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Diabetology

RSSDI

Yearbook of Diabetes 2017

Editor-in-Chief
Sujoy Ghosh

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Section 2: Epidemiology

SECTION AUTHORS: Amritava Ghosh, Sanjay Kalra, Anand Moses, Vijay Panikar

1. Mortality in Type 1 Diabetes in the DCCT/EDIC Versus the General Population

Ref: Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Mortality in type 1 diabetes in the DCCT/EDIC versus the general population. Diabetes Care. 2016;39(8):1378-83.

ABSTRACT

Objective: Historically, mortality in type 1 diabetes mellitus has exceeded that in the general population. We compared mortality in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study cohort to that of the current general US population.

Research Design and Methods: The DCCT (1983–1993) compared intensive versus conventional therapy, with HbA1c levels of approximately 7% vs. 9%, respectively, over an average of 6.5 years of treatment. The EDIC is the observational follow-up study of the DCCT (1994 to the present). Vital status was ascertained for 97.5% of the original DCCT cohort (n = 1,441) after a mean of 27 years follow-up. Expected mortality during DCCT/EDIC was estimated using the current age-, sex-, and race-specific risks in the general US population, and the observed versus expected mortality compared using standardized mortality ratios (SMRs) and Poisson regression models.

Results: Mortality in the DCCT intensive therapy group was no significantly lower than that in the general US population [SMR = 0.88 (95% CI 0.67, 1.16)], whereas mortality in the DCCT conventional therapy group was significantly greater than that in the general population [SMR = 1.31 (95% CI 1.05, 1.65)]. The SMR increased with increasing mean HbA1c, and above an HbA1c of 9%, the rate of increase in SMR among females was greater than that among males.

Conclusions: Overall mortality in the combined DCCT/EDIC cohort was similar to that of the general population but was higher in the DCCT conventional therapy group. Mortality increased significantly with increasing mean HbA1c, more so among females than males, especially for HbA1c >9%.

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The Diabetes Control and Complications Trial (DCCT) and its long-term follow-up study (Epidemiology of Diabetes Interventions and Complications [EDIC]) comprise the most definitive body of evidence regarding the short- and long-term benefits of managing hyperglycemia in people with type 1 diabetes mellitus (T1DM).[1] The DCCT recruited 1,441 individuals of mean age 27 years with 1–15 years' duration of T1DM who had no cardiovascular disease, hypertension, or dyslipidemia and randomly allocated them to more versus less intensive glycemic control. During a mean of 6.5 years of follow-up, the average HbA1c levels achieved in the intensive and conventional groups were 7% and 9%, respectively. By that time, participants who had been allocated to the intensive group had a much lower incidence of retinal, renal, and neurological disease compared with those allocated to the conventional group. Despite a subsequent average HbA1c of 8% in both groups, those who were initially allocated to the intensive group continued to experience less retinal, renal, and cardiovascular disease[2–4] and a 33% lower hazard of death during a total follow-up period of 27 years.[5]

In the present article, the researchers have compared the total mortality rates in the DCCT/EDIC participants to that of a matched general population of the US. Individuals who had been allocated to the intensive group had a mortality

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rate that was similar to that of the general population. Conversely, individuals who had been allocated to the conventional group had a mortality rate that was approximately 30% higher than that of the general population. Their analyses also reported a 49% higher mortality rate for participants formerly in the conventional versus intensive group. The standardized mortality ratios (SMRs) increased with increasing mean HbA1c, and above an HbA1c of 9%, the rate of increase in SMR among females was greater than that among males.

From the above results the following conclusions can be drawn: (1) People with recently diagnosed T1DM who are not intensively treated have a higher death rate than the general population; (2) At least 6.5 years of intensive insulin therapy in people with T1DM reduces this risk to normal; (3) Higher HbA1c levels predict a higher risk of death in people with T1DM.[6]

This is one of the largest intervention trials, followed by the longest post trial period of observation to document the mortality experience of patients with T1DM in relation to the general population. These clinical trial findings clearly reflect the long-term effect of intensive insulin therapy on mortality and are extremely encouraging to patients with diabetes and their health care providers.

