Prediabetes Defined by First Measured HbA_{1c} Predicts Higher Cardiovascular Risk Compared With HbA_{1c} in the Diabetes Range: A Cohort Study of Nationwide Registries

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OBJECTIVE

To assess the risk of major adverse cardiovascular events (MACE), all-cause mortality, and initiation of medical treatment in subjects with prediabetes according to first-time measured HbA_{1c}.

RESEARCH DESIGN AND METHODS

Through registry databases, we identified 326,305 Danish patients with a first HbA_{1c} between 40 and 51 mmol/mol (5.8–6.8%) from 2011 to 2017. After exclusion of patients with prior disease, 84,678 patients were followed 12 months after first HbA_{1c} measurement. Cox regression models were used to estimate hazard ratios (HRs) of MACE and standardized absolute risks. Cumulative incidences were used to analyze initiation of glucose-lowering, antihypertensive, cholesterol-lowering, and antithrombotic medication.

RESULTS

The 12-month risk of MACE and all-cause mortality increased gradually with increasing HbA_{1c} until 47 mmol/mol (6.5%). In comparisons of subjects with HbA_{1c} 40–41 mmol/mol (5.8–5.9%), subjects with HbA_{1c} 46–47 mmol/mol (6.4–6.5%) had a 0.79% (95% CI 0.33–1.24) higher standardized absolute risk and an HR of 2.21 (95% CI 1.67–2.92) of MACE. Patients with HbA_{1c} 48–49 mmol/mol (6.5–6.6%) had a 0.09% (95% CI −0.35 to 0.52) lower absolute risk and an HR of 1.33 (95% CI 0.87–2.05) of MACE. Initiation of medication was significantly lower among patients with HbA_{1c} of 46–47 mmol/mol (6.4–6.5%) than among patients with HbA_{1c} of 48–49 mmol/mol (6.5–6.6%).

CONCLUSIONS

In the Danish population screened for diabetes with HbA_{1c}, the highest risk of MACE and all-cause mortality was found in subjects with HbA_{1c} just below the diagnostic threshold for diabetes. Our results highlight the need for increased focus on the treatment of cardiovascular risk factors for subjects with prediabetes.

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With use of current diagnostic criteria for type 2 diabetes (1) a considerable number of individuals fall short of meeting the criteria for diagnosis and are characterized as individuals with prediabetes (2). Prediabetes is defined as an intermediate metabolic state between normoglycemia and diabetes and includes those with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). In clinical practice, hemoglobin A_{1c} (HbA_{1c}) is often used as the diagnostic criteria, and while diabetes is defined at $HbA_{1c} \geq 48$ mmol/mol (6.5%), the definitions and cutoff points for prediabetes differ between guidelines published by different organizations. Nevertheless, recent data show that among U.S. adults aged 18 years or older in 2013–2016, 34.5% had prediabetes defined as HbA_{1c} levels between 39 mmol/mol (5.7%) and 48 (6.5%) (3). Beside the increased risk of developing type 2 diabetes, studies have shown that prediabetes is also associated with a higher risk of cardiovascular disease and mortality (4–7).

In Denmark, newly diagnosed type 2 diabetes patients are usually treated according to national guidelines that are in accordance with an international European Association for the Study of Diabetes/American Diabetes Association (ADA) consensus report (8): lifestyle intervention, early treatment with glucose-lowering medications, and antihypertensive and cholesterol-lowering medications aiming to achieve recommended treatment goals, supported by aspirin in cases with clinical cardiovascular disease. After introduction of HbA_{1c} as the primary diagnostic tool for diagnosing diabetes (9), it has become an integral part of the health assessment by the general practitioner and in hospitals and is widely used as a screening tool. It has been proposed that subjects with HbA_{1c} in the upper normal range should repeat their measurement and undergo a cardiovascular risk assessment every year (10) and receive lifestyle intervention and medication accordingly (11). However, this did not lead to a national definition of prediabetes or guidelines for treatment. Indeed, a uniform definition of prediabetes is warranted and the evidence for intervention is conflicting, which is why subjects living with prediabetes in most cases are monitored without treatment (12).

The aim of this study was to describe how glucose-lowering, cholesterol-lowering, antihypertensive, and antithrombotic treatment is initiated in real-world clinical practice after a first-time HbA_{1c} measurement in the upper normal range, between 40 and 51 mmol/mol (5.8–6.8%), and furthermore, to assess cardiovascular risk and all-cause mortality in subjects with an HbA_{1c} just above and just below the therapeutic threshold for diabetes.

