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When Does Metabolic Memory Start? Insights From the Association of Medical Diabetologists Annals Initiative on Stringent HbA_{1c} Targets

Giuseppina T. Russo, Antonio Nicolucci, Giuseppe Lucisano, Maria Chiara Rossi, Antonio Ceriello, Francesco Prattichizzo, Valeria Manicardi, Alberto Rocca, Paolo Di Bartolo, Salvatore De Cosmo, Graziano Di Cianni, and Riccardo Candido

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CONTEXT

An early, intensive glycemic control has been associated with a long-term benefit in the development of cardiovascular disease, a phenomenon referred to as legacy effect. Evidence of the potential benefits obtained by achieving more stringent glycated targets, as close as possible to a normal HbA_{1c} value, i.e., HbA_{1c} < 5.7%, is very limited to date.

METHODS

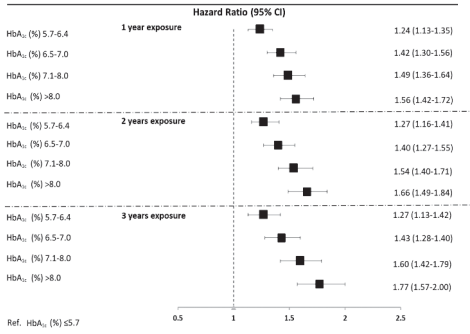
We used data from a large Italian clinical registry of people with type 2 diabetes the Association of Medical Diabetologists Annals Initiative Newly diagnosed patients free of cardiovascular disease at baseline were stratified according to the average HbA_{1c} attained during the first 12, 24 and 36 months from diagnosis and the incidence of cardiovascular disease in the following years was assessed.

Mean HbA_{1c} value for each of the three early exposure periods was categorized into either HbA_{1c} < 5.7%, 5.7–6.4%, 6.5–7.0%, 7.1–8.0%, and >8.0%. Cox proportional hazards models were used to examine associations between glycemic control and the risk of cardiovascular disease.

The analysis involved a total of 251,339 subjects with newly diagnosed type 2 diabetes and free of cardiovascular disease at baseline, seen between 2010 and 2019.

RESULTS

Compared to patients with a mean HbA_{1c} <5.7%, those above this threshold had an increased risk of cardiovascular disease at follow-up for all three early exposure periods and for all strata of glycemic control considered (figure).



Today, many glucose-lowering drugs do not cause hypoglycemia, allowing us to rethink proper glucose targets in many patients. Our study shows that, in routine care, the early achievement and maintenance of HbA_{1c} targets in the normal range (i e., HbA_{1c} <5.7%) is feasible and worthy in terms of cardiovascular disease prevention.

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Giuseppina T. Russo,[1] Antonio Nicolucci,[2] Giuseppe Lucisano,[2] Maria Chiara Rossi,[2] Antonio Ceriello,[3] Francesco Prattichizzo,[3] Valeria Manicardi,[4] Alberto Rocca,[5] Paolo Di Bartolo,[6] Salvatore De Cosmo,[7] Graziano Di Cianni,[8] and Riccardo Candido[9]

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Early, intensive glycemic control in patients with type 2 diabetes (T2D) is associated with long-term benefits in cardiovascular disease (CVD) development. Evidence on benefits of achieving HbA_{1c} targets close to normal values is scant. Individuals with newly diagnosed T2D, without CVD at baseline, were identified in an Italian clinical registry (*n* = 251,339). We adopted three definitions of early exposure periods (0–1, 0–2, and 0–3 years). Mean HbA_{1c} was categorized into HbA_{1c} <5.7%, 5.7–6.4%, 6.5–7.0%, 7.1–8.0%, and >8.0%. The outcome was the incidence of major cardiovascular events. After a mean follow-up of 4.6 ± 2.9 years, at multivariate Cox regression analysis, compared with mean HbA_{1c} <5.7% during the first year after diagnosis, the increase in the risk of CVD was 24%, 42%, 49%, and 56% for patients with HbA_{1c} of 5.7–6.4%, 6.5–7.0%, 7.1–8.0%, and >8.0%, respectively. The same trend was documented in all exposure periods. In conclusion, our data support that an early achievement of stringent targets of HbA_{1c} <5.7% is worthy for CVD prevention.