The large effect size and the fact that these findings are based on an intention-to-treat analysis of participants in a randomized controlled trial for whom long-term follow-up vital status was available in more than 97.5% are clear strengths that highlight the clinical importance and relevance of these findings.[6]

The small number of deaths (N = 125) limits the ability to assess the intervention's effect on mortality across study subgroups (e.g., those with vs. without retinopathy at baseline) and represents the major weakness of the study. The fact that the DCCT was not a blinded study precludes knowing whether the mortality benefit is due just to the degree of glycemic control or to all of the other things that a participant in the intensive group (or his/her providers) may or may not have done as a result of being in that group.[6]

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2. Frequency of Evidence-based Screening for Retinopathy in Type 1 Diabetes

Ref: Nathan DM, Bebu I, Hainsworth D, et al. Frequency of evidence-based screening for retinopathy in type 1 diabetes. N Engl J Med. 2017;376(16):1507-16.

ABSTRACT

Background: Recent recommendations concerning about the screening of diabetic retinopathy in patients suffering from type 1 diabetes mellitus from the last 5 years include annual dilated retinal examinations, which helps to detect proliferative retinopathy or clinically significant macular edema. Proliferative retinopathy or macular edema requires timely intervention to preserve vision. During

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30 years of the Diabetes Control and Complications Trial (DCCT) and a study by Epidemiology of Diabetes Interventions and Complications (EDIC) demonstrated that performing retinal photography intervals of 6 months to 4 years should be maintain.

Methods: In order to develop a rational screening frequency for retinopathy, retinal photographs from the DCCT/EDIC study were used. In patients with various initial retinopathy levels (none, mild, moderate, or severe nonproliferative diabetic retinopathy), the possibility of progression to proliferative diabetic retinopathy or clinically significant macular edema was determined by using Markov modeling. Various risk factors which are known for the progression of retinopathy were included in these models.

Results: In total, the probability of progression to proliferative diabetic retinopathy or clinically significant macular edema among patients who had no retinopathy, mild retinopathy, moderate retinopathy, and severe nonproliferative diabetic retinopathy was limited to approximately 5% between retinal screening examinations at 4 years, 3 years, 6 months, and 3 months, respectively. The risk of progression was also closely related to mean glycosylated hemoglobin (HbA1c) levels. Patients with a HbA1c level of 6%, the risk of progression from no retinopathy to proliferative diabetic retinopathy or clinically significant macular edema was 1.0% over 5 years, as compared to patients with a HbA1c level of 10% having progression risk 4.3% over 3 years. Over a period of 20 years, the rate of examining the eyes leads to substantial cost savings because examination by our practical and evidence-based schedule lowers to 58%, whereas the use of routine annual examinations was increased.

Conclusions: On the basis of patient's current state of retinopathy and HbA1c level, an individualized schedule for retinopathy screening was established, which reduced the frequency of eye examinations without delaying the diagnosis of clinically significant disease was demonstrated in our model.

Goal of diabetic retinopathy screening is the timely detection of retinopathy so that appropriate interventions can be done for the prevention of vision loss. In patients with type 1 diabetes mellitus (T1DM), screening for retinopathy starting 5 years after diagnosis has long been recommended. Current American Diabetes Association guidelines recommend screening at no less than 2-year intervals for patients who have no retinopathy on initial examination and at least annually for those with any degree of retinopathy.[1]

The Diabetes Control and Complications Trial (DCCT), which was conducted from 1983 through 1993, and the follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study (which has been ongoing since 1994) have followed a cohort of patients with T1DM with regularly scheduled fundus photography for more than 30 years.[2] Nathan et al., reporting for the DCCT/EDIC Research Group, provide data on an individualized schedule for screening for diabetic retinopathy in patients with T1DM.

A previous meta-analysis suggested that increasing the interval between screening visits for diabetic retinopathy beyond 1 year in low-risk patients was reasonable, since the data showed little difference between the 1-year and 2-year screening frequency with respect to clinical outcomes.[3] Aspelund et al. proposed an algorithm for individualized risk assessment using both epidemiologic and clinical data, including the type and duration of diabetes, glycated hemoglobin or mean blood glucose levels, blood pressure, and the presence and grade of retinopathy.[4]

Nathan et al. analyzed almost 30 years of fundus photographs in a cohort of 1,441 patients with T1DM in order to simplify individualized risk assessments. They found that an accurate assessment of the risk of proliferative diabetic retinopathy or clinically significant macular edema was possible with the use of only the patient's current retinopathy status and glycosylated hemoglobin levels. The authors provide a user-friendly web application that can calculate a recommended time until the next eye examination on the basis of these two factors with an acceptable risk level (defined as an approximately 5% chance that proliferative diabetic retinopathy or clinically significant

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macular edema will develop in the interval before the next examination). The algorithm extends the screening interval for patients with a low risk of proliferative retinopathy or clinically significant macular edema to 3 or 4 years, which would reduce the frequency of eye examinations in patients with T1DM resulting in significant cost saving.