RESEARCH DESIGN AND METHODS

Study Setting

Every resident in Denmark has a permanent and unique civil registration number that allows individual linkage of different administrative and nationwide registries. We collected and linked data from the following sources: *1*) the civil registration system, which holds information on date of birth and date of death as well as vital events and emigration status for all inhabitants in Denmark (13); *2*) the Danish National Patient Registry, which holds date of admission and discharge as well as an ICD-10 code for all hospital contacts in Denmark; *3*) the Danish National Prescription Registry (14,15), where every dispensed drug from a Danish pharmacy is coded according to the Anatomical Therapeutic Chemical (ATC) classification; and *4*) a large collection of laboratory databases covering most blood tests from hospitals and general practitioners in four of five major regions in Denmark.

Study Population

We identified 326,305 individuals with a first measurement of HbA_{1c} from 2011 to 2017. We excluded 9,375 patients with estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, where HbA_{1c} is difficult to interpret, and we excluded patients already receiving glucose-lowering (42,332) or cholesterol-lowering (78,605) treatment and treatment with renin-angiotensin system inhibitor (RASi) (46,733), acetylsalicylic acid (ASA) (7,431), calcium channel blocker (9,397), and β-blocker (7,407), since initiations of these treatments were used as outcomes in our study (Fig. 1). We also excluded 1,508 patients with prior cardiovascular disease, since new admissions coded with cardiovascular disease could be related to older events. In total, 84,678 patients were included and divided into six subgroups stratified by levels of HbA_{1c}: 40–41 mmol/mol (5.8–5.9%), 42–43 mmol/mol (6.0–6.1%), 44–45 mmol/mol (6.2–6.3%), 46–47 mmol/mol (6.4–6.5%), 48–49 mmol/mol (6.5–6.6%), and 50–51 mmol/mol (6.7–6.8%). We note that 47 mmol/mol and 48 mmol/mol are both converted to 6.5% according to the NGSP HbA_{1c} converter but are two clearly separated values in Danish laboratory measurements.

Baseline Characteristics

Baseline comedication was evaluated on the basis of claimed prescriptions 180 days before inclusion, and baseline comorbidity was calculated with use of hospital diagnoses within the previous 5 years before inclusion, as previously described (16,17). Diagnoses and pharmacotherapy used for defining the population, comorbidity, and outcomes can be found in Supplementary Table 1.

Outcomes

The primary end point was the first occurrence of a major adverse cardiovascular event (MACE), a composite end point of nonfatal myocardial infarction, nonfatal stroke, and death from cardiovascular causes. Secondary end points included all-cause mortality and initiation of medication: glucose-lowering medication, statins, RASi, and acetylsalicylic acid ASA. Initiation of medication was defined as the first date the patient claimed a prescription for the relevant medication. The ICD-10 diagnosis codes of myocardial infarction and stroke have both been validated in the Danish National Patient Registry with high positive predictive values (PPVs) (PPV = 100.0% [95% CI 97.5–100.0] for myocardial infarction and 97.0% [93.1–98.7] for stroke). All-cause mortality is registered with almost 100% validity and completeness in the civil registration system (13).

Statistical Analysis

Categorical covariates are presented as number with percentages, and continuous covariates are presented as median with interquartile range (IQR) or means with SD. We calculated unadjusted and adjusted hazard ratios (HRs) of MACE, all-cause mortality, and medication initiation according to HbA_{1c} subgroup using Cox regression analyses. We adjusted for age, sex, income, cohabitation status,

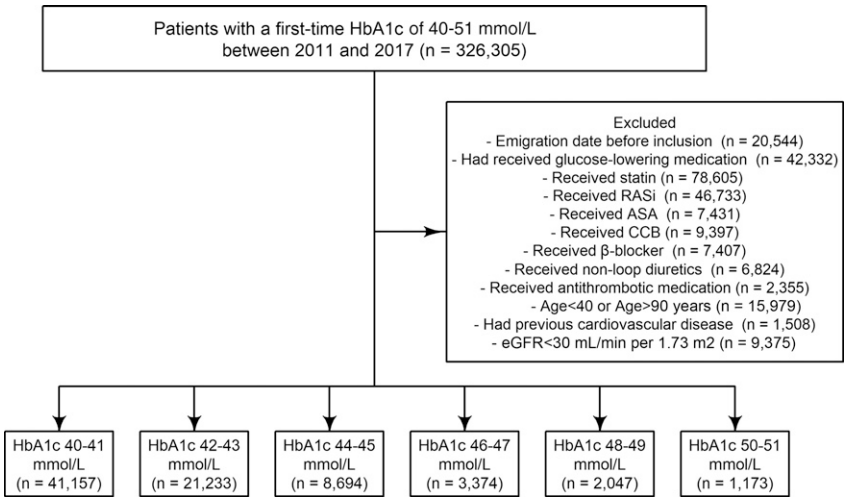

Figure 1—Flowchart of selection of study population showing exclusions. CCB, calcium channel blocker.

