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Comorbidity Affects the Relationship Between Glycemic Control and Cardiovascular Outcomes in Diabetes

A Cohort Study

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Background: Recent studies have shown mixed results regarding the effectiveness of intensive glucose-lowering therapy in reducing risk for cardiovascular events.

Objective: To determine whether attaining hemoglobin A_{1c} (HbA_{1c}) targets of 6.5% or less or 7.0% or less for glycemic control at baseline provides differential benefits for patients with high versus low-to-moderate levels of comorbidity.

Design: 5-year longitudinal observational study of patients with type 2 diabetes. Patients were categorized into high and low-to-moderate comorbidity subgroups by using the Total Illness Burden Index (TIBI), a validated patient-reported measure of comorbidity.

Setting: 101 diabetes outpatient clinics and 103 general practitioners' clinics in Italy.

Patients: 2613 (83%) of 3074 patients with type 2 diabetes, sampled randomly from diabetes outpatient clinic rosters and recruited consecutively from general practitioners' clinics, who completed the baseline questionnaire.

Measurements: TIBI score, total mortality, and incident cardiovascular events. Hazard ratios (HRs) were adjusted for age and sex.

Results: Attaining an HbA_{1c} level of 6.5% or less at baseline was associated with lower 5-year incidence of cardiovascular events in the low-to-moderate comorbidity subgroup (adjusted HR, 0.60 [95% CI, 0.42 to 0.85]; $P = 0.005$) but not in the high comorbidity subgroup (adjusted HR, 0.92 [CI, 0.68 to 1.25]; $P = 0.61$; P for subgroup by HbA_{1c} interaction = 0.048). Similarly, attaining a baseline HbA_{1c} level of 7.0% predicted fewer cardiovascular events in the low-to-moderate comorbidity subgroup (adjusted HR, 0.61 (CI, 0.44 to 0.83; $P = 0.001$) but not in the high comorbidity subgroup (adjusted HR, 0.88 [CI, 0.66 to 1.17]; $P = 0.38$; P for subgroup by HbA_{1c} interaction = 0.093).

Limitations: The observational nature of the study does not allow causal inference. The length of the data collection period was limited. Information on clinical management was not available.

Conclusion: Patients with the high levels of comorbidity common in type 2 diabetes may receive diminished cardiovascular benefit from intensive blood glucose control. Comorbidity should be considered when tailoring glucose-lowering therapy in patients with type 2 diabetes.

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Major professional organizations recommend that attaining a hemoglobin A1c (HbA_{1c}) value less than 7.0% may be less appropriate for patients with limited life expectancy, advanced complications, and extensive comorbidity (1–3). Evidence suggests that the benefit of intensive glucose-lowering therapy is not uniform across all patients with type 2 diabetes.

Three large randomized, controlled trials that used HbA_{1c} targets of 6.5% or lower (4–6) each found no association between intensive therapy and an overall reduction in risk for macrovascular complications. However, when data from these and other trials were considered in 2 recent meta-analyses (7, 8), the investigators observed statistically significant relationships between tight glycemic control and reduced cardiovascular events.

Post hoc analyses of data from these clinical trials suggest that benefit from aggressive glycemic control may be confined to younger diabetic patients (4) and patients without previous heart disease (4, 5). Data from the 10-year posttrial follow-up (9) to the UKPDS (United Kingdom Prospective Diabetes Study) (10) also showed a reduction in cardiovascular events from intensive glucose-lowering therapy initiated in a young and healthy sample of patients with recently diagnosed type 2 diabetes.

Recent decision analyses based on UKPDS risk models suggest that, independent of age, high levels of comorbidity may diminish the benefits of achieving tight control (11), owing to the complex interplay of multiple conditions, their treatments, and their burden on patient resources (12). Among the comorbid conditions prevalent among diabetic patients, cardiovascular diseases are the most important contributors to mortality and subsequent cardiovascular events. However, additional conditions,

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such as chronic lung disease, may also bring functional impairment, treatment burden, and risk for adverse events and may diminish a patient's likelihood to benefit from tight control (13, 14).