ARTICLE HIGHLIGHTS

- The cardiovascular disease (CVD) impact of achieving very strict HbA_{1c} targets soon after the type 2 diabetes diagnosis is unknown.
- Would near-normal mean HbA_{1c} levels 1–3 years after type 2 diabetes diagnosis reduce CVD risk?
- Compared with mean HbA_{1c} <5.7% during the first year after diagnosis, CVD risk was 24%, 42%, 49%, and 56% higher for patients with HbA_{1c} of 5.7–6.4%, 6.5–7.0%, 7.1–8.0%, and >8.0%, respectively.
- Early achievement of HbA_{1c} <5.7% is associated with a lower incidence of CV events.

Poor glycemic control in patients with type 2 diabetes (T2D) is associated with increased risk of cardiovascular diseases (CVD) (1). On the other hand, an early, intensive glycemic control has been associated with a long-term benefit in the development of CVD, a phenomenon referred to as the legacy effect (2). This phenomenon was first described in the follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) trial, showing that patients with a recent diagnosis of T2D benefited from an intensive glycemic control even after the intensive therapy was discontinued (3). While some subsequent studies in patients with more advanced stages of T2D did not confirm these results (4–6), three large observational studies and updated follow-up data of the same UKPDS cohort provided solid evidence that T2D patients with poor glycemic

[1]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[2]CORESEARCH – Center for Outcomes Research and Clinical Epidemiology, Pescara, Italy
[3]IRCCS MultiMedica, Milan, Italy
[4]AMD Foundation, Reggio Emilia, Italy
[5]G. Segalini H. Bassini Cinisello Balsamo ASST Nord, Milan, Italy
[6]Ravenna Diabetes Center, Department of Specialist Medicine, Romagna Local Health Authority, Ravenna, Italy
[7]Department of Medical Sciences, Scientific Institute "Casa Sollievo della Sofferenza," San Giovanni Rotondo, Italy
[8]Diabetes Unit, Livorno Hospital, Livorno, Italy
[9]Department of Medical Surgical and Health Sciences, University of Trieste, Trieste, Italy

Corresponding author: Antonio Nicolucci, nicolucci@coresearch.it

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control in the years following diagnosis have an increased risk of late CVD and death, supporting the existence of long-lasting damage promoted by hyperglycemia (7–10). However, in most of the studies exploring the legacy effect, strict metabolic control was obtained using sulfonylureas or insulin, and the elevated risk of cardiovascular events and death associated with hypoglycemia could mitigate the positive effects of tight metabolic control (11). For this reason, existing guidelines generally recommend an HbA_{1c} target <7.0% in the vast majority of patients or suggest <6.5% in selected subgroups (12,13).

Thus, evidence on the potential benefits obtained by achieving more stringent glycated targets, as close as possible to a normal HbA_{1c} value, that is, HbA_{1c} <5.7%, is very limited to date, especially in real-world studies in patients with T2D. To explore this aspect, we used data from a large Italian clinical registry of people with T2D, the Association of Medical Diabetologists (AMD) Annals Initiative. Newly diagnosed patients free of CVD at baseline were stratified according to the average HbA_{1c} attained during the first 12, 24, and 36 months from diagnosis, and the incidence of CVD in the following years was assessed.

RESEARCH DESIGN AND METHODS

Study Design and Population

Data were derived from the registry of the Italian AMD Annals Initiative, which was established in 2004 to monitor quality of diabetes care in Italy (14). The database includes information on all patients with T2D receiving care at over 300 diabetes clinics in Italy from 1 January 2004 to 31 December 2022. All diabetes clinics adhering to AMD Annals Initiative, a third of those existing throughout the country, used a common electronic clinical record system for the everyday management of outpatients, and software was specifically developed to extract information from these clinical databases. Anonymized data from all participating clinics were collected and centrally analyzed. Available data included demographic, clinical, and biochemical information. The use of specific classes of drugs (glucose-lowering, lipid-lowering, and antihypertensive agents), based on Anatomical Therapeutic Chemical codes, was available. Information on the presence of diabetes complications was based on *International Classification of Diseases*, Ninth Revision, Clinical Modification, codes. The study design is summarized in Fig. 1. To explore the effects of various periods of early glycemic exposure, we adopted three definitions of early exposure periods (0–1, 0–2, and 0–3 years). The mean HbA_{1c} value was calculated for each early exposure period by using all HbA_{1c} measurements, except the value at diagnosis. The value at diagnosis was excluded since it reflects control before treatment was initiated, and the glycemic legacy effect has been demonstrated only in populations receiving diabetes treatment. To assess the effect of various degrees of glycemic control, the mean HbA_{1c} value for each of the three early exposure periods was categorized into either HbA_{1c} <5.7% (<39 mmol/mol), 5.7–6.4% (39–46 mmol/mol), 6.5–7.0% (47–53 mmol/mol), 7.1–8.0% (53–64 mmol/mol), or >8.0% (>64 mmol/mol).

