent American College of Cardiology (ACC)/American Heart Association (AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults defined four major statin benefit groups identified by atherosclerotic cardiovascular disease risk and includes diabetes mellitus as a classificatory factor [10]. However, subsequent data from Haffner's study showed that the association of diabetes with increased cardiovascular mortality risk is indeed heterogeneous [11–14].

Possible sources of heterogeneity related to the occurrence of adverse outcomes among diabetic patients are duration of disease, glucose control, and concomitance of other cardiovascular risk factors. Glycated hemoglobin (HbA1c) reflects average glycemia over several months and has strong predictive value for diabetes complications, including cardiovascular outcomes [15,16]. Moreover, patients with insulin-treated diabetes may have higher rate of mortality and cardiovascular events compared with those not treated with insulin [17].

The broad range of cardiovascular risk reported for people with type 2 diabetes has been described in different countries [18], and it has implications for targeted preventive strategies in clinical practice. Considering that not all subjects with diabetes would be in such a high cardiovascular risk category, identifying these people would be beneficial to intensify risk factor management, while the identification of low cardiovascular risk subjects would prevent submitting them to such labeling and high cost interventions. This broad range of cardiovascular risk was reported for people with type 2 diabetes in many different countries [16,18], and it has implications for targeted preventive strategies in clinical practice. These previous studies were mainly conducted in the US and Western Europe. In this regard, large-scale and high-quality prospective data on populations from low and middle-income countries are lacking.

Thus, we aimed to determine the one year rate of major clinical events and its possible determinants in patients with diabetes without prior cardiovascular events as compared to patients without diabetes and no prior cardiovascular events, as well as in individuals with previous cardiovascular events (with or without diabetes) included in a large-scale multicenter registry in Brazil.

2. Material and methods

2.1. Study design

The REACT study (*Registro do Paciente de Alto risco Cardiovascular na práTica Clínica*) is an observational multicenter cohort aimed at documenting the clinical practice and established long term risk of clinical events of high cardiovascular risk patients in Brazil conducted from July 2010 to May 2016. The rationale and methods have been published in detail previously [19,20]. Briefly, REACT study is an observational and prospective registry with longitudinal follow-up of patients. The project was conceived and coordinated by the Brazilian Cardiology Society (SBC), with the participation of public and private centers from all regions of Brazil, respecting the distribution of population according to data from the Brazilian Institute of Geography and Statistics (Instituto Brasileiro

de Geografia e Estatística – IBGE). Public and private centers, academic or not, which met the minimum requirements of Good Clinical Research Practice were invited to participate in the study.

The current manuscript reports a sub analysis of REACT Registry focusing on the impact of diabetes on major clinical events.

2.2. Eligibility

We included men and women consecutive patients if they were over 45 years of age and had at least one of the following: evidence of coronary artery disease, evidence of previous ischemic stroke or transitory ischemic accident, evidence of peripheral vascular disease, diabetes, or presence of three cardiovascular risk factors, except diabetes (hypertension, smoking, dyslipidemia, over the age of 70 years, family history of coronary artery disease, asymptomatic carotid artery disease). Exclusion criteria included life expectancy of less than 6 months, neurocognitive or psychiatric conditions, and refusal to provide written informed consent.

2.3. Study procedures

We collected baseline data on clinical features, medical history, physical examination, pharmacological and non-pharmacological prescription and patients were followed for approximately 12 months. At six and 12 months after admission, patients completed a visit to assess data about adherence to evidence-based therapies and the occurrence of major clinical events.

2.4. Endpoints

For the current analysis, the primary medical endpoint is a combined outcome of major clinical events (all-cause mortality, non-fatal myocardial infarction, non-fatal cardiorespiratory arrest, or non-fatal stroke). Secondary endpoints considered all major clinical events of the primary outcome considered in their original form. A blinded and independent central committee adjudicated all endpoints using standardized definitions (Supplementary Material 1). These endpoints were evaluated according to the presence or not of diabetes and previous cardiovascular events.

2.5. Statistical analysis

Continuous variables were summarized as means and standard deviations and categorical variables were summarized as absolute counts and percentages. Comparisons at baseline were performed with Chi-Square test or ANOVA's *F* test where appropriate. Kaplan-Meier survival curves for the primary endpoint were plotted for each of the four groups according to the presence or absence of diabetes or prior cardiovascular events and were compared using unadjusted Cox proportional hazard models. The individual components of the primary composite endpoint were presented separately and described in each of the four groups and were compared with Chi-square test. In addition, for each individual component of the primary composite endpoint, Kaplan-Meier survival curves were plotted for each group and were compared using unadjusted Cox proportional hazard models.

We performed sensitivity analyses for the primary endpoint, in which Cox models were run considering previous cardiovascular events categories separately (previous acute myocardial infarction, peripheral vascular disease, stroke) and adjusted for the following co-variables: age, gender, renal failure, heart failure, body mass index (BMI) and smoking status. In the same model, we tested for a potential interaction between gender and diabetes.

Finally, in the subgroup of diabetic patients, a Cox model was performed to assess if HbA1c levels were independent prognostic factors for the primary endpoint. The model was adjusted for age, gender, renal failure, heart failure, BMI and smoking status. Moreover, for this subgroup analysis, patients with diabetes who had information on HbA1c at baseline were divided according to their baseline HbA1c: <8.0% (63.9 mmol/mol) for those with previous cardiovascular events, and <7.0% (53 mmol/mol) for those without previous cardiovascular events. These thresholds were selected based on current guidelines [21]. For this subgroup analysis, we performed two additional sensitivity analyses. In the first one, we replaced HbA1c levels for insulin use. In the second one, we redefined cardiovascular composited endpoint as: cardiovascular mortality (instead of all-cause mortality), non-fatal myocardial infarction, non-fatal cardiorespiratory arrest, or non-fatal stroke.

