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# Comorbidity evaluation in T2DM patients and its connection to glycemic control

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## Abstract

**Objective:** The effectiveness of intensive glucose-lowering medication in lowering risk for cardiovascular events has been the subject of conflicting recent investigations. The objective was to ascertain whether patients with high versus low-to-moderate levels of comorbidity benefit differently from achieving baseline hemoglobin A1C (HbA1c) objectives of 6.0% or less or 7.1% or less for glycemic management.

**Methods:** A total of 200 patients with Type 2 diabetes patients were the subject of a 1-year longitudinal observational study at Diabetes Care Centre, Bettiah. Using the Total Illness Burden Index (TIBI), a validated patient-reported comorbidity measure, patients were divided into subgroups with high and low-to-moderate comorbidity.

**Results:** The low-to-moderate comorbidity grouping (adjusted HR, 0.61 [95% CI, 0.41 to 0.84]; P< 0.004) but not the high comorbidity subgroup (adjusted HR, 0.91 [95% CI, 0.67 to 1.24]; P for subgroup by HbA1c interaction <0.047) achieved a HbA1c level of 6.0% or less at baseline. Similar to the low-to-moderate comorbidity subgroup, reaching a baseline HbA1c level of 7.5% predicted fewer cardiovascular events (adjusted HR, 0.60 (CI, 0.43 to 0.82; P<0.002) but not in the high comorbidity subgroup (adjusted HR, 0.87 [CI, 0.65 to 1.16]; P<0.37; P for subgroup by HbA1c interaction <0.092).

**Conclusion:** Individuals who have significant levels of comorbidity, which is typical of type 2 diabetes, may not gain as much from strict blood glucose management in terms of their cardiovascular health. While modifying glucose-lowering medication for patients with type 2 diabetes, comorbidity should be taken into account.

**Keywords:** Combordity, cardiovascular, glycemia, type 2 DM

## Introduction

Leading professional organizations advise that patients with a short life expectancy, advanced problems, and significant comorbidity may find it less acceptable to achieve a hemoglobin A1c (HbA1c) score of less than 7.5%. (1–3). Research suggests that not all patients with type 2 diabetes will benefit equally from intense glucose-lowering medication.

With HbA1c objectives of 6.5% or less (4-6), three sizable randomized, controlled trials demonstrated no correlation between intensive therapy and a lowered risk of macrovascular consequences overall. However, the researchers found statistically significant links between strict glycemic control and fewer cardiovascular events when data from these and other trials were taken into account in 2 recent meta-analyses (7, 8).

Younger diabetic patients and those without a history of heart disease may benefit from aggressive glycemic control, according to post hoc analyses of data from these clinical trials (4). (4, 5). Results from the UKPDS (United Kingdom Prospective Diabetes Study10-year )'s posttrial follow-up (9) demonstrated a decrease in cardiovascular events following the initiation of intensive glucose-lowering medication in a young, healthy sample of patients with newly diagnosed type 2 diabetes.

High levels of comorbidity may reduce the benefits of maintaining tight control, regardless of age, according to recent choice analyses based on UKPDS risk models (11), due to the complicated interactions between various illnesses, their treatments, and the burden they place on patients' resources (12).

The study, which was a 5-year longitudinal observational study (1999–2004) and is discussed in full elsewhere (15–17), looked at the relationship between the incidence of cardiovascular events and death and the quality of diabetes care. A median of 4.96 years was spent following the patients (interquartile range, 3.35 to 5.00 years).

Cardiovascular disorders are the main causes of mortality and subsequent cardiovascular events among the comorbid ailments that are common among diabetic patients [Figure 1]. However, additional illnesses, including chronic pulmonary disease, may also cause functional impairment, add to the cost of treatment, increase the risk of adverse events, and reduce the likelihood that a patient will benefit from strict control (13, 14).