The exposure period started at the date of diagnosis and ended after 12, 24, or 36 months from diagnosis. Accordingly, the follow-up period started after 12, 24, or 36 months from diagnosis (baseline/t0) and ended after the first occurrence of the outcome of interest or was censored at last visit. The outcome of interest was the composite of myocardial infarction, stroke, coronary or peripheral revascularization, and coronary or peripheral bypass. Patients with prevalent CVD at baseline were excluded. The risk factors used to adjust the analysis were measured at baseline. In case of missing data relative to covariates, a category of missing data was added for each covariate in the multivariate analysis.

The analyses are based on data relating to all newly diagnosed T2D patients seen by participating centers in the period 2010–2019.

Statistical Analysis

Data on patient characteristics were summarized using means and SDs for continuous variables and counts and percentages for categorical variables, and stratified by the five classes of mean HbA_{1c} in each early exposure period. Characteristics were compared by the Kruskal-Wallis one-way ANOVA and χ^2 test for continuous and categorical variables, respectively.

Cox proportional hazards models were used to examine associations between glycemic control and the risk of CVD. Cox models were adjusted for baseline potentially confounding variables: sex (male vs. female), age (by 5 years), total cholesterol (by 10 mg/dL), HDL cholesterol (by 10 mg/dL) and LDL cholesterol (by 10 mg/dL), triglycerides (by 10 mg/dL), BMI, systolic blood pressure (by 5 mmHg), smoking status (yes vs. no), eGFR (<60 vs. ≥60 mL/min/1.73 m^2), microalbuminuria (yes vs. no), use of different classes of glucose-lowering drugs (yes vs.

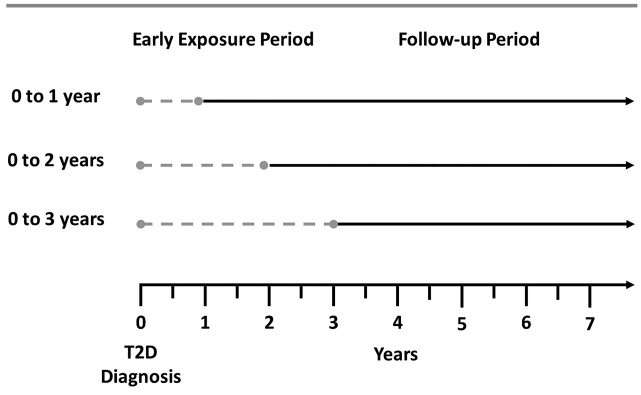

Figure 1—Study design.

no for each one), use of statin (yes vs. no), use of antihypertensive medication (yes vs. no), HbA_{1c}, and number of HbA_{1c} measurements during the exposure period. A backward selection was introduced in the Cox models to exclude the confounders without a significant association with the outcome. For each model, patient follow-up was censored after the first occurrence of the outcome of interest or last visit. Results of Cox models are expressed as hazard ratios (HRs) with their 95% CI. Descriptive and multivariate analyses were performed in the three cohorts. A two-sided $P < 0.05$ was considered statistically significant for all analyses. Analyses were performed using SAS 9.4 statistical software (SAS Institute, Cary, NC).

Data and Resource Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

The analysis involved a total of 251,339 individuals with newly diagnosed T2D and free of CVD at baseline, seen between 2010 and 2019. Overall, 5.7% of patients presented average HbA_{1c} values <5.7% during the first year after diagnosis, while 29.0% showed average values between 5.7 and 6.4%. Conversely, the average HbA_{1c} values during the first year exceeded 8.0% in 16.7% of case patients.

Clinical characteristics of the groups categorized according to the degree of glycemic control attained in the 12 months after diagnosis are reported in Table 1, while the characteristics of the groups categorized according to the degree of glycemic control attained in the 24 and 36 months after diagnosis are reported in Supplementary Tables 1 and 2.

Overall, individuals with HbA_{1c} <5.7% after diagnosis were younger and had lower BMI, a better lipid profile, and lower blood pressure levels as compared with the overall population. They also showed a lower prevalence of albuminuria and reduced eGFR. The groups showed statistically significant differences for all the characteristics assessed. Therefore, all these variables were added as covariates to adjust the subsequent multivariate analyses.