All analyses were performed with R 3.3.1 (R Core Team, Vienna, Austria, 2015, http://www.R-project.org/.), considering two-tailed significance level of 5% [22].

2.6. Ethical aspects

The protocol was approved by the Research Ethics Board of Heart Hospital, in São Paulo (SP), on June 22, 2010 under registration number 118/2010 and subsequently, each participating center also had its local approval. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent before their inclusion in the study.

2.7. Data management and quality control

All centers received protocol-dedicated and electronic system training, in person or by phone, supported by the coordination team. Data quality control was performed through electronic data capture system, central statistical monitoring, sending of reports containing the status of patients at participating centers and direct check of 10% of the records in five higher recruitment centers. Additionally 20% of the medical records were checked after being chosen randomly within each national demographic region. Finally, biannual meetings were held in order to update their status and discuss, among investigators, relevant points of the registry.

3. Results

Between July 2010 and August 2014, 5076 patients were enrolled and 5006 were eligible (Fig. 1). Only 26 individuals

were excluded because we did not have any baseline information from them. The mean follow-up was 11.7 ± 6.3 months. Forty-eight centers contributed with data (Supplementary Material 2); 99 patients (2.0%) were from the north, 523 (10.4%) were from the northeast and mid west regions, and 4384 (87.6%) were from the south and southeast regions of Brazil. Individuals enrolled were from primary care in 4.4% of cases ($n = 222$) and from secondary/tertiary care in 95.6% ($n = 4784$).

Table 1 shows the baseline characteristics of the 5006 included patients, according to the presence or not of diabetes and previous cardiovascular events (no diabetes and no previous cardiovascular event, $n = 430$; diabetes and no previous cardiovascular event, $n = 1138$; no diabetes and presence of previous cardiovascular event, $n = 1747$; and diabetes and presence of previous cardiovascular event, $n = 1691$). Of the 5006 patients, mean age was 65.2 ± 10.2 years, most of them were men, Caucasian, and had an intermediary risk classification in Framingham score. Among the cardiovascular risk factors, the most prevalent were hypertension and dyslipidemia. There were more men, more smokers, more patients with heart failure, and less from primary care in the groups with history of previous cardiovascular event; aspirin was more frequently used in patients with previous cardiovascular event.

From the included patients, 167 had died in six months (104 from cardiovascular causes) and 226 cumulative deaths occurred in one year of follow-up (143 from cardiovascular causes). Deaths and other endpoints are presented in Table 2. Major clinical events (all-cause mortality, non-fatal myocardial infarction, non-fatal cardiac arrest, or non-fatal stroke) in one-year of follow-up occurred in 332 (8.3%) patients and included 79 acute myocardial infarction, 64 non-fatal cardiac arrest, 53 ischemic stroke, and 226 deaths (143 cardiovascular cause).

Fig. 2 shows the Kaplan-Meier curves throughout the follow-up of the four groups of patients ($n = 4454$, 11.1% lost to follow up). These data show lower event-free survival in patients with previous cardiovascular events. Presence of diabetes did raise the risk, and there was no interaction ($p = 0.577$) between diabetes and previous CV. Therefore, the coefficient of interaction was suppressed and the estimated hazard ratio (HR) by unadjusted Cox's model for diabetes was 1.28 (95% CI 1.10–1.73, $p = 0.005$) and for previous cardiovascular event HR was 2.31 (95% CI 1.74–3.05, $p < 0.001$). Models separating the previous cardiovascular events and adjusted by age, gender, BMI, smoking, heart failure and renal failure are provided in Supplementary Material 3 – Table 1 presented similar inference.

Gender was considered as a fixed effect in this model and did not influence the results. Supplementary Material 3 – Table 2 shows the same model considering interaction between gender and diabetes and inference did not change.

There were 1400 patients with diabetes who had information on HbA1c at baseline. Of this total, 947 patients had previous cardiovascular events and 482 did not have a previous cardiovascular event. Considering more flexible targets for glucose control in patients with established cardiovascular disease [HbA1c < 8.0% (63.9 mmol/mol) for those with previous cardiovascular events, and <7.0% (53 mmol/mol) for those without previous cardiovascular events], patients who did not reach these targets had lower event-free survival rates (HR estimated by unadjusted Cox model 1.69 95% IC 1.02–2.80, $p = 0.041$) (Fig. 3). After adjusting for possible confounders in a Cox model (Table 3), HbA1c cutoffs were associated with the primary endpoint (HR 1.70, CI 1.01–2.84, $p = 0.044$). In this analysis, presence of heart failure and previous myocardial infarction were also variables involved with higher risk of major clinical events. The HR for each one-year increase in