While the authors accounted for factors such as age, sex, diabetes duration, smoking status, hypertension, and hyperlipidemia, other risk factors such as renal failure and foot ulcers were not considered.[5]

In an accompanying editorial, Rosenberg JB et al., caution that if the proposed individualizing of the current screening schedule is adopted, determining the frequency of screening would be more complicated for patients and their doctors to follow than the present screening practice; this could lower screening rates below the intended thresholds. The authors acknowledge that potential issue, but state that, care providers may use automated scheduling systems to cope with this challenge. Rosenberg JB et al., also pointed out that the algorithm derived from the DCCT/EDIC study was designed to limit the risk of progression to proliferative diabetic retinopathy or clinically significant macular edema, both of which require treatment in order to preserve or improve vision. However, the definition of diabetic retinopathy that requires treatment may be changing because of the expansion of the indications for antivascular endothelial growth factor (VEGF) intravitreal injections. Thus, screening algorithms and intervals may be entirely different in the future.[6]

Other issues to be considered are that the DCCT/EDIC cohort is a "highly motivated" group of patients who have been closely monitored. Also the results depend on photographic images, which aren't always used in clinical practice. Therefore, applicability of this algorithm to patients in the community may be limited.[5]

If the concerns discussed here can be addressed, targeted screening intervals could be a step forward in detecting diabetic retinopathy and go a long way to decrease the burden of screening on patients and on the health care system.

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3. Cardiovascular Autonomic Neuropathy and Cardiovascular Outcomes in the Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study

Ref: Pop-Busui R, Braffett BH, Zinman B, et al. Cardiovascular Autonomic Neuropathy and Cardiovascular Outcomes in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. Diabetes Care. 2017;40(1):94-100.

ABSTRACT

Objective: To examine whether cardiovascular autonomic neuropathy (CAN) is an independent risk factor of cardiovascular disease (CVD) events during DCCT/EDIC.

Research Design and Methods: Standardized cardiovascular autonomic reflex tests (R-R response to paced breathing, Valsalva maneuver, postural changes in blood pressure) were performed at DCCT baseline, every 2 years throughout DCCT, and at two time points in EDIC. CVD events were ascertained throughout the study and adjudicated by a review committee. Cox proportional hazards models were used to estimate the effect of CAN at DCCT closeout on subsequent CVD risk.

Results: There were 299 adjudicated CVD events in 165 participants following the DCCT closeout assessment: 132 of 1,262 subjects (10%) without CAN at DCCT closeout who experienced 244 CVD events versus 33 of 131 subjects (25%) with CAN at DCCT closeout who experienced 55 events (hazard ratio 2.79, 95% CI 1.91–4.09 for time to first CVD event). The cumulative incidence of the first occurrence of any CVD event during EDIC was significantly higher in participants with CAN at DCCT closeout compared with those without CAN. The association remained marginally significant after adjustment for multiple risk factors, including the EDIC updated mean HbA1c. When analyzed as a continuous variable, R-R variation was significantly lower at DCCT closeout in participants who experienced a CVD event compared with those who did not ($p = 0.0012$).

Conclusions: In the DCCT/EDIC cohort, individuals diagnosed with CAN at DCCT closeout experienced a higher long-term risk of CVD events during follow-up in EDIC. This association was not independent of historic glycemic exposure and its metabolic memory effect, the principal determinant of both long-term CVD risk and CAN in type 1 diabetes.

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Cardiovascular Autonomic Neuropathy (CAN) defined as impaired autonomic control of the cardiovascular system is one of the long term complications of diabetes mellitus (DM). Subclinical autonomic neuropathy can ultimately progress to clinically evident disease and have important prognostic implications for the development of cardiac dysfunction. It can manifest clinically as resting tachycardia, exercise intolerance, orthostatic hypotension, silent ischemia, and is associated with cardiovascular mortality. It can also lead to intraoperative adverse outcomes in the form of intraoperative hypothermia and more pronounced intraoperative blood pressure reductions.