During a mean follow-up of 4.6 ± 2.9 years, 13,822 patients (5.5%) developed a major cardiovascular event.

Cox analysis shows that, compared with patients with a mean HbA_{1c} <5.7%, those above this threshold had an increased risk of CVD at follow-up for all the three early exposure periods and for all strata of glycemic control considered (Fig. 2). In detail, compared with mean HbA_{1c} <5.7% during the first year after diagnosis, patients with mean HbA_{1c} between 5.7 and 6.4% had a 24% increased risk of CVD (HR = 1.24; 95% CI 1.13–1.35), those with HbA_{1c} between 6.5 and 7.0% had a 42% increased risk (HR = 1.42; 95% CI 1.30–1.56), those with HbA_{1c} between 7.1 and 8.0% had a 49% increased risk (HR = 1.49; 95% CI 1.36–1.64), and patients with HbA_{1c} >8.0% had a 56% increased risk of CVD (HR = 1.56; 95% CI 1.42–1.72). The same trend was documented for the 0- to 2-year and the 0- to 3-year exposure periods (Fig. 2). Results of Cox models in the three different periods of exposure are reported in Supplementary Table 3.

DISCUSSION

The legacy effect is a well-recognized phenomenon clearly documented in cohort studies and in selected clinical trials, suggesting that poor glycemic control after T2D diagnosis promotes enduring damage on the vasculature (2,7–10). A recent analysis from the UKPDS study evaluated the impact of historical HbA_{1c} values on CVD risk, demonstrating that a 1% HbA_{1c} reduction obtained at diagnosis was able to reduce CVD risk by 27%, but the same reduction obtained 10 years later lost most of its beneficial potential in CVD risk (10).

It is well known that, in T2D patients, cardiovascular risk is a continuum that starts early in the clinical history of the disease, because of the contribution of several risk factors including hyperglycemia. Although lipidologists recommend achieving LDL cholesterol targets as stringent as possible according to the principle of "lower is better" and, after the introduction in the market of PCSK-9 inhibitors, "lowest is best," this principle was hard to propose in the diabetology field because of the risks associated with hypoglycemia.

However, today, many drugs do not cause hypoglycemia, allowing us to rethink proper glucose targets in many patients. In fact, recommended glucose-lowering drugs with proven cardiovascular benefit, for example, sodium–glucose transport protein 2 inhibitors (SGLT2i) and GLP1 receptor agonists (GLP1-RA), are not burdened by the risk of hypoglycemia, also allowing the safe attainment of stringent glycemic targets. Furthermore, the SURPASS study program (15) showed that treatment with the new incretin system receptor agonist tirzepatide was associated with a high percentage of patients safely achieving the HbA_{1c} target of <6.5%. At maximum dosage, one in two patients reached a "normal" glycated hemoglobin value, that is, a value <5.7%, suggesting the possibility of potential new therapeutic approaches and new metabolic targets (13), which are still hard to achieve in the clinical practice (16).

In this regard, the strategy to readily address glucose control with a combination therapy at T2D diagnosis has been tested in Vildagliptin Efficacy in Combination with Metformin for Early Treatment of Type 2 Diabetes (VERIFY), a large randomized, double-blind, parallel-group study of newly diagnosed patients with T2D conducted across 34 countries. This study demonstrated the long-lasting beneficial effects of an early intensive combination intervention on glucose control, compared with the standard approach over the 5-year study duration. Moreover, this strategy was not associated with unexpected or safety issues, including hypoglycemia (17).

Table 1—Characteristics of the study population according to levels of metabolic control in the 12 months after diagnosis of T2D