education, year of inclusion, zip code, loop diuretics, antidepressives, chronic obstructive pulmonary disease (COPD), cancer, and eGFR. Patients were followed from date of first HbA_{1c} measurement until whichever of the following occurred first: 1 year after baseline, event of interest, death, or emigration. The proportional hazards assumption was examined with use of Schoenfeld residuals, and interactions between HbA_{1c} and sex, age, income, and eGFR were tested in all reported models. We found no relevant violations of model assumptions. We used the g-formula to calculate standardized absolute 1-year risks according to HbA_{1c} based on Cox models for MACE as well as Cox models for competing risk. We conducted the following sensitivity analyses: First, we calculated HR of MACE according to HbA_{1c} following patients for a maximum of 2 years instead of 1 year. Second, we calculated HR of MACE according to HbA_{1c} when including a wider population with previous cardiovascular disease and previous antihypertensive, cholesterol-lowering, and antithrombotic treatment. Third, we calculated HR of MACE according to HbA_{1c} when adjusting for LDL cholesterol among patients with available LDL cholesterol at inclusion. Furthermore, we calculated cumulative incidence of a second HbA_{1c} measurement according to baseline HbA_{1c}, and we calculated initiation of statin initiation according to LDL cholesterol among patients with prediabetes and available LDL cholesterol values. *P* values <0.05 and 95% CIs not including 1.00 were considered statistically significant. All analyses were conducted with SAS, version 9.4, statistical software (SAS Institute, Cary, NC), and R package, version 3.4.1.

Ethics

Registry-based studies do not require ethics approval in Denmark, and data were anonymized with no possibility of identification of individual patients.

RESULTS

Characteristics of the Study Population

The included study population was comprised of 84,678 subjects with a first-time baseline measurement of HbA_{1c} (Table 1): 48,157 subjects (57%) with HbA_{1c} 40–41 mmol/mol (5.8–5.9%), 21,233 subjects (25%) with HbA_{1c} 42–43 mmol/mol (6.0–6.1%), 8,694 subjects (10%) with HbA_{1c} 44–45 mmol/mol (6.2–6.3%), 3,374 subjects (4%) with HbA_{1c} 46–47 mmol/mol (6.4–6.5%), 2,047 patients living with diabetes (2%) with HbA_{1c} 48–49 mmol/mol (6.5–6.6%), and 1,173 patients living with diabetes (1%) with HbA_{1c} 50–51 mmol/mol (6.7–6.8%). In the subgroup with lowest HbA_{1c}, 45.3% were men, and the proportion of male subjects increased with increasing first-time HbA_{1c} measurement to 60.0% in the HbA_{1c} 50–51 mmol/mol (6.7–6.8%) subgroup. Median age varied from 58.4 years (IQR 50.7–66.8) to 61.8 years (IQR 53.3–70.3) between the groups, as subjects were generally comparable across HbA_{1c} subgroups, both with regard to age, living situation, and income and with regard to comedication and comorbidity (Table 1).

HbA_{1c} Subgroups and Risk of Incident MACE

During the follow-up period of 1 year, a total of 799 individuals (0.94%) experienced a MACE. We found a dose-response relationship between higher HbA_{1c} and incident MACE in the HbA_{1c} range between 40 and 47 mmol/mol (5.8–6.5%). In comparisons with the reference group with HbA_{1c} 40–41 mmol/mol (5.8–5.9%), subjects with HbA_{1c} 42–43 mmol/mol (6.0–6.1%) and HbA_{1c} 44–45 mmol/mol (6.2–6.3%) had HRs of 1.28 (95% CI 1.08–1.51) and 1.59 (95% CI 1.29–1.97), respectively. The highest risk of MACE was found in the subgroup without diabetes with HbA_{1c} 46–47 mmol/mol (6.4–6.5%) (HR 2.21, 95% CI 1.67–2.92). For risk of MACE in the groups with diabetes, HbA_{1c} 48–49 mmol/mol (6.5–6.6%) and 50–51 mmol/mol (6.7–6.8%), HR was 1.33 (95% CI 0.87–2.05) and 1.70 (95% CI 1.03–2.81), respectively. Associations between the different HbA_{1c} subgroups and MACE are summarized in Table 2. Adjustment for age, sex, income, cohabitation status, education, year of inclusion, zip code, loop diuretics, antidepressives, COPD, cancer, and eGFR did not change the results. In Fig. 2, the absolute risks, standardized absolute risks, and differences of risk are shown as a forest plot. In comparisons with the reference group, HbA_{1c} 40–41 mmol/mol (5.8–5.9%), there was a higher standardized absolute risk of MACE in the five other subgroups. The subgroup of HbA_{1c} 44–45 mmol/mol (6.2–6.3%) and HbA_{1c} 46–47 mmol/mol (6.4–6.5%) had significantly higher risks, with differences at 0.31% (95% CI 0.06–0.56) and 0.79% (95% CI 0.33–1.24). The subgroups passing the threshold of diabetes, HbA_{1c} 48–49 mmol/mol (6.5–6.6%) and 50–51 mmol/mol (6.7–6.8%), had lower standardized absolute risks, at 1.03% (95% CI 0.67–1.53) and 1.53% (95% CI 0.92–2.41), compared with the subgroup just under the threshold, HbA_{1c} 46–47 mmol/mol (6.4–6.5%) with 1.73% (95% CI 1.33–2.22). Supplementary Table 3 shows data for a 2-year follow-up. The highest risk of MACE was still found in the subgroup with HbA_{1c} 46–47 mmol/mol (HR 1.66, 95% CI 1.35–2.06). Furthermore, Supplementary Table 5 shows