In patients with type 1 diabetes mellitus (T1DM), existing diabetic autonomic neuropathy (DAN) was associated with a fourfold increase of mortality.[1,2] Longitudinal studies of individuals with diabetes mellitus and CAN have shown 5-year mortality rates between 16–50%,[3–7] with a high proportion of deaths attributed to sudden cardiac death.[4,8] The increased mortality seen in patients with CAN seems to be independent of conventional cardiovascular risk factors.[9,10] A number of potential causes have been suggested to be contributory to the increased rate of sudden cardiac death seen in this patient group. For example, autonomic imbalance between sympathetic

and parasympathetic transmitters is associated with abnormal norepinephrine signaling and metabolism and could be the cause for the increased rate of cardiac arrhythmias and sudden death.[11] CAN-associated QT prolongation is an additional independent predictor of mortality in diabetes mellitus;[10] CAN has direct effects on heart function that can contribute to the development of cardiomyopathy and LV dysfunction and subsequently lead to increased mortality. Increase of the sympathetic tone[12] leads to nocturnal hypertension, which in itself is associated with LV hypertrophy[13] and an increased prevalence of both fatal and nonfatal severe cardiovascular events.[14,15] Another possible explanation for the increased risk of mortality in patients with CAN might be silent ischemia or its associated cardiac arrhythmias.[16] A pooled risk ratio calculated from 12 cross-sectional studies involving 1,468 patients with diabetes mellitus estimated the prevalence of silent ischemia in patients with CAN at 1.96 (CI 95%, 1.53–2.51) compared with patients without CAN.[17] CAN is associated with a prolonged subjective anginal threshold.[18] Consequently patients are at increased risk of a cardiovascular event while exercising, as they might be affected by myocardial ischemia despite being asymptomatic. A French multicenter study in patients with diabetes mellitus reported a threefold greater relative risk for the occurrence of a major cardiac event in the presence of CAN. Furthermore, a combination of CAN and silent ischemia in patients was associated with a relative risk of 4.16 compared with patients with neither condition.[19] The underlying pathophysiology explaining silent ischemia is not fully understood. Contributory mechanisms include sub-threshold ischemia, transformed pain threshold, as well as dysfunctional efferent autonomic nerve fibers.[20]

The present analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study adds to the existing evidence that CAN in T1DM may predict higher long-term risk of cardiovascular disease (CVD) events. Following the DCCT closeout assessment (the baseline), more participants with CAN (25%) had a CVD event during the EDIC follow-up than those who did not have CAN at baseline (10%). The cumulative incidence of first occurrence of CVD events was also reportedly significantly higher in the participants with CAN at baseline. However, after adjusting for numerous factors relating to CVD risk, including HbA1c, the independent association between CAN and CVD became attenuated. In particular, nearly all differences between the prior treatment groups could be explained by differences in HbA1c. Although CAN was not an independent predictor with respect to the glucose control over time as documented by the HbA1c, it is to be noted that the HbA1c is one of the major determinants of CAN in these patients. Thus, a diagnosis of CAN identifies individuals with T1DM at high risk for developing major CVD events over time.

In addition to the strengths of DCCT/EDIC study discussed previously - including a long follow up period and careful characterization of multiple cardiovascular complications and risk factors - the other strengths of this analysis include robust CAN definitions and a highly reproducible and sensitive CAN protocol.

Limitations of this analysis include the relatively low rates of CAN during the DCCT and the low rates of CVD events in EDIC reducing the power of the study to determine the predictive value of CAN for future CVD events. The relatively young age of this cohort, without preexisting hypertension, hyperlipidemia, or CVD at baseline, limits the applicability of these results to the entire population of patients with T1DM.

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4. Hemoglobin A1c and Mortality in Older Adults with and without Diabetes: Results from the National Health and Nutrition Examination Surveys (1988–2011)

Ref: Palta P, Huang ES, Kalyani RR, et al. Hemoglobin A1c and mortality in older adults with and without diabetes: Results from the national health and nutrition examination surveys (1988-2011). Diabetes Care. 2017;40(4):453-60.

ABSTRACT

Objective: Hemoglobin A1c (HbA1c) level has been associated with increased mortality in middle-aged populations. The optimal intensity of glucose control in older adults with diabetes remains uncertain. We sought to estimate the risk of mortality by HbA1c levels among older adults with and without diabetes.