In a 5-year observational study of a community-based sample of older patients with type 2 diabetes, we tested whether attaining glycemic control targets of HbA_{1c} levels of 6.5% or less or 7.0% or less at baseline provided differential benefits for patients with higher versus lower levels of comorbidity. We further compared the unique contribution of comorbid conditions with that of other risk factors (such as age or duration of diabetes) to the differential benefit from glycemic control on future cardiovascular events.

Context

The effectiveness of glycemic control in reducing cardiovascular events among patients with type 2 diabetes is uncertain. Recent analyses of trial data suggest that the benefit of tight control may differ according to a person's age and comorbid conditions.

Contribution

This observational study of 2613 patients with type 2 diabetes in 205 practices in Italy found that tight control was associated with lower risk for cardiovascular events over 5 years in patients with low to moderate, but not high, comorbidity.

Caution

Observational data cannot prove a causal association between glycemic control and outcomes.

Implication

The relationship of glycemic control and cardiovascular outcomes differs by patients' level of comorbidity.

—The Editors

METHODS

Our study, described in detail elsewhere (15–17), was a 5-year longitudinal observational study (1999 to 2004) that examined the association of the quality of diabetes care with the incidence of cardiovascular events and mortality. Patients were followed for a median of 4.96 years (interquartile range, 3.35 to 5.00 years).

Patients

We identified medical practices in all regions of Italy and selected them according to their willingness to participate in the project. Participating practices included 101 of approximately 605 eligible diabetes outpatient clinics and 103 of approximately 1000 eligible community-based general practitioners enrolled in a nationwide network of practitioners interested in facilitating research.

We considered all patients with type 2 diabetes mellitus (fasting venous plasma glucose concentration ≥7.8 mmol/L [140 mg/dL] on ≥2 separate occasions or treated with antidiabetic drugs) to be eligible for the project, regardless of age, diabetes duration, or treatment. At the diabetes outpatient clinics, patients were randomly sampled from clinic rosters and stratified by patient age (<65 or ≥65 years). We asked each diabetes outpatient clinic to recruit at least 30 patients. Community-based general practitioners consecutively enrolled only patients for whom they were primarily responsible for diabetes care, up to a maximum of 10 patients.

Clinical Measures

The main outcome of the study was incident cardiovascular events, defined as any of the following outcomes: angina, myocardial infarction, stroke, transient ischemic attack, coronary revascularization procedures, lower limb complications (claudication, ulcer, gangrene, amputation, or aortic–femoral revascularization procedures), or cardiovascular mortality. Participating physicians certified the occurrence of any cardiovascular event over the 5-year study period, on the basis of study-wide criteria. In addition, participating physicians reported the death of any study patient from any cause; this information was used to compute total mortality rates.

Participating physicians abstracted demographic and clinical data, including age, body mass index, duration of diabetes, HbA_{1c} level, lipid levels, and blood pressure (collected and entered into models as continuous variables), as well as sex, smoking status and the presence of diabetes complications (collected and entered into models as categorical variables) from clinical records and reported these data to the coordinating center at Mario Negri Sud. Because normal ranges for HbA_{1c} varied in the different centers, the percentage change with respect to the upper normal value (actual value vs. upper limit of normal) was estimated and multiplied by 6.0 (16). Total cholesterol was used as a measure of lipid control because low-density lipoprotein levels were not routinely measured in many of the study patients. We used the last blood pressure value in the clinical record before the data collection point. Data were collected at baseline and at 6-month intervals for 5 years.

Measure of Comorbidity

We requested that all recruited patients complete the Total Illness Burden Index (TIBI) questionnaire (18–20). The TIBI, which was specifically developed for office practice populations, uses patient reports to assess 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) by using items similar to those in the traditional review of systems. We scored these responses to assess the