Table 1—Baseline characteristics of the study population by first-time baseline measurement of HbA_{1c}

	HbA_{1c} 40–41 mmol/mol	HbA_{1c} 42–43 mmol/mol	HbA_{1c} 44–45 mmol/mol	HbA_{1c} 46–47 mmol/mol	HbA_{1c} 48–49 mmol/mol	HbA_{1c} 50–51 mmol/mol
No. of patients	48,157	21,233	8,694	3,374	2,047	1,173
Age, median (IQR)	60.1 (51.9–68.6)	61.2 (52.9–69.6)	61.8 (53.3–70.3)	61.2 (52.9–70.1)	60.5 (52.2–69.2)	58.4 (50.7–66.8)
Male sex, *n* (%)	21,826 (45.3)	9,919 (46.7)	4,280 (49.2)	1,693 (50.2)	1,120 (54.7)	704 (60.0)
Income group, *n* (%)						
Q1	7,057 (14.7)	3,621 (17.1)	1,628 (18.7)	670 (19.9)	391 (19.1)	191 (16.3)
Q2	13,800 (28.7)	6,630 (31.2)	2,887 (33.2)	1,095 (32.5)	662 (32.3)	390 (33.2)
Q3	15,174 (31.5)	6,452 (30.4)	2,505 (28.8)	1,011 (30.0)	603 (29.5)	354 (30.2)
Q4	12,126 (25.2)	4,530 (21.3)	1,674 (19.3)	598 (17.7)	391 (19.1)	238 (20.3)
Living alone, *n* (%)	16,016 (33.3)	7,290 (34.3)	3,177 (36.5)	1,222 (36.2)	764 (37.3)	451 (38.4)
Medication and comorbidities, *n* (%)						
Loop diuretics	645 (1.3)	370 (1.7)	227 (2.6)	95 (2.8)	67 (3.3)	34 (2.9)
Antidepressives	3,504 (7.3)	1,666 (7.8)	734 (8.4)	287 (8.5)	190 (9.3)	93 (7.9)
COPD	800 (1.7)	535 (2.5)	234 (2.7)	114 (3.4)	55 (2.7)	30 (2.6)
Cancer	1,396 (2.9)	684 (3.2)	305 (3.5)	132 (3.9)	71 (3.5)	27 (2.3)
Education level, *n* (%)						
Low	14,408 (29.9)	7,019 (33.1)	3,067 (35.3)	1,214 (36.0)	759 (37.1)	431 (36.7)
Medium	23,358 (48.5)	10,133 (47.7)	4,106 (47.2)	1,623 (48.1)	957 (46.8)	557 (47.5)
High	10,391 (21.6)	4,081 (19.2)	1,521 (17.5)	537 (15.9)	331 (16.2)	185 (15.8)
eGFR, mL/min/1.73 m^2, *n* (%)						
>90	21,505 (44.7)	9,304 (43.8)	3,783 (43.5)	1,516 (44.9)	1,016 (49.6)	613 (52.3)
45–60	24,397 (50.7)	10,691 (50.4)	4,351 (50.0)	1,638 (48.5)	923 (45.1)	503 (42.9)
30–45	2,255 (4.7)	1,238 (5.8)	560 (6.4)	220 (6.5)	108 (5.3)	57 (4.9)

Q, quarter.

MACE with inclusion of patients on statins, glucose-lowering medications, and antihypertensive and antithrombotic treatment, all of whom were excluded initially, with the same pattern of outcomes of HR.

HbA_{1c} Subgroups and Risk of All-Cause Mortality

A total of 1,123 subjects died during the first year after first measurement of HbA_{1c}. In comparisons with those with baseline HbA_{1c} 40–41 mmol/mol (5.8–5.9%), subgroup patients with HbA_{1c} 42–43 mmol/mol (6.0–6.1%) and HbA_{1c} 44–45 mmol/mol (6.2–6.3%) had HRs of 1.53 (95% CI 1.33–1.77) and 1.96 (95% CI 1.64–2.34), respectively. As in incident MACE, we found an association between higher HbA_{1c} and all-cause mortality until HbA_{1c} reached 47 mmol/mol (6.5%). With adjustment for LDL cholesterol and total cholesterol we found the same results as shown in Table 2, and additionally the same pattern was found in the 2-year follow-up where subjects with HbA_{1c} 42–43 mmol/mol (6.0–6.1%) and HbA_{1c} 44–45 mmol/mol (6.2–6.3%) had HRs of 1.29 (95% CI 1.17–1.43) and 1.50 (95% CI 1.32–1.70), respectively. Here, the highest risk of all-cause mortality was also found in the subgroup with HbA_{1c} 46–47 mmol/mol (HR 2.18, 95% CI 1.85–2.56). These associations are summarized in Supplementary Table 3. As Supplementary Tables 7 and 8 show, the results are maintained with use of HbA_{1c} <40 mmol/mol (5.8%) as a reference point as well as with use of larger subgroups.