Variable	Total	HbA_{1c} <5.7%	HbA_{1c} 5.7–6.4%	HbA_{1c} 6.5–7.0%	HbA_{1c} 7.1–8.0%	HbA_{1c} >8.0%	*P* value*
No. of patients (%)	251,339	14,355 (5.7)	72,983 (29.0)	63,419 (25.2)	58,626 (23.3)	41,956 (16.7)	
Age at baseline, years	63.6 ± 12.4	60.5 ± 13.1	63.6 ± 11.9	64.8 ± 11.9	64.2 ± 12.7	61.9 ± 13.3	<0.0001
Sex, % males	57.0	63.7	57.8	54.1	56.6	58.0	<0.0001
BMI, kg/m^2	29.8 ± 5.6	29.2 ± 5.3	29.6 ± 5.4	29.9 ± 5.6	30.0 ± 5.7	30.0 ± 6.0	<0.0001
Smoking, %	20.2	17.0	18.2	19.2	21.6	24.5	<0.0001
HbA_{1c} at baseline, %	6.8 ± 1.2	5.4 ± 0.3	6.1 ± 0.3	6.6 ± 0.4	7.1 ± 0.7	8.2 ± 1.8	<0.0001
HbA_{1c} at diagnosis, %	8.4 ± 2.3	7.7 ± 2.4	7.7 ± 2.1	8.0 ± 2.0	8.9 ± 2.2	10.2 ± 2.4	<0.0001
Total cholesterol, mg/dL	187.5 ± 40.7	182.0 ± 39.2	186.9 ± 39.5	188.1 ± 40.0	186.7 ± 41.0	190.3 ± 43.7	<0.0001
HDL cholesterol, mg/dL	49.0 ± 13.1	49.4 ± 13.7	50.1 ± 13.1	49.7 ± 13.0	48.3 ± 12.8	47.1 ± 12.9	<0.0001
LDL cholesterol, mg/dL	110.7 ± 35.0	107.4 ± 33.7	110.8 ± 34.3	111.1 ± 34.7	109.9 ± 35.2	112.1 ± 36.7	<0.0001
Triglycerides, mg/dL	143.8 ± 89.5	128.4 ± 78.5	133.6 ± 78.1	141.5 ± 81.2	148.6 ± 91.7	163.1 ± 113.3	<0.0001
Systolic blood pressure, mmHg	133.9 ± 18.1	131.5 ± 18.0	133.3 ± 17.7	134.2 ± 17.8	134.7 ± 18.3	134.3 ± 18.8	<0.0001
Diastolic blood pressure, mmHg	78.9 ± 9.9	78.0 ± 9.9	78.6 ± 9.7	78.8 ± 9.8	79.0 ± 10.0	79.4 ± 10.3	<0.0001
Albuminuria, %	31.5	28.1	28.5	29.7	33.3	37.7	<0.0001
eGFR <60 mL/min/1.73 m^2, %	17.8	15.0	16.6	18.3	19.2	17.9	<0.0001
Antihypertensive medication, %	47.7	45.2	48.4	49.8	48.0	43.7	<0.0001
Lipid-lowering medication, %	34.5	26.8	34.6	37.0	35.6	31.5	<0.0001
Glucose-lowering medication, %							
Metformin	58.9	48.9	50.0	56.2	68.0	69.4	<0.0001
Sulfonylureas	9.5	6.2	5.6	6.8	12.1	18.0	<0.0001
Glinides	3.1	2.2	2.3	2.5	4.1	4.7	<0.0001
DPP4i	7.7	4.7	4.6	5.8	11.5	11.4	<0.0001
GLP1-RAs	2.2	1.8	1.2	1.5	2.9	4.0	<0.0001
SGLT2i	3.2	1.8	1.9	2.5	4.1	5.9	<0.0001
Thiazolidinediones	2.0	1.3	1.4	1.7	2.7	3.1	<0.0001
Acarbose	1.5	1.0	1.0	1.3	2.0	2.0	<0.0001
Insulin	17.9	15.3	10.0	10.1	19.7	41.8	<0.0001
Follow-up, years	4.6 ± 2.9	4.5 ± 2.9	4.6 ± 2.9	4.7 ± 2.9	4.6 ± 2.9	4.4 ± 2.9	<0.0001
Composite cardiovascular outcome, %**	5.5	3.8	5.0	5.8	6.0	5.7	<0.0001
HbA_{1c} measurements during exposure period	2.6 ± 1.1	2.3 ± 1.0	2.4 ± 1.0	2.5 ± 1.0	2.8 ± 1.2	2.8 ± 1.3	<0.0001

Data are mean and SD or proportions. *Kruskal-Wallis one-way ANOVA or χ^2 test. **Composite of myocardial infarction, stroke, coronary or peripheral revascularization, and coronary or peripheral bypass.

However, the benefit of achieving such stringent HbA_{1c} targets in a real-world setting has not been proven so far.