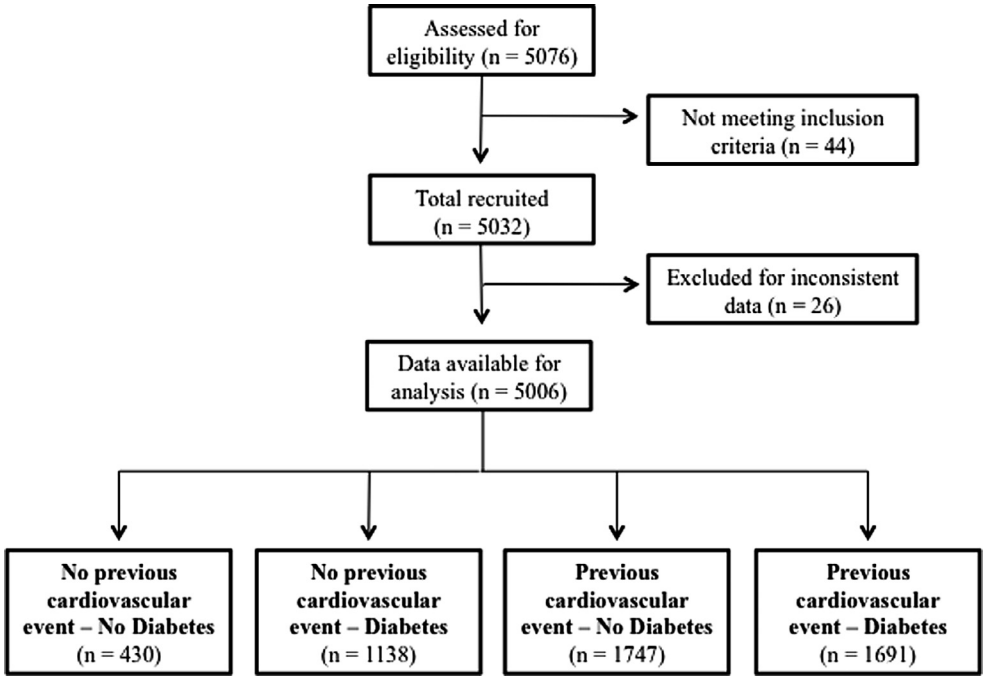

Fig. 1 – Flow diagram of REACT substudy.

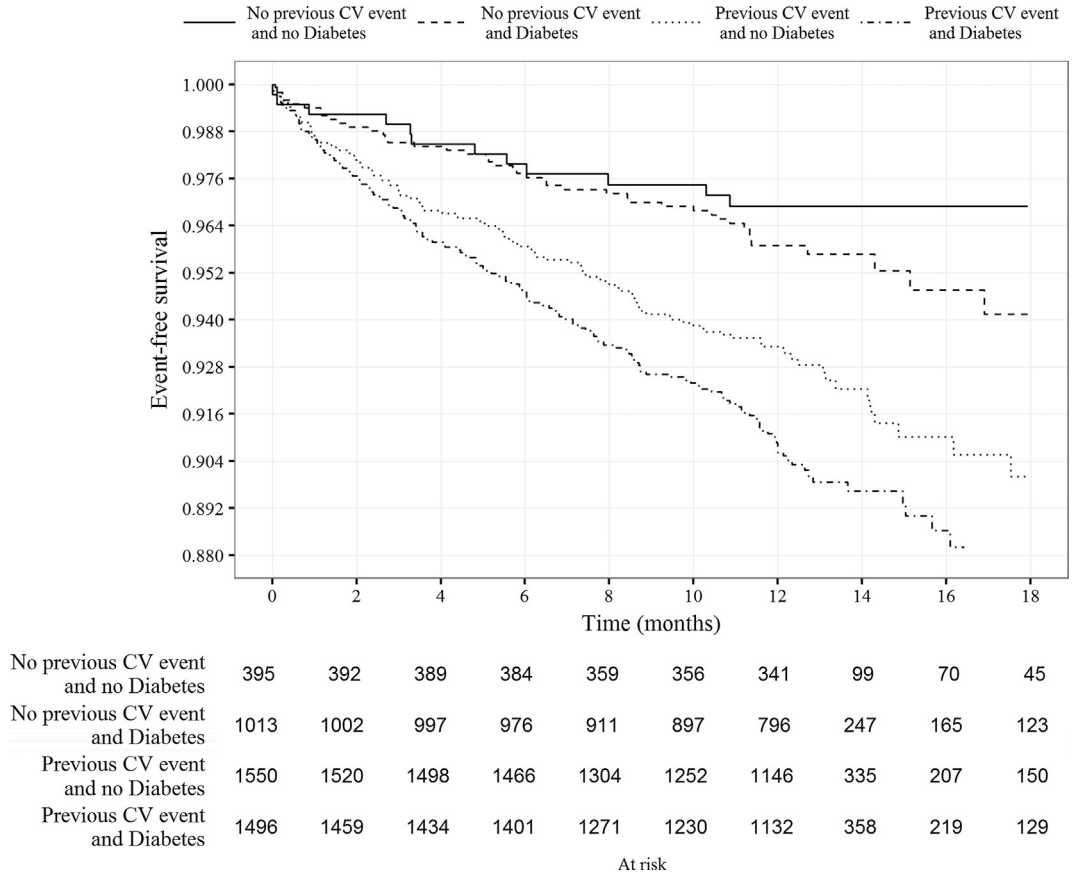

Fig. 2 – Survival curves for primary endpoint of REACT patients. Diabetes HR 1.28 95% CI [1.10–1.73], $p = 0.005$; Previous cardiovascular event HR 2.31 95% CI [1.74–3.05], $p < 0.001$. HR were estimated from unadjusted Cox models without interaction between diabetes and cardiovascular history.

age at major clinical events was 1.03 (95% CI, 1.02–1.07, Table 3). The control of HbA1c levels is collinear with the use of insulin. An alternative model adjusted with the use of insulin estimated a HR of 1.62 (CI 1.167–2.25, $p = 0.004$, Supplementary Material 3 – Table 3).