Research Design and Methods: We analyzed data from adults aged ≥65 years (n = 7,333) from the Third National Health and Nutrition Examination Survey (NHANES III) (1998–1994) and Continuous NHANES (1999–2004) and their linked mortality data (through December 2011). Cox proportional hazards models were used to examine the relationship of HbA1c with the risk of all-cause and cause-specific (cardiovascular disease [CVD], cancer, and non-CVD/noncancer) mortality, separately for adults with diabetes and without diabetes.

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Results: Over a median follow-up of 8.9 years, 4,729 participants died (1,262 from CVD, 850 from cancer, and 2,617 from non-CVD/non-cancer causes). Compared with those with diagnosed diabetes and an HbA1c <6.5%, the hazard ratio (HR) for all-cause mortality was significantly greater for adults with diabetes with an HbA1c >8.0%. HRs were 1.6 (95% CI 1.02, 2.6) and 1.8 (95% CI 1.3, 2.6) for HbA1c 8.0–8.9% and ≥9.0%, respectively (P for trend <0.001). Participants with undiagnosed diabetes and HbA1c >6.5% had a 1.3 (95% CI 1.03, 1.8) times greater risk of all-cause mortality compared with participants without diabetes and HbA1c 5.0–5.6%.

Conclusions: An HbA1c >8.0% was associated with increased risk of all-cause and cause-specific mortality in older adults with diabetes. Our results support the idea that better glycemic control is important for reducing mortality; however, in light of the conflicting evidence base, there is also a need for individualized glycemic targets for older adults with diabetes depending on their demographics, duration of diabetes, and existing comorbidities.

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In the late 1990s, the UK Prospective Diabetes Study (UKPDS) showed a reduction in microvascular complications (e.g., neuropathy and retinopathy) associated with intensive glucose lowering[1,2] which led to the recommendation of more intensive treatment to lower HbA1c <7.0% in adults with diabetes mellitus (DM). However, in the late 2000s, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group found that very intensive therapy (i.e., HbA1c <6.5%) resulted in increased mortality over 3.5 years.[3] The Veterans Affairs Diabetes Trial (VADT) also found that very intensive glucose lowering did not reduce mortality or DM-related complications.[4] These led to revision of the recommended glycemic targets for older adults with DM to <7.5% for healthy patients with few comorbidities and intact functional abilities, and <8.0% for patients with existing comorbidities.[5] However, lack of positive outcomes associated with intensive glucose management, and therefore differential risk of mortality, may be a result of an individual's duration of DM, comorbidities and risk-factor profile. A *post hoc* epidemiologic analysis of the ACCORD trial showed that those participants with a higher mortality in the intensive treatment arm were individuals whose HbA1c did not respond to intensive glucose management.[6] Current guidelines propose that glycemic goals should be individualized and depend on the patient's health status, life expectancy, and personal goals. Largely, data on the outcomes associated with HbA1c lowering remain heterogeneous, particularly among older adults.[7–10] Papademetriou et al.,[11] demonstrated that the excess mortality among the intensively treated group in the ACCORD study was in individuals who exhibited detectable but low levels of renal function that were not large enough to warrant exclusion from study entry. In a retrospective cohort study of 71,092 patients with type 2 diabetes mellitus (T2DM) 60 years of age and older enrolled in Kaiser Permanente Northern California, a U-shaped relationship was observed between HbA1c and mortality.[12] Compared with the patients with HbA1c <6.0%, mortality risk was lower for HbA1c levels between 6.0 and 9.0% and higher at HbA1c ≥11.0%. Similarly, a U-shaped association was also seen in the UK General Practice Research cohort study of patients aged 50 years and older with T2DM, which showed lowest HR at an HbA1c of ~7.5%.[13] Insurance claim information from the Sharon-Shomron District of Israel found that among 2,994 older adult participants with newly diagnosed DM, an HbA1c level ≥7.5% was associated with an increased risk of all-cause mortality, compared with those with HbA1c between 6.5 and 7% (HR 1.4 [95% CI 1.1, 1.6]).[14]

The current study utilized data from the NHANES III (1988–1994) and Continuous NHANES (1999–2004) and their linked mortality data (through December 2011) to determine the risk of all-cause and cause-specific (CVD, cancer, and non-CVD/noncancer) mortality by levels of HbA1c in older adults (≥65 years) with and without DM. The risk of all-cause, CVD, and cancer mortality appeared to increase significantly above an

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HbA1c of 8.0% among older adults with DM, particularly for participants with DM and prevalent CVD. These data tend to support the current recommendations of glycemic targets among older adults with DM. For participants without DM or with undiagnosed DM, the risk of all-cause and non-CVD/noncancer mortality also increased with a higher HbA1c level, compared to an HbA1c level between 5.0–5.6%.