Moreover, it has been increasingly acknowledged that using only HbA_{1c} measurement does not allow evaluation of other important aspects of glycemic disturbance, such as glycemic variability, which has been previously demonstrated to predict CVD complications in this same cohort of individuals with T2D, irrespective of the achievement of targets (18). In the current analysis, we looked at another unsolved issue, which is whether the HbA_{1c} goals that we pursue in accordance with current guidelines would really reflect the CVD risk of our patients.

Accordingly, the current analysis from the AMD Annals data set aimed to answer two important clinical questions.

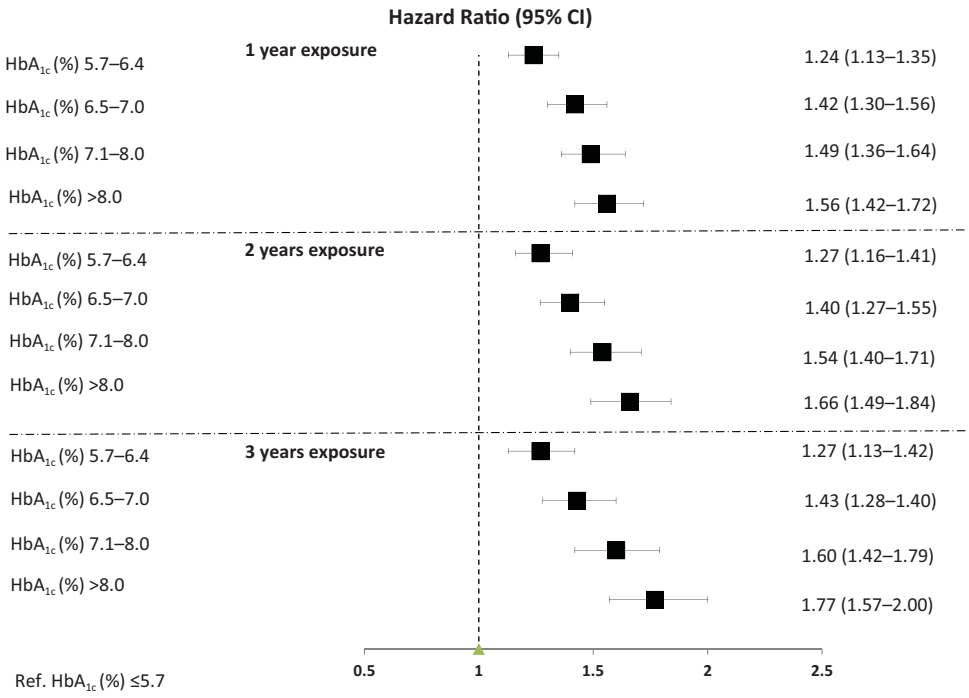

Figure 2—Level of early glycemic control and subsequent risk of cardiovascular diseases. Pseudo-forest plot showing the adjusted HRs with the relative 95% CI, derived from the Cox regression analyses exploring the relationship of the associations between glycemic control and the risk of the CVD at follow-up to the degree of glycemic control. HbA_{1c} <5.7% is the reference.

First, is it feasible to achieve glucose targets in the "normal range," that is, HbA_{1c} values <5.7% in our T2D outpatients? Second, is it worthy from a CVD risk perspective?

To address these questions, we evaluated a large cohort of newly diagnosed T2D patients with no CVD at baseline and followed up with them for >4 years to assess the incidence of CVD events (composite end point) according to different HbA_{1c} cut-offs achieved during 1, 2, and 3 years of their initial clinical history.

Here we show, in a sample of over 250,000 newly diagnosed T2D patients, the benefits of reaching and maintaining ambitious targets immediately after diagnosis, in terms of reducing cardiovascular risk. Comparing patients who maintained HbA_{1c} levels <5.7% during the first year after diagnosis to those who had HbA_{1c} between 5.7 and 6.4%, our data show, for the latter, an increase in CVD risk of 24%, rising to 27% if the target HbA_{1c} <5.7% was maintained for 2 or 3 years. The excess CVD risk reached 42% in patients who showed HbA_{1c} levels between 6.5 and 7.0%, the target generally recommended by existing guidelines for the majority of patients, excluding elderly, frail individuals and those with severe comorbidities. The CVD risk further increased in poorly controlled individuals, reaching 56%, 66%, and 77% among those with average HbA_{1c} levels >8.0% during 1, 2, and 3 years after diagnosis, respectively.

Notably, the risk associated with HbA_{1c} levels just above the "diagnostic" cut-off values was independent from major risk factors, including sex, age, lipid profile, BMI, systolic blood pressure, smoking status, renal function, use of different classes of glucose-lowering drugs, statins, and antihypertensive medication, and the number of HbA_{1c} measurements during the exposure period.