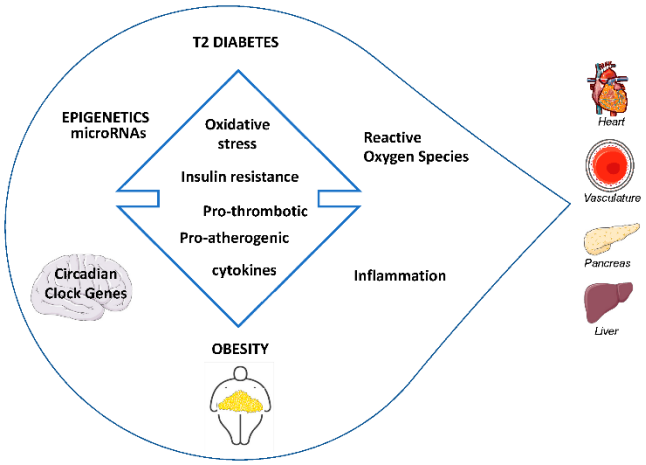


Figure 1: Combordities related to T2DM

**Method**

**Study design:** This study was a 1-year longitudinal study fromJune 2021 to June 2022 Diabetes Care Centre, Bettiah.

**Methodology:** Angina, myocardial infarction, stroke, transient ischemic attack, coronary revascularization procedures, lower limb problems (claudication, ulcer, gangrene, amputation, or aortic-femoral revascularization procedures), or cardiovascular death were the study's primary outcomes. Based on study-wide criteria, participating doctors attested to the incidence of any cardiovascular incident over the 1-year study period. Also, participating doctors reported any study patient deaths for any reason, and this data was utilized to calculate total fatality rates. Taking information from clinical records, participating doctors abstracted demographic and clinical information, including age, body mass index, duration of diabetes, HbA1c level, lipid levels, and blood pressure (collected and entered into models as continuous variables), as well as gender,

smoking status, and the presence of diabetes complications (collected and entered into models as categorical variables), and reported this information to the Diabetes Care Centre, Bettiah coordinating center. The real value vs. upper limit of normal percentage change was approximated due to the fact that the normal ranges for HbA1c varied between centres and multiplied by 6.0. (16). Due to the fact that low-density lipoprotein levels were frequently unmeasured in many of the study participants, total cholesterol was utilised as a proxy for lipid control. Prior to the data collection point, the last blood pressure reading from the clinical record was used. During a year, data were gathered at the beginning and every six months after that. All patients who are recruited complete the Total Illness Burden Index (TIBI) survey (18–20). The TIBI, which was created especially for populations in office practices, uses patient reports to evaluate the presence and severity of 8 dimensions of comorbid conditions, problems, and diseases (atherosclerotic heart disease, lung disease, congestive heart failure, arthritis, genitourinary disease, vision loss, gastrointestinal conditions, and foot disease) using items similar to those in the conventional review of systems. These replies were used to evaluate the severity of the eight dimensions, and the scores were then combined using an algorithm that gave each dimension a different weight based on how it was expected to affect the functional outcomes. To investigate the impact of the noncardiac components of the TIBI on future occurrences, analyses were undertaken using a version of the TIBI score that omitted prior cardiovascular events. The noncardio vascular TIBI score is the name we give to this variation. The TIBI has been verified as a predictor of 3.5-year mortality (20) and health-related quality of life, and it may be completed and scored in office settings for use by doctors at the time of therapy (18, 19).

**Sample Size:** 200 patients who met the inclusion criteria were eligible for this study.

**Statistical analysis:** The patient characteristics, reported means and SDs for continuous variables, and frequencies and percentages for categorical variables were all described using univariate analysis. The Kaplan-Meier method was used to calculate the odds of incident cardiovascular events, and the log-rank test was used to make comparisons. To determine whether a dichotomized TIBI score was an independent predictor of clinical outcomes, we used multivariate Cox proportional hazards regression models, stratified by center, to take into account the hierarchical nature of the data (patients clustered within the center) and to control for potential confounding or clustering by the center of variables. Hazard ratios (HRs) with 95% confidence intervals in all analyses to represent outcome risk in models that were corrected for age (as a continuous variable) and sex (as a categorical variable) were used.

**Results**

200 (82%) of the 280 type 2 diabetes patients who were initially enrolled in the study and who completed the baseline questionnaire were included in the final analytic sample. **Table 1** lists the baseline patient characteristics for the two comorbidity groupings.Patients in the high comorbidity subgroup were more likely to report never smoking (46.8% vs. 43.1%; P<0.002), to have a higher BMI (28.4 vs. 27.4 kg/$m^2$; P<0.02), to have had diabetes for a longer period of time (11.8 vs. 9.6 years; P<0.002),and slightly higher levels of total cholesterol (5.5 mmol/L [217 mg/dL] vs. 5.4 mmol/L [212 mg/dL]; P <0.002) and HbA1c (7.2% vs. 7.1%; P <0.020).