Strengths of the study: This study utilizes data from a nationally representative sample. Sample size was relatively large. Comparisons were made across individuals without DM and with DM (both undiagnosed and diagnosed) to examine a spectrum of glucose states.

Limitations of the study: The NHANES data was cross-sectional. Hence a change in HbA1c over the period of follow-up was not taken into consideration. Second, the smaller sample size of older adults in NHANES resulted in reduced numbers in the highest categories of HbA1c and may introduce a bias. Furthermore, DM type is not available within the NHANES data. Since the parameters for which NHANES data was available were limited, other factors which could have influenced the outcome were not assessed.

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5. Early Glycemic Control and Magnitude of HbA1c Reduction Predict Cardiovascular Events and Mortality: Population-Based Cohort Study of 24,752 Metformin Initiators

Ref: Svensson E, Baggesen LM, Johnsen SP, et al. Early Glycemic Control and Magnitude of HbA1c Reduction Predict Cardiovascular Events and Mortality: Population-Based Cohort Study of 24,752 Metformin Initiators. Diabetes Care. 2017;40(6):800-7.

ABSTRACT

Objective: We investigated the association of early achieved HbA1c level and magnitude of HbA1c reduction with subsequent risk of cardiovascular events or death in patients with type 2 diabetes who initiate metformin.

Research Design and Methods: This was a population-based cohort study including all metformin initiators with HbA1c tests in Northern Denmark, 2000–2012. Six months after metformin initiation, we classified patients by HbA1c achieved (<6.5% or higher) and by magnitude of HbA1c change from the pretreatment baseline. We used Cox regression to examine subsequent rates of acute myocardial infarction, stroke, or death, controlling for baseline HbA1c and other confounding factors.

Results: We included 24,752 metformin initiators (median age 62.5 years, 55% males) with a median follow-up of 2.6 years. The risk of a combined outcome event gradually increased with rising levels of HbA1c achieved compared with a target HbA1c of <6.5%: adjusted hazard ratio (HR) 1.18 (95% CI 1.07–1.30) for 6.5–6.99%, HR 1.23 (1.09–1.40) for 7.0–7.49%, HR 1.34 (1.14–1.57) for 7.5–7.99%, and HR 1.59 (1.37–1.84) for ≥8%. Results were consistent for individual outcome events and robust by age-group and other patient characteristics. A large absolute HbA1c reduction from baseline also predicted outcome: adjusted HR 0.80 (0.65–0.97) for $\Delta = 24$, HR 0.98 (0.80–1.20) for $\Delta = 23$, HR 0.92 (0.78–1.08) for $\Delta = 22$, and HR 0.99 (0.89–1.10) for $\Delta = 21$ compared with no HbA1c change ($\Delta = 0$).

Conclusions: A large initial HbA1c reduction and achievement of low HbA1c levels within 6 months after metformin initiation are associated with a lower risk of cardiovascular events and death in patients with type 2 diabetes mellitus.

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Lowering glycosylated hemoglobin (HbA1c) levels to <7% in most adults with type 2 diabetes mellitus has been a recommended target in treatment guidelines[1-4] because of the documented effect in reducing microvascular complications.[5] In contrast, it remains debated whether even tighter glucose control (such as HbA1c <6.5%) may be more beneficial or harmful.[6] Some studies found a linear relationship between successively lower glycemic levels and fewer cardiovascular events,[7-9] whereas others reported a J- or U-shaped curve.[10-12] Also, although current guidelines emphasize the importance of tight glycemic control early after diabetes diagnosis, before complications have occurred,[4] the true effect of tight early glucose control on subsequent cardiovascular disease is still debated.[13]

The present study used data obtained from Danish medical registries, to investigate the association of achieved HbA1c level and magnitude of HbA1c reduction with subsequent risk of myocardial infarction, stroke, and death in a large population-based cohort of 24,752 patients with incident T2DM initiating metformin. Patients requiring further glucose-lowering add-on therapy were also included.