In this regard, a meta-analysis recently demonstrated that the intensive antihyperglycemic approach significantly reduces the incidence of cardiovascular outcomes (major adverse cardiovascular events) compared with conventional treatment when all available studies are considered (odds ratio [OR] = 0.86; 95% CI 0.77–0.96; P = 0.007), with a more consistent effect in the case of randomized controlled trials (RCTs) that enrolled patients with diabetes lasting <10 years (OR = 0.73; 95% CI 0.56–0.94; P = 0.01), and an even more pronounced protection when analyzing only RCTs that enrolled patients without previous cardiovascular events at baseline (OR = 0.64; 95% CI 0.48–0.86; P = 0.003). These results support the recommendation to intensify antihyperglycemic treatment with a view to cardiovascular prevention, in patients with short duration of diabetes, without previous cardiovascular disease and with a long life expectancy (6).

Of note, the positive results of our study were obtained despite the fact that only a minority of patients were treated with an SGLT2i or a GLP1-RA. These glucose-lowering agents were consistently proven to provide cardiorenal protection while showing a very low risk of hypoglycemia (19). Furthermore, a recent, large study on data derived from the AMD Annals database suggested that the early introduction of

SGLT2i might be able to ameliorate or even suppress the noxious long-term consequence of early, poor glycemic control on the vasculature (9).

Our study has important strengths, particularly the very large sample size, representative of routine clinical practice, and the long follow-up.

The study also has limitations. Despite our effort to adjust for all known risk factors, residual unmeasured confounders are inherently linked to all registry-based studies. Moreover, differences in baseline disease severity are likely intertwined with the inability of reaching HbA_{1c} targets early in the course of the disease. It is important to note that, as the reference group used less medications (for instance, insulin therapy was reported in 16% vs. 42% of the $<5.7\%$ vs. $>8\%$ HbA_{1c} groups, respectively), the possibility that our results may reflect an earlier stage of the disease cannot be ruled out, because of the observational nature of our study, despite multivariate adjustments for all major CVD risk factors and diabetes-related variables, and the large study sample. Finally, no information on hypoglycemic episodes was available, since it is not usually reported in a standard classification in medical records, precluding the possibility of investigating this important aspect. However, our results showing that the lower the HbA_{1c} level, the lower the risk of CV events suggest that the availability of modern glucose-lowering drugs associated with a very low hypoglycemic risk should allow the safe attainment of a more ambitious HbA_{1c} target.

Despite these limitations, the study showed a consistent trend of CVD risk with increasing average HbA_{1c} levels, and the same trend was confirmed when analyzing data relative to 1, 2, or 3 years of early exposure, thus testifying to the robustness of our findings.

Achieving more ambitious glycemic targets, immediately after diagnosis, may prevent cardiovascular risk in patients with T2D, and the findings of the current analysis support the importance of not neglecting the treat-to-target approach in a treat-to-benefit era, provided that an optimal metabolic control is achieved with the most appropriate drugs.

In conclusion, our results suggest that, in a large population of T2D outpatients, in routine care, the early achievement of more stringent targets of HbA_{1c} in the normal range (i.e., HbA_{1c} $<5.7\%$) is feasible and worthy in terms of CVD prevention. Further specifically designed RCTs are urgently needed to confirm our observational data.

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Duality of Interest. G.T.R. is on the advisory board and does consultancy and lectures for Novo Nordisk, AstraZeneca, Sanofi, Boehringer, Lilly, Mundipharma, and Sanchio. A.N. has received honoraria from AstraZeneca, Eli Lilly, and Novo Nordisk, and research support from Alfasigma, Novo Nordisk, Sanofi, Shionogi, and Sobi. M.C.R. has received research support from Alfasigma, Novo Nordisk, Sanofi, Shionogi, and Sobi. A.C. is on the advisory board and does consultancy and lectures for AstraZeneca, Berlin-Chemie, Eli Lilly, Novo Nordisk, Mitsubishi, Roche Diagnostics, and Theras Lifetech. F.P. is a lecturer for Berlin-Chemie. V.M. has received lecture fees from MSD, AstraZeneca, and Eli Lilly. S.D.C. received honoraria for lectures from Eli Lilly, Boehringer, AstraZeneca, Mundipharma, MSD, Sanofi, Novo Nordisk, Daiichi Sankyo, and Bayer. R.C. has received consultancy fees from Boehringer Ingelheim, Eli-Lilly, Novo Nordisk, AstraZeneca, Sanofi-Aventis, Roche Diabetes Care; speaking fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi, Mundipharma Pharmaceutical, Abbott, MSD, Neopharmed Gentili, Menarini, Essex Italia, and Ascensia Diabetes. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. G.T.R. and A.N. conceived the idea and wrote the manuscript. A.N., G.L., and M.C.R. contributed to study design, made the statistical analysis, and discussed the manuscript. A.C., F.P., V.M., A.R., P.D.B., S.D.C., G.D.C., and R.C. reviewed the manuscript for intellectual content. All authors collected data and approved the final version of the manuscript. R.C. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. Ann Intern Med 2004;141:421–431