Table 1. **Baseline Patient Characteristics, by Comorbidity Level**

Characteristic	Comorbidity Level		*P* Value*
	Low to Moderate (TIBI Score <12)	High (TIBI Score ≥12)	
Patients, *n*	1498	1115	
Mean age (SD), *y*	61.7 (10.5)	64.3 (9.5)	<0.001
Men, %	58.3	50.2	<0.001
Mean body mass index (SD), kg/m^2	27.5 (4.3)	28.4 (4.7)	<0.001
Smoking status, %			<0.001
Never smoked	43.0	46.9	
Current smoker	17.4	16.5	
Former smoker	34.5	35.3	
Unknown	5.1	1.3	
Mean diabetes duration (SD), *y*	9.7 (8.0)	11.9 (9.0)	<0.001
HbA_{1c} level ≤7.0%, %	52.4	46.9	0.009
Mean HbA_{1c} level (SD), %	7.2 (1.7)	7.4 (1.7)	0.021
Mean total cholesterol level (SD)			0.002
mmol/L	5.5 (1.1)	5.6 (1.1)	
mg/dL	213 (41)	218 (42)	
Mean systolic blood pressure (SD), *mm Hg*	143.2 (17.6)	144.4 (18.4)	0.115
Mean diastolic blood pressure (SD), *mm Hg*	82.9 (8.5)	82.5 (8.6)	0.31

HbA_{1c} = hemoglobin A_{1c}; TIBI = Total Illness Burden Index.
* *P* values refer to the Pearson chi-square and Mann–Whitney U tests for categorical and continuous variables, respectively.

severity of the 8 dimensions and then aggregated the scores by using an algorithm that weighted each dimension according to its predicted effect on functional outcomes. We also performed analyses that used a version of the TIBI score that excluded previous cardiovascular events to examine the effects of the noncardiac components of the TIBI on future events. We refer to this version as the *noncardiovascular TIBI* score.

The TIBI can be completed and scored in office practices for use by physicians at the time of treatment and has been validated as a predictor of 3.5-year mortality (20) and health-related quality of life (18, 19).

Statistical Analysis

We conducted univariate analyses to describe patient characteristics and reported means and SDs for continuous variables and frequencies and percentages for categorical variables.

We calculated the probabilities of incident cardiovascular events by using the Kaplan–Meier method and carried out comparisons by using the log-rank test. We divided patients into 2 prespecified subgroups at a threshold TIBI score of 12, which has been demonstrated to discriminate between persons at greater and lesser risk for death (20). We defined patients with TIBI scores less than 12 as the low-to-moderate comorbidity subgroup and patients with scores of 12 or greater as the high comorbidity subgroup.

To account for the hierarchical nature of the data (patients clustered within center), and to control for possible confounding or clustering by center of variables, we used multivariate Cox proportional hazards regression models, stratified by center, to investigate whether a dichotomized TIBI score was an independent predictor of clinical outcomes. In all analyses, we expressed outcome risk in terms of hazard ratios (HRs) with 95% CIs in models adjusted for age (as a continuous variable) and sex (as a categorical variable).

To demonstrate that the threshold TIBI score of 12 differentiated patients' risk both for cardiovascular events and for total mortality in the current sample, we computed hazard ratios for relative risk for each outcome between participants with TIBI scores of 12 or greater and patients with scores less than 12. To demonstrate that any association observed between comorbidity and outcome risk was not an artifact of the selected TIBI score cut-point, we computed hazard ratios for both cardiovascular event risk and mortality risk by using the TIBI score as a continuous, independent variable. We replicated the analysis by using the "noncardiovascular TIBI score" to examine its association with future cardiovascular events and mortality.

To determine whether the benefit of attaining recommended targets for glycemic control was greater for patients with low-to-moderate or high levels of comorbidity, we tested whether baseline HbA_{1c} levels of 6.5% or less or 7.0% or less were associated with lower incidence of cardiovascular events in each comorbidity subgroup. To examine whether any observed association between attaining glycemic control targets and reduced cardiovascular event risk was sensitive to the choice of TIBI cutoff thresholds, we replicated these analyses in subgroups defined by tertiles of TIBI scores for each target HbA_{1c} value. We also tested whether we could detect differential benefits of attaining the glycemic control target in subgroups defined by high versus low noncardiovascular TIBI scores alone. Finally, to consider the contributions of variables that could be related to comorbidity, we tested separate models that included

interaction terms between HbA_{1c} level and age, duration of diabetes, sex, education, and income—each considered as a continuous variable (with the exception of sex, which is categorical). For each of these analyses, we tested the interaction of HbA_{1c} level with TIBI subgroup and with other patient characteristics (age, sex, duration of diabetes, education, and income) to assess differential levels of benefit associated with attaining tight control. We used SAS, version 9.1 (SAS Institute, Cary, North Carolina), for all analyses.