Sensitivity analyses within diabetic patients considering cardiovascular mortality instead of all-cause mortality in composite endpoint are presented in Supplementary Material 3 – Table 4.

4. Discussion

The REACT Registry represents the first study that has prospectively evaluated the occurrence of major clinical events in patients with or without a previous cardiovascular event, and with or without diabetes in Brazil, an upper middle-income country. The present results indicate that patients with previous cardiovascular events are at higher risk of developing major clinical events, as is well-known; diabetic patients without previous cardiovascular events are also at higher risk of future major clinical events, but this risk is not as high. Moreover, our findings suggest that diabetes is not a cardiovascular risk equivalent.

The disagreement between our study and previous evidence can be partially explained by differences in sample size, selection criteria, population characteristics, follow up time, and endpoint evaluation. In the study published by Haffner et al., all subjects with diabetes were on anti-diabetic agents, and had a mean duration of disease of 8 years, configuring a group with greater disease burden than would be seen in all individuals with diabetes. Moreover, the group with diabetes without myocardial infarction at baseline probably contains a substantial number of individuals with silent coronary heart disease, as symptoms were needed to classify them [8]; approximately one third of patients with diabetes have silent ischemic heart disease [23]. A systematic review and meta-analysis of observational studies comparing coronary disease events risk in individuals with diabetes with those with prior myocardial infarction but without diabetes also reported significantly lower overall relative odds of these events in subjects with diabetes [18]. However, studies included in this meta-analysis were mainly performed in populations from the United Kingdom and United States of America populations; none was designed to evaluate a Latin American population as our study was. More recently, another meta-analysis showed similar mortality risk for diabetic subjects and patients who had experienced a stroke previously; however, more men and more smokers were included in the study, as compared to our data [24].

Some studies have suggested that diabetes might be a coronary risk equivalent for women, but not for men [25], but this was not the case for the present data. Maybe these

Table 1 – Baseline characteristics of the patients studied, according to the presence or not of diabetes and previous cardiovascular events.