Table 1: Baseline characteristics of patients

| Characteristics | Combordity Level | | P-Value |
|---|---|---|---|
| | Low to Moderate (TIBI Score <12) | High (TIBI Score >12) | |
| Mean age (SD) | 61.6 (10.4) | 64.2 (9.4) | <0.002 |
| Men (%) | 58.2 | 50.1 | <0.002 |
| Mean BMI (SD) kg/m$^2$ | 27.4 (4.2) | 28.3 (4.6) | <0.002 |
| Duration of Diabetes | 9.6 (8.1) | 11.8 (9.1) | <0.002 |
| Smoking Status | | | |
| Never Smoked | 43.1 | 46.8 | <0.002 |
| Current Smoker | 17.3 | 16.4 | |
| Former Smoker | 34.4 | 35.2 | |
| Unknown | 5.0 | 1.2 | |
| HB1Ac <7.5% | 52.3 | 46.8 | <0.002 |
| Mean Hb1Ac (SD) | 7.1 (1.6) | 7.3 (1.6) | 0.020 |
| Mean SBP (mg/dl) | 143.1 (17.5) | 144.3 (18.3) | 0.114 |
| Mean DBP (mg/dl) | 82.8 | 82.4 | 0.30 |

6.4% of patients died and 16.2% experienced a cardiovascular event throughout the 1-year follow-up period. We modeled cardiovascular event risk and total mortality risk by TIBI level to confirm the suitability of a TIBI threshold score of 12 to define subgroups. For the 1-year observation period, patients in the high comorbidity group had a higher risk of cardiovascular events (HR, 1.51 [95% CI, 1.21 to 1.88]; P <0.002) and death (HR, 1.38 [95% CI, 0.96 to 1.98]; P <0.073) than those in the low-to-moderate comorbidity group. This was true after controlling for age, gender, smoking, body mass index, and HbA1.

When TIBI was examined as a continuous variable, the correlation between the TIBI score and the clinical outcomes persisted. Following correction, each unit change in the continuous TIBI score was linked to an increase of 1% in the risk of total mortality (HR, 1.01 [CI, 1.01 to 1.02]; P <0.013) and cardiovascular events (HR, 1.01 [CI, 1.00 to 1.01]. In addition, after adjusting for age and sex, patients in the highest quartile of noncardio vascular TIBI scores had an 88% higher risk of incident cardiovascular events than those in the lowest quartile (HR, 1.88[CI, 1.38to 2.57]; P <0.001), and after excluding previous cardiovascular events, total mortality increased marginally in the 1-year period (HR, 1.51 [CI, 0.95 to 2.41]; P <0.081).

Following that, it was investigated if achieving an HbA1c target of either 6.0% or less or 7.5% or less at baseline was linked to a decreased risk of later cardiovascular events in the high (TIBI score 12) versus low-to-moderate (TIBI score 12) comorbidity categories throughout follow-up. With an unadjusted HR of 0.57 (CI, 0.40 to 0.81; P 0.002) and an adjusted HR of 0.61 (CI, 0.41 to 0.84) (P0.04), patients in the low-to-moderate comorbidity subgroup experienced lower rates of incident cardiovascular events if they achieved the HbA1c target of 6.0% or less than if they did not (2.1 events vs. 3.7 events).

Cardiovascular event rates in the high comorbidity subgroup were 4.8 events vs. 5.1 events, with an unadjusted HR of 0.92 (CI, 0.67 to 1.25) (P=0.63) and an adjusted HR of 0.91 (CI, 0.67 to 1.24; P=0.60), showing no difference between patients who met the HbA1c target of 6.0% or less and those who did not. The P value for the interaction between the TIBI subgroup and HbA1c level was 0.035 in the unadjusted model and 0.047 in the adjusted model, suggesting that there was a difference between the low-to-moderate comorbidity subgroup and the high comorbidity subgroup in the cardiovascular event risk reduction associated with achieving the HbA1c target of 6.0% or less.

Examining the benefits of achieving a HbA1c level of 7.5% or below revealed a similar pattern. The incidence of cardiovascular events was lower among patients in the low-to-moderate comorbidity category who met that goal than in those who did not (2.3 events vs. 4.0 events, with an uncorrected HR of 0.58 (CI, 0.43 to 0.80) (P <0.001) and an adjusted HR of 0.60 (CI, 0.43 to 0.82) (P <0.002). Cardiovascular event rates in the high comorbidity subgroup were the same for patients with and without a HbA1c level of 7.5% or below (4.6 events vs. 5.2 events, with an uncorrected HR of 0.87 (CI, 0.65 to 1.16) and an adjusted HR of 0.85 (CI, 0.63 to 1.13) (P <0.31). In the unadjusted model, the P value for the interaction between the TIBI subgroup and HbA1c level was 0.060, while in the adjusted model, it was 0.092.The findings from a replication of these analyses in TIBI score tertile-based subgroups further imply that not all patients benefit equally from achieving tight glycemic control. Whether they met the HbA1c target of 6.0% or less or not, patients in the highest tertile had similar rates of cardiovascular events (4.7 events vs. 5.1 events), with an uncorrected HR of 0.87 (CI, 0.61 to 1.23) and an adjusted HR of 0.85 (CI, 0.60 to 1.22) (P<0.40). Cardiovascular events occurred at a lower rate among patients in the second tertile who met the HbA1c target of 6.0% or less (2.7 events vs. 4.7 events, with an uncorrected HR of 0.61 (CI, 0.38 to 0.90) (P <0.015) and an adjusted HR of 0.61 (CI, 0.38 to 0.90; P <0.016) than in those who did not.