Role of the Funding Source

The study was funded by Pfizer of Italy. The funding source had no role in the design, conduct, analysis or reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

Of the 3074 initially enrolled patients with type 2 diabetes, 2613 (83%) completed the baseline questionnaire and were included in our final analytic sample. **Table 1** reports patient characteristics at baseline for the 2 comorbidity subgroups. Patients in the high comorbidity subgroup tended to be older than those in the low-to-moderate comorbidity subgroup (mean age, 64.3 vs. 61.7 years; $P < 0.001$), and fewer were male (50.2% vs. 58.3%; $P < 0.001$); they also were more likely to report never smoking (46.9% vs. 43.0%; $P < 0.001$) and had higher body mass indexes (28.4 vs. 27.5 kg/m^2; $P < 0.001$), longer duration of diabetes (11.9 vs. 9.7 years; $P < 0.001$), and marginally higher levels of HbA_{1c} (7.4% vs. 7.2%; $P = 0.021$) and total cholesterol (5.6 mmol/L [218 mg/dL] vs. 5.5 mmol/L [213 mg/dL]; $P = 0.002$). During the 5-year follow-up period, 426 patients (16.3%) developed a cardiovascular event and 168 patients (6.5%) died.

To confirm the appropriateness of a TIBI threshold score of 12 to define subgroups, we modeled cardiovascular event risk and total mortality risk by TIBI level. Controlling for age, sex, smoking, body mass index, HbA_{1c} level, total cholesterol level, and blood pressure, patients in the high comorbidity group had a higher risk for cardiovascular events (HR, 1.52 [95% CI, 1.21 to 1.89]; $P < 0.001$) and death (HR, 1.39 [CI, 0.97 to 1.99]; $P = 0.074$) than those in the low-to-moderate comorbidity group for the 5-year observation period (**Table 2**).

The association between TIBI score and clinical outcomes persisted when we analyzed TIBI as a continuous variable. After adjustment, each unit change in the continuous TIBI score was associated with a 2% increase in both cardiovascular event risk (HR, 1.02 [CI, 1.01 to 1.02]; $P < 0.001$) and total mortality risk (HR, 1.02 [CI, 1.00 to 1.03]; $P = 0.014$). In addition, when we rescored the TIBI to exclude previous cardiovascular events, patients in the highest quartile of noncardiovascular TIBI scores experienced an 89% increase in risk for incident cardiovascular events compared with those in the lowest quartile, after adjustment for age and sex (HR, 1.89 [CI, 1.39 to 2.58]; $P = 0.002$), and showed a marginal increase in total mortality in the 5-year period after adjustment (HR, 1.52 [CI, 0.96 to 2.40]; $P = 0.082$).

We then tested whether attaining an HbA_{1c} target of either 6.5% or less or 7.0% or less at baseline was associated with a lower incidence of subsequent cardiovascular events in the high (TIBI score ≥12) versus low-to-moderate (TIBI score 12) comorbidity subgroups during follow-up (**Table 3**). Patients in the low-to-moderate comorbidity subgroup experienced lower rates of incident cardiovascular events if they attained the HbA_{1c} target of 6.5% or less than if they did not (2.2 events vs. 3.8 events per 100 patient-years), with an unadjusted HR of 0.58 (CI, 0.41 to 0.82) ($P = 0.002$) and an adjusted HR of 0.60 (CI, 0.42 to 0.85) ($P = 0.005$). In the high comorbidity subgroup, cardiovascular event rates did not differ between patients who attained the HbA_{1c} target of 6.5% or less and those who did not (4.9 events vs. 5.2 events per 100 patient-years), with an unadjusted HR of 0.93 (CI, 0.68 to 1.26) ($P = 0.64$) and an adjusted HR of 0.92 (CI, 0.68 to 1.25) ($P = 0.61$). The P value for the interaction between TIBI subgroup and HbA_{1c} level was 0.036 in the

Table 2. **Association Between TIBI and Risk for Cardiovascular Events or Death**