Characteristic	No previous CV event		Previous CV event		Total (n = 5006)	p
	No diabetes (n = 430)	Diabetes (n = 1138)	No diabetes (n = 1747)	Diabetes (n = 1691)		
Men	179/430 (41.6%)	471/1138 (41.4%)	1090/1747 (62.4%)	898/1691 (53.1%)	2638/5006 (52.7%)	<0.001
Age (years)	65.0 ± 11.4 (n = 430)	64.4 ± 9.7 (n = 1138)	65.6 ± 10.5 (n = 1741)	65.5 ± 9.7 (n = 1686)	65.2 ± 10.2 (n = 4995)	0.01
Caucasian	333/430 (77.4%)	775/1138 (68.1%)	1191/1747 (68.2%)	1144/1691 (67.7%)	3443/5006 (68.8%)	<0.001
From primary attention	39/430 (9.1%)	91/1138 (8%)	50/1747 (2.9%)	42/1691 (2.5%)	222/5006 (4.4%)	<0.001
Hypertension	388/430 (90.2%)	1041/1138 (91.5%)	1493/1747 (85.5%)	1556/1691 (92%)	4478/5006 (89.5%)	<0.001
Dyslipidemia	365/430 (84.9%)	802/1138 (70.5%)	1186/1747 (67.9%)	1301/1691 (76.9%)	3654/5006 (73%)	<0.001
Heart failure	44/430 (10.2%)	109/1138 (9.6%)	382/1747 (21.9%)	427/1691 (25.3%)	962/5006 (19.2%)	<0.001
Valvulopathy	31/430 (7.2%)	70/1138 (6.2%)	144/1747 (8.2%)	131/1691 (7.7%)	376/5006 (7.5%)	0.21
COPD	22/430 (5.1%)	32/1138 (2.8%)	107/1747 (6.1%)	87/1691 (5.1%)	248/5006 (5%)	0.00
Renal failure	14/430 (3.3%)	73/1138 (6.4%)	134/1747 (7.7%)	165/1691 (9.8%)	386/5006 (7.7%)	<0.001
Atrial fibrillation	38/430 (8.8%)	69/1138 (6.1%)	153/1747 (8.8%)	123/1691 (7.3%)	383/5006 (7.7%)	0.04
Smoking						
Never	234/430 (54.4%)	662/1138 (58.2%)	709/1747 (40.6%)	758/1691 (44.8%)	2363/5006 (47.2%)	<0.001
Ex	135/430 (31.4%)	398/1138 (35%)	818/1747 (46.8%)	770/1691 (45.5%)	2121/5006 (42.4%)	
Current	61/430 (14.2%)	78/1138 (6.9%)	220/1747 (12.6%)	163/1691 (9.6%)	522/5006 (10.4%)	
Framingham score						
≤10%	32/280 (11.4%)	70/757 (9.2%)	113/968 (11.7%)	74/977 (7.6%)	289/2982 (9.7%)	0.03
10–20%	237/280 (84.6%)	662/757 (87.5%)	823/968 (85%)	855/977 (87.5%)	2577/2982 (86.4%)	
>20%	11/280 (3.9%)	25/757 (3.3%)	32/968 (3.3%)	48/977 (4.9%)	116/2982 (3.9%)	
Drugs in use						
Metformin	10/430 (2.3%)	850/1138 (74.7%)	39/1747 (2.2%)	1043/1691 (61.7%)	1942/5006 (38.8%)	<0.001
Sulfonyurea	0/430 (0%)	300/1138 (26.4%)	0/1747 (0%)	332/1691 (19.6%)	632/5006 (12.6%)	<0.001
Insulin	0/430 (0%)	277/1138 (24.3%)	0/1747 (0%)	580/1691 (34.3%)	857/5006 (17.1%)	<0.001
Diuretic	176/430 (40.9%)	573/1138 (50.4%)	535/1747 (30.6%)	667/1691 (39.4%)	1951/5006 (39%)	<0.001
ACEi or ARA II	309/430 (71.9%)	872/1138 (76.6%)	1283/1747 (73.4%)	1310/1691 (77.5%)	3774/5006 (75.4%)	0.01
Statins	277/430 (64.4%)	718/1138 (63.1%)	1354/1747 (77.5%)	1255/1691 (74.2%)	3604/5006 (72%)	<0.001
Aspirin	219/430 (50.9%)	723/1138 (63.5%)	1375/1747 (78.7%)	1323/1691 (78.2%)	3640/5006 (72.7%)	<0.001
Antiplatelet other	224/430 (52.1%)	729/1137 (64.1%)	1415/1747 (81%)	1360/1691 (80.4%)	3728/5005 (74.5%)	<0.001
Anticoagulants	37/430 (8.6%)	60/1138 (5.3%)	148/1747 (8.5%)	110/1691 (6.5%)	355/5006 (7.1%)	0.00
BMI						
25–30 kg/m^2	171/430 (39.8%)	405/1132 (35.8%)	735/1743 (42.2%)	626/1685 (37.2%)	1937/4990 (38.8%)	<0.001
<25 kg/m^2	133/430 (30.9%)	185/1132 (16.3%)	620/1743 (35.6%)	375/1685 (22.3%)	1313/4990 (26.3%)	
>30 kg/m^2	126/430 (29.3%)	542/1132 (47.9%)	388/1743 (22.3%)	684/1685 (40.6%)	1740/4990 (34.9%)	
Systolic BP (mmHg)	130.1 ± 18.4 (n = 430)	135.9 ± 21.6 (n = 1138)	128.7 ± 20 (n = 1747)	134.9 ± 20.9 (n = 1691)	132.5 ± 20.8 (n = 5006)	<0.001
Diastolic BP (mmHg)	79.7 ± 12.2 (n = 430)	81.6 ± 12.6 (n = 1138)	78.1 ± 12.2 (n = 1747)	79.6 ± 12.4 (n = 1691)	79.6 ± 12.4 (n = 5006)	<0.001
Total cholesterol (mg/dL)	195.3 ± 42.4 (n = 289)	181.3 ± 46.7 (n = 771)	176.4 ± 74.6 (n = 991)	171.9 ± 50.8 (n = 1000)	178 ± 58.4 (n = 3051)	<0.001
HDL cholesterol (mg/dL)	49.3 ± 13.6 (n = 280)	46.6 ± 14.9 (n = 762)	45.5 ± 13.5 (n = 980)	43.1 ± 14.6 (n = 984)	45.4 ± 14.3 (n = 3006)	<0.001
Triglycerides (mg/dL)	146.8 ± 76.1 (n = 285)	163.7 ± 124.2 (n = 755)	145.9 ± 99.8 (n = 1016)	174.9 ± 132 (n = 1003)	159.8 ± 116.2 (n = 3059)	<0.001
Glycemia (mg/dL)	97 ± 13.2 (n = 284)	144.8 ± 60 (n = 839)	98.6 ± 18 (n = 1076)	147.6 ± 65.6 (n = 1136)	126.8 ± 55.2 (n = 3335)	<0.001
HbA1c (mmol/mol)	39.6 ± 14.6 (n = 150)	56.7 ± 20.1 (n = 656)	42.6 ± 16.8 (n = 408)	62.8 ± 24.7 (n = 744)	54.8 ± 22.7 (n = 1958)	<0.001
Creatinine (mg/dL)	1 ± 0.5 (n = 275)	1.1 ± 0.7 (n = 787)	1.1 ± 0.7 (n = 1154)	1.2 ± 0.9 (n = 1104)	1.1 ± 0.8 (n = 3320)	<0.001

Mean ± standard deviation, or n (%).
ACEi: angiotensin converting enzyme inhibitors.
ARA II: angiotensin II receptor blockers.
BMI: body mass index.
BP: blood pressure.
Previous cardiovascular disease included myocardial infarction, coronary artery bypass graft surgery and percutaneous coronary revascularization.
P values according Chi-square test, except for age, which uses ANOVA's F test instead.

differences appeared in previous studies because younger women were evaluated, as women's protection from cardiovascular risk is lost after menopause [26]; the mean age of women in the REACT study was 66.1 ± 10.3 years.

Interestingly, other reports showed that hypertension (OR 2.01, 95% CI 1.23–3.30) and diabetes (OR 1.62, 95% CI 1.07–2.46) were significant predictors of neurological outcomes (lacunar stroke recurrence) [27]. However, the in-hospital mortality in ischemic stroke patients with diabetes was reported to be 12.5% and 14.6% in those without [28].