Attaining a stringent HbA1c goal of <6.5% within 6 months was associated with lower risk of cardiovascular events and mortality, with the risk gradually increasing at higher HbA1c levels. Additionally, the magnitude of early HbA1c reduction was found to be an independent predictor of lower cardiovascular risk and death independent of baseline HbA1c levels at treatment initiation, it is possible that

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rapid glycemic responders to therapy initiation (i.e., more easy-to-treat patients) may have a different pathological trajectory and a milder variant of T2DM than patients who are poor responders. Another explanation for the same is that it is the young patients with T2DM without complications that clinicians dare to treat intensively.[14]

A clear association between early control and improved outcomes were also observed in people older than 70 years. Thus achievement of stringent glycemic levels is possible in real life in at least some elderly patients with comorbidities and reaching such levels predicts lower risk of vascular events and death. The elderly patients with complications who attained stringent HbA1c levels may have been selected by caregivers by individualization on the basis of a low risk of hypoglycemia or high patient motivation and self-care.[3] Current recommendations also permit stringent targets for selected individual patients.[13]

The strengths of this study include a population-based design and large sample size. Inclusion of only metformin initiators increased the homogeneity of the population studied and is also representative of the clinical practice today as metformin is the preferred initial pharmacological agent for type 2 diabetes.[4] The limitations of the study are its observational nature and short duration of follow-up (median 2.6 years).

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6. Association between Inpatient Sleep Loss and Hyperglycemia of Hospitalization

Ref: DePietro RH, Knutson KL, Spampinato L, et al. Association between inpatient sleep loss and hyperglycemia of hospitalization. Diabetes Care. 2017;40(2):188-93.

ABSTRACT

Objective: To determine whether inpatient sleep duration and efficiency are associated with a greater risk of hyperglycemia in hospitalized patients with and without diabetes.

Research Design and Methods: In this retrospective analysis of a prospective cohort study, medical inpatients ≥50 years of age were interviewed, and their charts were reviewed to obtain demographic data and diagnosis. Using World Health Organization criteria, patients were categorized as having normal blood glucose, impaired fasting blood glucose, or hyperglycemia based on morning glucose from the electronic health record. Wrist actigraphy measured sleep. Multivariable ordinal logistic regression models, controlling for subject random effects, tested the association between inpatient sleep duration and proportional odds of hyperglycemia versus impaired fasting blood glucose or impaired fasting blood glucose versus normal blood glucose in hospitalized adults.

Results: A total of 212 patients (60% female and 74% African American) was enrolled. Roughly one-third (73, 34%) had diabetes. Objective inpatient sleep measures did not differ between patients with or without diabetes. In ordinal logistic regression models, each additional hour of in-hospital sleep was associated with an 11% (odds ratio 0.89 [95% CI 0.80, 0.99]; P = 0.043) lower proportional odds of a higher glucose category the next morning (hyperglycemia vs. elevated and elevated vs. normal). Every 10% increase in sleep efficiency was associated with an 18% lower proportional odds of a higher glucose category (odds ratio 0.82 [95% CI 0.74, 0.89]; P < 0.001).

Conclusions: Among medical inpatients, both shorter sleep duration and worse sleep efficiency were independently associated with greater proportional odds of hyperglycemia and impaired fasting glucose.

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Hyperglycemia is common among hospitalized patients, even in those patients who have not been previously diagnosed with diabetes. Hyperglycemia during hospitalization is associated with worse patient outcomes, including higher risk of myocardial infarction and stroke.[1] Although the general mechanism for hyperglycemia of hospitalization has always been assumed to be physiologic stress of the acute illness leading to hospitalization, it is possible that sleep loss and/or reduced sleep quality during hospitalization plays a role. Studies show that medical patients not only achieve 2 h less sleep in the hospital than at home, but also suffer from increased sleep fragmentation, compared with sleep at home.[2] Laboratory studies demonstrate that a few days of sleep restriction or of experimentally induced sleep fragmentation can result in impaired glucose tolerance.[3–7] Prospective epidemiological studies also demonstrate a relationship between shorter sleep duration or poorer sleep quality and the risk of incident diabetes in community-dwelling adults.[8–10]

Multiple mechanisms may be responsible for the adverse effects of sleep loss on glucose tolerance. These could include abnormalities in several hormones involved in glucose regulation, including cortisol, growth hormone, leptin, and ghrelin. In addition, increases in sympathetic nervous system activity and decreases in cerebral glucose metabolism resulting from the sleep debt may play a role. Also, the modified release of adipokines—especially IL-6, TNF-α and adiponectin—during stress and following disturbances of the sleep pattern leads to a systemic chronic sub-inflammatory state in the adipose tissue that

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