Outcome and TIBI Score	Univariate Analysis				Multivariate Cox Hierarchical Analysis	
	Events, *n*	Patients, *n*	Survival at 5 y (95% CI), %	Log-Rank *P* Value	Hazard Ratio (95% CI)*	*P* Value
Total cardiovascular events						
TIBI score <12	207	1498	83.7 (81.6–85.7)	<0.001	1.00	–
TIBI score ≥12	219	1115	76.6 (73.8–79.4)		1.52 (1.21–1.89)	<0.001
Total mortality						
TIBI score <12	74	1498	94.2 (92.9–95.5)	<0.001	1.00	–
TIBI score ≥12	94	1115	89.9 (88.0–91.9)		1.39 (0.97–1.99)	0.074

TIBI = Total Illness Burden Index.
* Adjusted for age, sex, smoking, body mass index, baseline levels of hemoglobin A_{1c} and total cholesterol, and blood pressure.

Table 3. **Reduction in Risk for Cardiovascular Events Associated With HbA_{1c} Level 6.5% or Less or 7.0% or Less, by TIBI Subgroup**

Subgroup	HbA_{1c} Target ≤6.5%						
	Cardiovascular Event Rate, *n per 100 patient-years*			Unadjusted Model		Adjusted Model*	
	HbA_{1c} ≤6.5%	HbA_{1c} >6.5%	Change	HR (95% CI)	*P* Value†	HR (95% CI)	*P* Value†
TIBI score					0.036		0.048
<12	2.2	3.8	1.6	0.58 (0.41–0.82)‡		0.60 (0.42–0.85)‡	
≥12	4.9	5.2	0.3	0.93 (0.68–1.26)		0.92 (0.68–1.25)	
TIBI score tertile					0.32		0.34
1st	2.3	3.1	0.7	0.76 (0.49–1.20)		0.82 (0.52–1.28)	
2nd	2.9	4.9	2.0	0.60 (0.39–0.91)‖		0.60 (0.39–0.91)‖	
3rd	4.8	5.2	0.5	0.88 (0.62–1.24)		0.86 (0.61–1.23)	

HbA_{1c} = hemoglobin A_{1c}; HR = hazard ratio; TIBI = Total Illness Burden Index.
* Adjusted for age and sex.
† Value for interaction between TIBI subgroup and HbA_{1c} level.
‡ $P < 0.010$.
§ $P < 0.001$.
‖ $P < 0.050$.

unadjusted model and 0.048 in the adjusted model, which suggests that the cardiovascular event risk reduction associated with attaining the HbA_{1c} target of 6.5% or less in the low-to-moderate comorbidity subgroup differed from that in the high comorbidity subgroup.

We observed a similar pattern when we examined the benefit of attaining an HbA_{1c} level of 7.0% or less. Patients in the low-to-moderate comorbidity subgroup who attained that target had a lower incidence of cardiovascular events than those who did not (2.4 events vs. 4.1 events per 100 patient-years), with an unadjusted HR of 0.59 (CI, 0.44 to 0.81) ($P < 0.001$) and an adjusted HR of 0.61 (CI, 0.44 to 0.83) ($P = 0.001$). In the high comorbidity subgroup, cardiovascular event rates did not differ between patients who attained an HbA_{1c} level of 7.0% or less and those who did not (4.8 events vs. 5.4 events per 100 patient-years), with an unadjusted HR of 0.88 (CI, 0.66 to 1.17) ($P = 0.38$) and an adjusted HR of 0.86 (CI, 0.64 to 1.14) ($P = 0.30$). The *P* value for the interaction of TIBI subgroup and HbA_{1c} level was 0.061 in the unadjusted model and 0.093 in the adjusted model.