Prescribed and Redeemed Medicine

Table 2 summarizes the HR calculated in looking at prescribed and redeemed medication in our study population. The HR increases with HbA_{1c} for all medications registered: glucose-lowering medication, ASA, RASi, and statin. The cumulative incidences are shown in Fig. 2. In looking at patients who met the criteria for type 2 diabetes, 497 (24%) patients from the subgroup HbA_{1c} 48–49 mmol/mol (6.5–6.6%) were started on glucose-lowering medication, 418 (20,4%) on statins, and 329 (16%) on RASi within a year after first HbA_{1c} measurement. In the subgroup of the patients in our study with the highest first measurement, HbA_{1c} 50–51 mmol/mol (6.7–6.8%), 514 (44%) patients were started on glucose-lowering medication, 317 (27%) on statins, and 231 (20%) on RASi within a year after first measurement. For patients who were just below the threshold for type 2 diabetes, the numbers were lower: 259 (8%) patients from the subgroup HbA_{1c} 46–47 mmol/mol (6.4–6.5%) were started on glucose-lowering medication, 383 (11%) on statins, and 408 (12%) on RASi within a year after first measurement. As Table 2 shows, the percentage of patients initiated with any of the medications increased with the level of HbA_{1c}. Supplementary Table 4 shows the association between levels of LDL cholesterol and number of patients initiated on statins, with a higher number of patients with type 2 diabetes starting treatment compared with individuals just under the threshold. Supplementary Table 6 shows the number of subjects on statins, glucose-lowering medication, and antihypertensive and antithrombotic

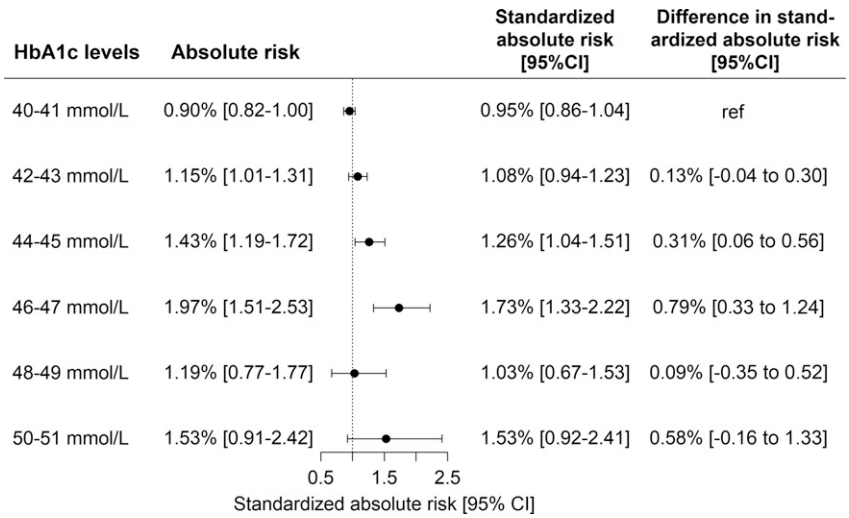

Figure 2—Forrest plot showing absolute risk, standardized absolute risk, and difference in standardized absolute risk of MACE during 1st year after index. Standardized for age, sex, income, cohabitation status, education, year of inclusion, zip code, loop diuretics, antidepressives, COPD, cancer, eGFR, LDL cholesterol, and total cholesterol.

treatment and how many were on several medications simultaneously. The amount increases with HbA_{1c} level. Of those in the subgroups of HbA_{1c} 48–49 mmol/mol (6.5–6.6%) and HbA_{1c} 50–51 mmol/mol (6.7–6.8%), 39.2% and 29.2%, respectively, were not on any medication despite passing the threshold of diabetes.