The implications of our findings go beyond excessive labeling of patients as high-risk, extending to over prescription of aspirin and statins and also leading to use of high statin doses in order to reach very strict LDL targets. Analysis of data on the use of these drugs in primary prevention of cardiovascular events in all people does not support recommendations for their widespread use, aiming for very strict LDL targets [29], if a balance between benefits, harms, and costs is considered [30–32]. In spite of this large and consistent body of evidence, the recent AHA guidelines include diabetes as one of the four major statin benefit groups in which the atherosclerotic cardiovascular risk reduction will outweigh the risks of adverse events [10]. Although risk equations can overestimate coronary heart disease risk [33,34], our findings suggest that

Table 2 – Follow up characteristics of the patients studied, according to the presence or not of diabetes and previous cardiovascular events.

Events	No previous cardiovascular event		Previous cardiovascular event		Total (n = 5006)	p
	No diabetes (n = 430)	Diabetes (n = 1138)	No diabetes (n = 1747)	Diabetes (n = 1691)		
Until 6 months						
Myocardial infarction	0/395 (0%)	3/1013 (0.3%)	23/1550 (1.5%)	20/1496 (1.3%)	46/4454 (1%)	0.003
Cardiac arrest	2/395 (0.5%)	9/1013 (0.9%)	11/1550 (0.7%)	21/1496 (1.4%)	43/4454 (1%)	0.172
Stroke	2/395 (0.5%)	4/1013 (0.4%)	16/1550 (1%)	15/1496 (1%)	37/4454 (0.8%)	0.247
Death	6/395 (1.5%)	27/1013 (2.7%)	55/1550 (3.5%)	79/1496 (5.3%)	167/4454 (3.7%)	<0.001
Cardiac death	4/395 (1%)	18/1013 (1.8%)	40/1550 (2.6%)	42/1496 (2.8%)	104/4454 (2.3%)	0.098
Combined event	8/395 (2%)	34/1013 (3.4%)	85/1550 (5.5%)	105/1496 (7%)	232/4454 (5.2%)	<0.001
Until 1 year						
Myocardial infarction	1/366 (0.3%)	8/920 (0.9%)	33/1340 (2.5%)	37/1331 (2.8%)	79/3957 (2%)	0.001
Cardiac arrest	3/366 (0.8%)	15/924 (1.6%)	17/1340 (1.3%)	29/1333 (2.2%)	64/3963 (1.6%)	0.164
Stroke	4/366 (1.1%)	5/920 (0.5%)	21/1339 (1.6%)	23/1332 (1.7%)	53/3957 (1.3%)	0.085
Death	8/366 (2.2%)	37/927 (4%)	75/1343 (5.6%)	106/1337 (7.9%)	226/3973 (5.7%)	<0.001
Cardiac death	5/366 (1.4%)	25/926 (2.7%)	52/1341 (3.9%)	61/1333 (4.6%)	143/3966 (3.6%)	0.01
Combined event	12/366 (3.3%)	50/927 (5.4%)	117/1349 (8.7%)	153/1339 (11.4%)	332/3981 (8.3%)	<0.001

n (%); Previous cardiovascular disease included myocardial infarction, coronary artery bypass graft surgery and percutaneous coronary revascularization.
P values according Chi-square test.

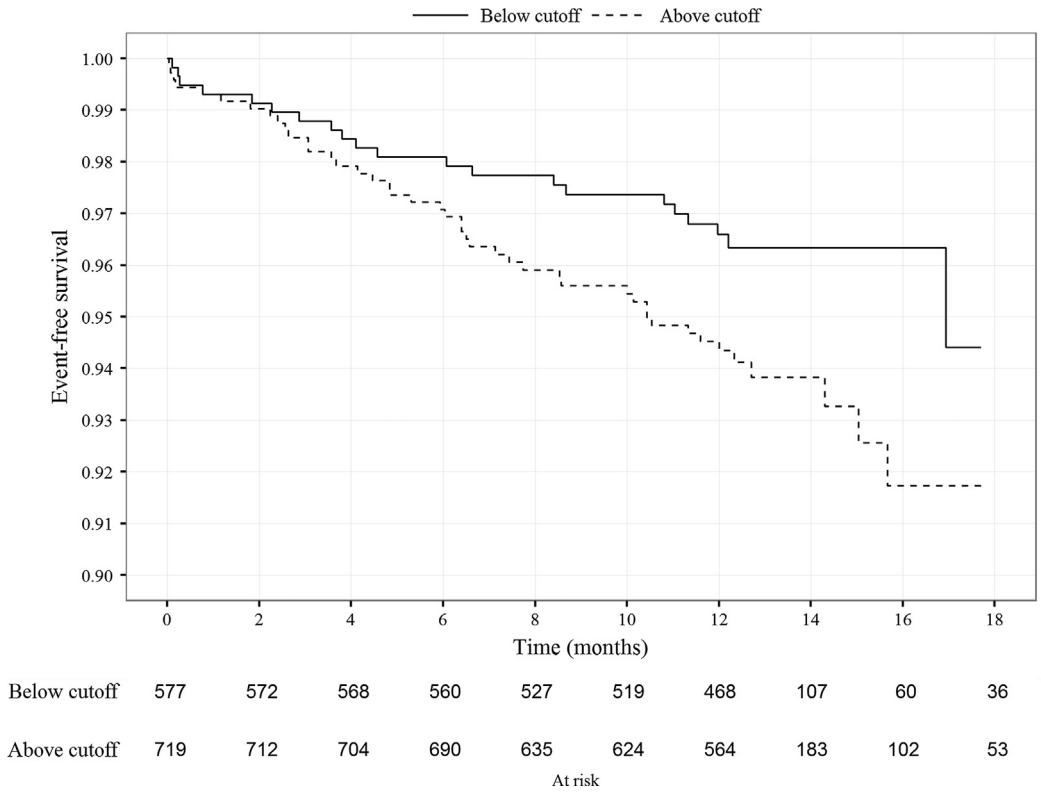

Fig. 3 – Survival curves for primary endpoint of patients with diabetes according to baseline HbA1c. Target for HbA1c was considered to be lower than 7% (53 mmol/mol) for those who did not have a previous cardiovascular event, and lower than 8% (63.9 mmol/mol) for those who had a previous cardiovascular event. HR were estimated from adjusted Cox models in Table 3 (HR 1.70 95% CI [1.01–2.84]) without interaction between diabetes and cardiovascular history.