Patients in the lowest tertile experienced similar cardiovascular event rates regardless of whether they met the HbA1c target of 6.0% or less (2.1 events vs. 3.1 events, with an unadjusted HR of 0.74 (CI, 0.47 to 1.21) (P <0.22) and an adjusted HR of 0.81 (CI, 0.51 to 1.27) (P <0.37). These patients had low cardiovascular event rates in the 1-year period because they had little to no comorbidity. The interaction between the TIBI subgroup and HbA1c level had a P value <0.33. When we looked at the advantages of achieving a HbA1c level of 7.5% or less at baseline for each TIBI tertile subgroup, the findings were comparable.

While separate analyses of interactions between achieving a HbA1c level of 7.5% or less and other patient characteristics (age, gender, duration of diabetes, education, and income) did not indicate differential benefit for achieving tight control across different levels of these characteristics, they did show a similar pattern of results with subgroups defined using the noncardio vascular TIBI score.

**Discussion**

The results are consistent with recommendations (1-3) to concentrate intensive glycemic therapy on younger patients with less comorbidity and to set less demanding HbA1c targets for patients with severe sequelae and concomitant diseases. We discovered that baseline HbA1c levels were linked to a lower incidence of subsequent cardiovascular events over the course of a year among individuals with low- to moderate comorbidities. On the other hand, among individuals with significant levels of comorbidity, there was no correlation between meeting baseline HbA1c objectives of 6.0% or 7.5% and having a cardiovascular incident throughout the course of the 1-year research.

The results might clarify the apparent discrepancy between the outcomes of three recent randomised controlled trials (4-6), which included older patients with more comorbid conditions, and those of a meta-analysis (7, 8), which included a larger representation of all patients, particularly younger patients with less comorbid conditions. The proportion of research

participants from each group will have an impact on the "average effect" if older patients with significant comorbidity are less likely to benefit from intensive glycemic control and younger patients with less comorbidity are more likely to benefit.

The hypothesis-generating post hoc analyses of recent randomised clinical trials (4, 5) highlight the need to establish a priori subgroups to minimise "averaging" effects that's could give null results. Similar age and comorbidity characteristics were shared by patients in the high comorbidity subgroup in our analysis and those in a trial that found no benefit from strict management (4). Benefits were seen in the low-to-moderate comorbidity subgroup in our study that were comparable to those seen in post hoc analyses among patients in that trial (4) who had "no history of macro vascular disease" and were under 65 years old, as well as in another trial who had "no prior cardiovascular event" (5).

This study also raises the possibility that, even among individuals with lower levels of comorbidity, the advantages of achieving tight glycemic control may not be consistent over the course of a year. Patients with TIBI scores in the lowest tertile exhibited no benefits from achieving HbA1c targets, but they might have if they had been monitored for a longer period of time. With a patient sample similar to the lowest-risk category in our analysis, the UKPDS (10), significant decreases in cardiovascular event risk were not seen until 10 years after the trial (9).

Tight glycemic control's impaired ability to lower cardiovascular events in patients with high TIBI scores is likely a result of a combination of these patients' extremely low life expectancies and the challenges of managing them. When we rescored the TIBI to exclude questions that evaluated prior cardiac disease, the correlation between the TIBI score and risk for death or incident cardiovascular events continued. These results imply that pulmonary dysfunction, gastrointestinal disease, and arthritis, which are noncardiac concomitant diseases, may independently reduce a patient's ability to benefit from stringent glycemic management**.**

**Conclusion**

According to the findings of a one-year observational trial, not all patient subgroups may experience the same reduction in risk for cardiovascular events as a result of strict glycemic control. Only clinical studies with diabetic patients who are reasonably healthy and young can causally show that individuals with little comorbidity can benefit from achieving tight glycemic control. The study does, however, reveal that for a sizable proportion of patients with type 2 diabetes who have high levels of comorbidity, stringent glucose management may not have the protective effect on cardiovascular event risk that is expected. When customizing glucose-lowering medication for patients with type 2 diabetes, comorbidity may be a crucial factor.

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