HbA_{1c} During Follow-up

Time for measurements of second HbA_{1c} varied during follow-up. In the lowest group of HbA_{1c}, 40–41 mmol/mol (5.8–5.9%), 72% of patients were without a second measurement in the following year. Just over one-half of the subgroup with HbA_{1c} 46–47 mmol/mol (6.4–6.5%) had a follow-up measurement. Almost none of patients in the lowest group of HbA_{1c} developed diabetes, whereas 9.2% of patients with first measurement of HbA_{1c} 44–45 mmol/mol (6.2–6.3%) developed type 2 diabetes within the year of follow-up. Almost 23% of patients with first measured HbA_{1c} 46–47 mmol/mol (6.4–6.5%) developed type 2 diabetes during follow-up. Among patients with HbA_{1c} over the threshold of diabetes in the first measurement, 36% and 46%, respectively, of subgroups 48–49 mmol/mol (6.5–6.6%) and 50–51 mmol/mol (6.7–6.8%) participants still had HbA_{1c} $>$48 mmol/mol (6.5%) during follow-up. The full list of HbA_{1c} measurements during the first year of follow-up can be found in Supplementary Table 2 and Supplementary Fig. 1.

CONCLUSIONS

We demonstrate that the highest risk of MACE and all-cause mortality is among patients with HbA_{1c} just below the diagnostic threshold for diabetes in a population with first-time HbA_{1c} measurements between 40 and 51 mmol/mol (5.8 and 6.8%) without previous diabetes or cardiovascular disease. Moreover, significantly fewer patients with a first-time HbA_{1c} measurement just below the threshold for type 2 diabetes, at HbA_{1c} 46–47 mmol/mol (6.4–6.5%), were started on glucose-lowering medication, statins, and RASi compared with the patients just above the threshold HbA_{1c} of 48–49 mmol/mol (6.5–6.6%) within a year after first HbA_{1c} measurement.

Prediabetes is an intermediate metabolic state between normal glucose metabolism and diabetes, and according to the ADA up to 70% of individuals with prediabetes will develop type 2 diabetes over time (18). A systematic review showed that the 5-year risk of diabetes, if the patient's HbA_{1c} level was at least 6.0% (42 mmol/mol), ranged from 25 to 50% and the relative risk of diabetes was 20 times higher if the HbA_{1c} was $\geq$6%, in comparison with an HbA_{1c} of $\leq$5% (19). In addition, studies have also associated prediabetes with increased risk of cardiovascular disease, coronary heart disease, and mortality (20).

Although there is agreement on the risks associated with prediabetes, different organizations have defined prediabetes with their own criteria that are not in consensus. The World Health Organization (WHO) has defined prediabetes as a state of intermediate hyperglycemia using two specific parameters—IFG, defined as fasting plasma glucose 6.1–6.9 mmol/mol (110–125 mg/dL), and IGT, defined as 2-h plasma glucose 7.8–11.0 mmol/mol (140–200 mg/dL) after ingestion of a 75-g oral glucose load—or a combination of the two (18). The ADA uses the same cutoff value for IGT but has a lower cutoff value for IFG (100–125 mg/dL) and has added an HbA_{1c} criteria of 5.7–6.4% (39–46 mmol/mol) for the definition of prediabetes (21). These discrepancies, although small, have played a role in the research data on patients with prediabetes. A systematic review from 2016 found that intermediate hyperglycemia, defined using IFG or IGT (both ADA and World Health Organization definitions), was associated with all-cause mortality (20). This was not the case when the ADA HbA_{1c}-based criterion (5.7–6.4% [39–46 mmol/mol]) or the International Expert Committee (IEC) HbA_{1c}-based definition of intermediate hyperglycemia, HbA_{1c} 42–47 mmol/mol (6.0–6.5%), was used. Previous meta-analyses have also shown inconsistent results on the different definitions of prediabetes when looking at mortality or other cardiovascular end points (20,22).

It can be argued that a more uniform understanding of prediabetes would help with earlier identification, thereby allowing earlier intervention, potentially lowering the number of patients who develop diabetes and complications in the future. As studies have shown, the association with, for example, mortality varies with use of different diagnostic criteria of the leading organizations. Our approach looks beyond the defined thresholds and divides the patients in subgroups according to their first-time HbA_{1c} measurements. In this way, we notice an increased risk as the HbA_{1c} levels increase without regard to the discrepancy in the different definitions of prediabetes. The weakness of this approach, however, is that we do not account for IFG and IGT.

Our study shows that the highest risk of MACE and all-cause mortality is in the subgroup with HbA_{1c} just below the diagnostic criteria for type 2 diabetes. We also found significantly lower

Table 2—Number of events and HRs (95% CI) during 1 year of follow-up according to HbA_{1c}