Table 3 – Cox model estimative for major clinical events[a] in patients with diabetes only adjusted as shown.

Factor	Hazard ratio	95% CI		*p*
		Lower	Upper	
Elevated HbA1c[b]	1.698	1.014	2.844	0.044
Previous MI	1.652	0.985	2.772	0.057
Peripheral artery disease	1.272	0.713	2.267	0.415
Previous stroke	1.116	0.600	2.076	0.728
Age (years)[c]	1.042	1.015	1.069	0.002
Men	1.015	0.610	1.691	0.954
BMI (kg/m^2)[c]	0.972	0.928	1.017	0.219
Previous or actual smoker	0.987	0.591	1.649	0.962
Heart failure	3.021	1.820	5.014	<0.001
Renal failure	1.405	0.768	2.571	0.270

MI: myocardial infarction.
BMI: body mass index.
[a] All-cause mortality, non-fatal myocardial infarction, non-fatal cardiac arrest, or non-fatal stroke.
[b] Elevated HbA1c was considered >8% (63.9 mmol/mol) for those with previous cardiovascular events, and >7% (53 mmol/mol) for those without previous cardiovascular events.
[c] Included as continuous co-variable (HR reflects the effect of 1 unit increment).

individual risk assessment remains necessary in patients with diabetes, which is particularly important in healthcare services with limited resources, as in the case of Brazil. An alternative approach could be intensifying medical treatment to populations for whom clinical trials have demonstrated benefit [35].

The present data is in accordance with recent guidelines, that recommend less stringent HbA1c goals for patients with previous severe hypoglycemia, limited life expectancy, advanced diabetes complications, or extensive comorbidities [21]. A comprehensive approach taking into account the multiple modifiable risk factors for late complications in patients

with diabetes has the greatest potential for prevention [36]. Moreover, the use of insulin, which generally heralds advanced disease [17], was *per se* associated with higher cardiovascular risk in this population.

The strengths of the REACT study are the large sample size, prevention of selection bias by using a consecutive sample, the prospective nature of data collection, the careful baseline measurement of cardiovascular risk factors, use of evidence-based medications, and individual characteristics. Besides, being the unique cohort study in Latin America on this issue is indeed of utmost importance.

4.1. *Limitations*

Our study has some limitations that merit consideration: first, the relatively short follow-up period. Second, lack of information on type of diabetes, duration of diabetes and information for calculating cardiovascular risk using specific calculators for diabetes. Third, the limited representativeness and reproducibility of the data since most patients came from tertiary care institutions, which may differ from community patients. Finally, our results may not be readily extrapolated to other countries and settings.

We conclude that in Brazil, as in many other countries, diabetes confers a high risk for major clinical events in a relatively short-term period. Importantly, this high-risk condition is not equivalent to having a previous cardiovascular event. Our results may be useful to inform clinical practice and also to guide public healthcare policies, as intensive medical treatment should not be prescribed and supported by the government for all patients with diabetes, irrespective of their baseline cardiovascular risk. This will avoid exposing patients at not so high cardiovascular risk to lifelong treatment with adverse effects and polypharmacy, at the expense of high cost to the Brazilian Public Health System. Identifying correctly who, among all subjects with diabetes, will benefit from intensive medical treatment for cardiovascular prevention is a difficult, but necessary task to develop, employing risk calculators or maybe using a trial-based approach for managing these patients.

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Competing interests

The authors have no conflict of interest to declare.

Contributorship statement

Conception and design: BDS, LAPM, OB.

Data search: BDS, JAFN, DM, DBP, CAM, LBM, PL, ALB, FMP, EH, SM.

Analysis and interpretation of data: BDS, LD, SBP.

Drafting of the manuscript: BDS, SBP.

Revising it critically for important intellectual content: BDS, LAPM, FCC, AP, JA, JIG, OB.

Final approval of the manuscript submitted: BDS, LAPM, FCC, OB.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2017.03.021.

REFERENCES

[1] Preis SR, Hwang SJ, Coady S, Pencina MJ, D'Agostino Sr 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(13):1728–35.

[2] Schmidt MI, Duncan BB, Azevedo e Silva G, Menezes AM, Monteiro CA, Barreto SM, et al. Chronic non-communicable diseases in Brazil: burden and current challenges. Lancet 2011;377(9781):1949–61.

[3] Kim S, Boye KS. Excessive hospitalizations and its associated economic burden among people with diabetes in the United States. Value Health 2009;12(2):267–72.

[4] Bahia LR, Araujo DV, Schaan BD, Dib SA, Negrato CA, Leão MP, et al. The costs of type 2 diabetes mellitus outpatient care in the Brazilian public health system. Value Health 2011;14(5 Suppl. 1):S137–40.