2. Chalmers J, Cooper ME. UKPDS and the legacy effect. N Engl J Med 2008;359:1618–1620

3. Adler AI, Coleman RL, Leal J, Whiteley WN, Clarke P, Holman RR. Post-trial monitoring of a randomised controlled trial of intensive glycaemic control in type 2 diabetes extended from 10 years to 24 years (UKPDS 91). Lancet 2024;404:145–155

4. ACCORD Study Group. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. Diabetes Care 2016;39:701–708

5. Zoungas S, Chalmers J, Neal B, et al.; ADVANCE-ON Collaborative Group. Follow-up of blood-pressure lowering and glucose control in type 2 diabetes. N Engl J Med 2014;371:1392–1406

6. Prattichizzo F, de Candia P, De Nigris V, Nicolucci A, Ceriello A. Legacy effect of intensive glucose control on major adverse cardiovascular outcome: systematic review and meta-analyses of trials according to different scenarios. Metabolism 2020;110:154308

7. Paul SK, Klein K, Thorsted BL, Wolden ML, Khunti K. Delay in treatment intensification increases the risks of cardiovascular events in patients with type 2 diabetes. Cardiovasc Diabetol 2015;14:100

8. Laiteerapong N, Ham SA, Gao Y, et al. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (The Diabetes & Aging Study). Diabetes Care 2019;42:416–426

9. Ceriello A, Lucisano G, Prattichizzo F, et al.; AMD Annals study group. The legacy effect of hyperglycemia and early use of SGLT-2 inhibitors: a cohort study with newly-diagnosed people with type 2 diabetes. Lancet Reg Health Eur 2023;31:100666

10. Lind M, Imberg H, Coleman RL, Nerman O, Holman RR. Historical HbA_{1c} values may explain the type 2 diabetes legacy effect: UKPDS 88. Diabetes Care 2021;44:2231–2237

11. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418

12. Davies MJ, Aroda VR, Collins BS, et al. Management of hyperglycemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2022;45:2753–2786

13. Sistema Nazionale Linee Guida. Linea guida della Società Italiana di Diabetologia (SID) e dell'Associazione dei Medici Diabetologi (AMD): La terapia

del diabete mellito di tipo 2, 2022. Accessed 30 July 2024. Available from https://www.siditalia.it/pdf/LG_379_diabete_ed2022_feb2023.pdf
14. Rossi MCE, Nicolucci A, Arcangeli A, et al.; Associazione Medici Diabetologi Annals Study Group. Baseline quality-of-care data from a quality-improvement program implemented by a network of diabetes outpatient clinics. Diabetes Care 2008;31:2166–2168
15. Min T, Bain SC. The role of tirzepatide, dual GIP and GLP-1 receptor agonist, in the management of type 2 diabetes: the SURPASS clinical trials. Diabetes Ther 2021;12:143–157
16. Russo G, Di Bartolo P, Candido R, et al.; AMD Annals Study Group. The AMD ANNALS: a continuous initiative for the improvement of type 2 diabetes care. Diabetes Res Clin Pract 2023;199:110672
17. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S, VERIFY study group. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): a 5-year, multicentre, randomised, double-blind trial. Lancet 2019;394:1519–1529
18. Ceriello A, Lucisano G, Prattichizzo F, et al. HbA1c variability predicts cardiovascular complications in type 2 diabetes regardless of being at glycemic target. Cardiovasc Diabetol 2022;21:13
19. Ali MU, Mancini GBJ, Fitzpatrick-Lewis D, et al. The effectiveness of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists on cardiorenal outcomes: systematic review and meta-analysis. Can J Cardiol 2022;38:1201–1210