	HbA_{1c} 40–41 mmol/mol	HbA_{1c} 42–43 mmol/mol	HbA_{1c} 44–45 mmol/mol	HbA_{1c} 46–47 mmol/mol	HbA_{1c} 48–49 mmol/mol	HbA_{1c} 50–51 mmol/mol
MACE events, *n* (%)	382 (0.79)	213 (1.00)	109 (1.25)	57 (1.69)	22 (1.07)	16 (1.36)
Unadjusted HR	1.00 (ref)	1.28 (1.08–1.51)	1.59 (1.29–1.97)	2.21 (1.67–2.92)	1.33 (0.87–2.05)	1.70 (1.03–2.81)
Adjusted HR*	1.00 (ref)	1.16 (0.98–1.37)	1.35 (1.09–1.67)	1.91 (1.44–2.53)	1.14 (0.74–1.76)	1.63 (0.99–2.70)
All-cause mortality, *n* (%)	465 (0.97)	311 (1.46)	163 (1.87)	98 (2.90)	58 (2.83)	28 (2.39)
Unadjusted HR	1.00 (ref)	1.53 (1.33–1.77)	1.96 (1.64–2.34)	3.12 (2.51–3.88)	2.89 (2.20–3.79)	2.44 (1.67–3.58)
Adjusted HR*	1.00 (ref)	1.33 (1.15–1.54)	1.54 (1.29–1.84)	2.53 (2.03–3.15)	2.37 (1.80–3.12)	2.49 (1.70–3.65)
Initiated GLM, *n* (%)	84 (0.17)	113 (0.53)	239 (2.75)	259 (7.68)	497 (24.28)	514 (43.82)
Unadjusted HR	1.00 (ref)	3.62 (2.76–4.76)	16.04 (12.51–20.56)	46.97 (36.72–60.06)	160.91 (127.69–202.76)	351.16 (278.79–442.31)
Adjusted HR*	1.00 (ref)	3.65 (2.78–4.79)	16.25 (12.67)	48.85 (38.16–62.54)	154.76 (122.70–195.19)	330.88 (262.39–417.25)
Initiated statin, *n* (%)	3,116 (6.47)	1,632 (7.69)	800 (9.20)	383 (11.35)	418 (20.42)	317 (27.02)
Unadjusted HR	1.00 (ref)	1.20 (1.13–1.28)	1.45 (1.34–1.57)	1.83 (1.65–2.03)	3.35 (3.03–3.71)	4.61 (4.11–5.17)
Adjusted HR*	1.00 (ref)	1.16 (1.09–1.23)	1.38 (1.27–1.49)	1.76 (1.58–1.96)	3.14 (2.83–3.48)	4.37 (3.89–4.91)
Initiated RASi, *n* (%)	3,371 (7.00)	1,800 (8.48)	868 (9.98)	408 (12.09)	329 (16.07)	231 (19.69)
Unadjusted HR	1.00 (ref)	1.23 (1.16–1.30)	1.46 (1.35–1.57)	1.81 (1.63–2.00)	2.38 (2.12–2.66)	3.01 (2.64–3.44)
Adjusted HR*	1.00 (ref)	1.16 (1.09–1.23)	1.38 (1.27–1.49)	1.76 (1.58–1.96)	3.14 (2.83–3.48)	4.37 (3.89–4.91)
Initiated ASA, *n* (%)	1,234 (2.56)	623 (2.93)	308 (3.54)	139 (4.12)	95 (4.64)	54 (4.60)
Unadjusted HR	1.00 (ref)	1.16 (1.05–1.27)	1.40 (1.23–1.58)	1.66 (1.39–1.98)	1.81 (1.47–2.23)	1.81 (1.38–2.37)
Adjusted HR*	1.00 (ref)	1.19 (1.13–1.26)	1.39 (1.29–1.50)	1.73 (1.56–1.92)	2.24 (2.00–2.51)	2.84 (2.46–3.25)

GLM, glucose-lowering medication; ref, reference. *Adjustment for age, sex, income, cohabitation status, education, year of inclusion, zip code, loop diuretics, antidepressives, COPD, cancer, and eGFR.

cumulative incidence of initiation of cardioprotective and glucose-lowering medication among patients just below the diagnostic threshold for diabetes, compared with patients just above the therapeutic threshold. It is likely that the decreased risk of MACE when HbA_{1c} $\geq$48 mmol/mol (6.5%) is connected to the more aggressive treatment of cardiovascular risk factors initiated among patients with diagnosed diabetes as recommended in national guidelines compared with treatment of patients with prediabetes. It is also possible that patients with diabetes are much more likely to receive self-management education and change lifestyle accordingly compared with subjects with prediabetes. Interestingly, the proportion of male subjects increased with increasing first-time HbA_{1c} measurement from <50% to 60.0% in the HbA_{1c} 50–51 mmol/mol (6.7–6.8%) subgroup in our cohort. This is not surprising, as previous studies (23,24) have shown a higher prevalence of type 2 diabetes in men compared with women, explained not only by factors such as differences in visceral fat mass, diet, alcohol consumption, and smoking habits but also by lifestyle, as men tend to seek health care professionals later than women.