[5] Franco M, Bilal U, Orduñez P, Benet M, Morejón A, Caballero B, et al. Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980–2010: repeated cross sectional surveys and ecological comparison of secular trends. BMJ 2013;346:f1515.

[6] Monteiro CA, Conde WL, Popkin BM. Income-specific trends in obesity in Brazil: 1975–2003. Am J Publ Health 2007;97(10):1808–12.

[7] Mendes AB, Fittipaldi JA, Neves RC, Chacra AR, Moreira Jr ED. Prevalence and correlates of inadequate glycaemic control: results from a nationwide survey in 6,671 adults with diabetes in Brazil. Acta Diabetol 2010;47(2):137–45.

[8] Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339(4):229–34.

[9] Third Report of the National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106(25):3143–421.

[10] Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(25 Suppl. 2):S1–S45.

[11] Dora JM, Kramer CK, Canani LH. Standards of medical care in diabetes–2008: response to Hirsch, Inzucchi, and Kirkman. Diabetes Care 2008;31(5):e44.

[12] Lee CD, Folsom AR, Pankow JS, Brancati FL, Atherosclerosis Risk in Communities (ARIC) Study Investigators. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. Circulation 2004;109(7):855–60.

[13] Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. BMJ 2002;324(7343):939–42.
[14] Booth GL, Kapral MK, Fung K, Tu JV. Relation between age and cardiovascular disease in men and women with diabetes compared with non-diabetic people: a population-based retrospective cohort study. Lancet 2006;368(9529):29–36.
[15] Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–12.
[16] Rana JS, Liu JY, Moffet HH, Jaffe M, Karter AJ. Diabetes and prior coronary heart disease are not necessarily risk equivalent for future coronary heart disease events. J Gen Intern Med 2016;31:387–93.
[17] Munnee K, Bundhun PK, Quan H, Tang Z. Comparing the clinical outcomes between insulin-treated and non-insulin-treated patients with type 2 diabetes mellitus after coronary artery bypass surgery: a systematic review and meta-analysis. Medicine (Baltimore) 2016;95:e3006.
[18] Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Ann Int Diabet Med 2009;26(2):142–8.
[19] Piva e Mattos LA. Rationality and methods – registry of clinical practice in high-risk cardiovascular patients. Arq Bras Cardiol 2011;97(1):3–7.
[20] Berwanger O, Piva e Mattos LA, Martin JF, Lopes RD, Figueiredo EL, Magnoni D, et al. Evidence-based therapy prescription in high-cardiovascular risk patients: the REACT study. Arq Bras Cardiol 2013;100(3):212–20.
[21] American Diabetes Association. Standards of medical care in diabetes – 2016. Diabetes Care 2016;38(Suppl. 1):S33–40.
[22] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2013. ISBN 3-900051-07-0. <http://www.R-project.org>.
[23] Burgess DC, Hunt D, Li L, Zannino D, Williamson E, Davis TM, et al. Incidence and predictors of silent myocardial infarction in type 2 diabetes and the effect of fenofibrate: an analysis from the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Eur Heart J 2010;31:92–9.
[24] Emerging Risk Factors Collaboration, Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, et al. Association of cardiometabolic multimorbidity with mortality. JAMA 2015 Jul 7;314(1):52–60.
[25] Hu G, Jousilahti P, Qiao Q, Katoh S, Tuomilehto J. Sex differences in cardiovascular and total mortality among diabetic and non-diabetic individuals with or without history of myocardial infarction. Diabetologia 2005;48(5):856–61.
[26] Ho JE, Paultre F, Mosca L. The gender gap in coronary heart disease mortality: is there a difference between blacks and whites? J Womens Health (Larchmt) 2005;14(2):117–27.
[27] Arboix A, Font A, Garro C, García-Eroles L, Comes E, Massons J. Recurrent lacunar infarction following a previous lacunar stroke: a clinical study of 122 patients. J Neurol Neurosurg Psychiatry 2007;78(12):1392–4.
[28] Arboix (1) A, Rivas A, García-Eroles L, de Marcos L, Massons J, Oliveres M. Cerebral infarction in diabetes: clinical pattern, stroke subtypes, and predictors of in-hospital mortality. BMC Neurol 2005;5(1):9.
[29] Hayward RA, Krumholz HM, Zulman DM, Timbie JW, Vijan S. Optimizing statin treatment for primary prevention of coronary artery disease. Ann Intern Med 2010;152(2):69–77.
[30] De Berardis G, Sacco M, Strippoli GF, Pellegrini F, Graziano G, Tognoni G, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ 2009;339:b4531.
[31] Taylor FC, Huffman M, Ebrahim S. Statin therapy for primary prevention of cardiovascular disease. JAMA 2013;310(22):2451–2.
[32] Ray KK, Seshasai SR, Erqou S, Sever P, Jukema JW, Ford I, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Int Med 2010;170(12):1024–31.
[33] Stevens RJ, Kothari V, Adler AI, Stratton IMUnited Kingdom Prospective Diabetes Study (UKPDS) Group. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101(6):671–9.
[34] Bannister CA, Poole CD, Jenkins-Jones S, Morgan CL, Currie C, Elwyn G. Validation of UKPDS risk engine predictions among patients with type 2 diabetes routinely managed in UK primary care. Diabetes 2013;62(Suppl. 1):A71.
[35] Ridker PM, Wilson PW. A trial-based approach to statin guidelines. JAMA 2013;310(11):1123–4.
[36] 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(6):580–91.