Managing prediabetes is an important aspect of the overall fight against diabetes and relates to both prevention of blood glucose levels progressing to diabetes and prevention of metabolic diseases such as hypertension, obesity, and dyslipidemia. Global guidelines focus mostly on lifestyle change, i.e., diet and exercise, as the main intervention (25). The Diabetes Prevention Program Research Group (DPPRG) showed that lifestyle interventions such as diet, physical activity, and ultimately weight loss led to a 58% risk reduction in developing diabetes in a 2.8-year follow-up (26,27). In a large follow-up study, lifestyle intervention lowered incidence of type 2 diabetes with 43% over a 20-year period in 577 adults with IGT from 33 clinics in China (28). The Finnish Diabetes Prevention Study, published in 2003, showed similar results, with incidence of conversion from prediabetes to diabetes being lower among subjects in the intervention group who lost at least 5% of their body weight during the trial compared with the control group (29).

Regarding medical treatment there are mixed reports on whether treatment should be initiated in patients with diabetes. ADA has recommended the use of metformin in certain individuals at high risk but with no clear goal of treatment (21,22). The DPPRG showed that metformin led to a 31% risk reduction in developing diabetes—almost as good as lifestyle interventions. A systematic review concluded that metformin lowers risk of type 2 diabetes by 45% in patients with prediabetes (30). However, when it comes to diabetes, outcome research and international guidelines specifically focus on both lowering HbA_{1c} and minimizing risk factors of the abovementioned complications, but in reality the diagnosis of diabetes is often delayed until complications are clinically present (27). Although several intervention studies have examined subjects with prediabetes, studies rarely address cardiovascular risk factors or microvascular outcomes in general, and no general guideline with specific goals for medical treatment of prediabetes exists. With patients just under the threshold having the highest risk of MACE and all-cause mortality, the argument could be made that a patient would be better off being diagnosed with type 2 diabetes, as it increases the chance of treatment for cardiovascular risk factors. In a national sample from Sweden it was shown that wider use of lipid-lowering drugs benefits micro- and macrovascular complications as well as diabetes-related mortality (31). Furthermore, among patients with IGT and cardiovascular risk factors, the use of a RASi for 5 years, along with lifestyle modification, led to a relative reduction of 14% in the incidence of diabetes (32).

A discussion of timing of initiation of glucose-lowering, cholesterol-lowering, antihypertensive, and antithrombotic treatment in patients with diabetes and prediabetes seems imminent. Interestingly, our study shows that only a small portion of patients with type 2 diabetes are being treated with cardiovascular disease risk–modifying drugs within the first year after measurement of HbA_{1c} just above the diabetes threshold. Less than one-third of the included patients with HbA_{1c} 50–51 mmol/mol (6.7–6.8%) were on statin treatment a year after their first measurement, and less than one-half were started on glucose-lowering medication, with even lower numbers in the subgroup with HbA_{1c} 48–49 mmol/mol (6.5–6.6%). After 2 years of follow-up (Supplementary Table 3), twice as many are on relevant medication, probably reflecting that many general practitioners and patients await possible effect of lifestyle changes the first year. Bearing the increased risk in mind, these points raise the question of whether medical treatment should be more aggressive and whether we should start treating cardiovascular risk factors even before the patients cross the diabetes threshold.

Our study had several strengths but some important limitations as well. The major strengths of this large study include the diminished risk of selection bias and the minimal loss of follow-up ensured by the comprehensive Danish registries, including hospital diagnoses, prescription claims, and blood samples. The large sample size allowed us to stratify data and determine associations of each subgroup of HbA_{1c} with risk of MACE. We chose quite narrow HbA_{1c} categories, and as a consequence CIs for risk of adverse events overlap between several of the subgroups. A larger number of included events could have allowed for more detailed risk stratification between subgroups. We were also able to control for comorbidities potentially present, including COPD and kidney disease, as well as age, sex, and income. Conversely, given the observational nature of this study, several important limitations need to be addressed. Firstly, the unmeasured confounding: although we were able to adjust for several comorbidities, data on certain modifiable risk factors, including exercise, smoking, alcohol intake, BMI, and diet, were not available. Secondly, surveillance bias is likely to have affected our results, as being in contact with the health care system increases the chance of diagnosing prediabetes. In our analyses with examination of use of medication, we do not look at the association with MACE and all-cause mortality risks at an individual level, so the analyses could be subject to ecological bias. Furthermore, medications examined are those that are redeemed and do not necessarily represent medications used or to what extent or whether subjects are treated to guideline targets. Some included subjects might have had an earlier measurement of HbA_{1c} from another laboratory, although they were excluded if medication had been initiated. Finally, we were not able to control for race. This is likely less of an issue in the more racially homogeneous population of Denmark, where there exists a universal health care system funded by grants from tax revenues; however, it will make it harder for our results to be generalized to other populations.

In conclusion, our study demonstrates an increased risk of MACE and all-cause mortality in the upper normal range of HbA_{1c} as compared with HbA_{1c} >48 mmol/mol (6.5%), the level typically prompting multifactorial treatment of type 2 diabetes. These results support the hypothesis that treatment for cardiovascular risk factors should start before type 2 diabetes develops and suggest that more attention and potentially evidence-based guidelines are needed in the management of prediabetes with better monitoring of this patient group.

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