Our results from replication of these analyses in subgroups defined by TIBI score tertiles (**Table 3**) further suggest that not all patients experience equivalent benefit from attaining tight glycemic control. Patients in the highest tertile experienced similar rates of cardiovascular events whether they attained the HbA_{1c} target of 6.5% or less or did not (4.8 events vs. 5.2 events per 100 patient-years), with an unadjusted HR of 0.88 (CI, 0.62 to 1.24) ($P = 0.46$) and an adjusted HR of 0.86 (CI, 0.61 to 1.23) ($P = 0.41$). Patients in the second tertile who attained the HbA_{1c} target of 6.5% or less had lower rates of cardiovascular events than those who did not (2.9 events vs. 4.9 events per 100 patient-years), with an unadjusted HR of 0.60 (CI, 0.39 to 0.91) ($P = 0.016$) and an adjusted HR of 0.60 (CI, 0.39 to 0.91) ($P = 0.017$). Patients in the lowest tertile, who had little or no comorbidity and therefore had low cardiovascular event rates in the 5-year period, also experienced similar cardiovascular event rates whether they attained the HbA_{1c} target of 6.5% or less or did not (2.3 events vs. 3.1 events per 100 patient-years), with an unadjusted HR of 0.76 (CI, 0.49 to 1.20) ($P = 0.24$) and an adjusted HR of 0.82 (CI, 0.52 to 1.28) ($P = 0.38$). The *P* value for the interaction of TIBI subgroup and HbA_{1c} level was 0.34. Results were similar when we examined the benefit of attaining an HbA_{1c} level of 7.0% or less at baseline for each of the TIBI tertile subgroups (**Table 3**).

We found a similar pattern of results with subgroups defined using the noncardiovascular TIBI score (data not shown), but separate tests of interactions between attaining an HbA_{1c} level of 7.0% or less and other patient characteristics (age, sex, duration of diabetes, education, and income) did not suggest differential benefit for attaining tight control across different levels of these characteristics (data not shown).

DISCUSSION

Our findings support recommendations (1–3) to focus intensive glycemic therapy on younger patients with less comorbidity and to require less stringent HbA_{1c} targets for patients with extensive complications and comorbid conditions. Among patients with low-to-moderate comorbidity, we found that baseline HbA_{1c} level was associated with reduced incidence of subsequent cardiovascular events within a 5-year period. Conversely, among patients with high levels of comorbidity, we found no association between attaining HbA_{1c} targets of 6.5% or less or 7.0% or less at baseline and experiencing a cardiovascular event during the 5-year study period.

Table 3—**Continued**

HbA_{1c} Target ≤7.0%						
Cardiovascular Event Rate, *n per 100 patient-years*			Unadjusted Model		Adjusted Model*	
HbA_{1c} ≤7.0%	HbA_{1c} >7.0%	Change	HR (95% CI)	*P* Value†	HR (95% CI)	*P* Value†
				0.061		0.093
2.4	4.1	1.7	0.59 (0.44–0.81)§		0.61 (0.44–0.83)‡	
4.8	5.4	0.6	0.88 (0.66–1.17)		0.86 (0.64–1.14)	
				0.36		0.35
2.5	3.2	0.7	0.80 (0.52–1.21)		0.84 (0.55–1.27)	
3.1	5.4	2.3	0.59 (0.41–0.84)‡		0.58 (0.40–0.84)‡	
4.6	5.5	0.9	0.81 (0.58–1.12)		0.79 (0.57–1.10)	

Our findings could shed light on the observed discrepancy between the results of the 3 recent randomized, controlled trials (4–6) that included older patients with greater comorbidity and those of the meta-analysis (7, 8) that included a broader representation of all patients, specifically younger patients with less comorbidity. If older patients with substantial comorbidity are less likely to benefit from intensive glycemic control and younger patients with less comorbidity are more likely to benefit, then the "average effect" will be influenced by the proportion of study patients that represent each group.

The hypothesis-generating post hoc analyses of recent randomized clinical trials (4, 5) illustrate the need to identify a priori subgroups to avoid "averaging" effects that could yield null results. Patients in the high comorbidity subgroup in our study had similar age and comorbidity characteristics to those in a trial that showed no benefit from tight control (4). The low-to-moderate comorbidity subgroup from our study experienced benefits that paralleled those observed in post hoc analyses among patients with "no history of macrovascular disease" and those younger than 65 years in that trial (4), and in those with "no previous cardiovascular event" in another trial (5).

Our study also suggests that even among patients with lower levels of comorbidity, the benefits of attaining tight glycemic control may not be uniform in a 5-year period. Patients with TIBI scores in the lowest tertile showed no benefit from attaining HbA_{1c} targets but may have shown benefit from tight control if they had been observed for a longer interval. The UKPDS (10), with a patient sample similar to the lowest-risk subgroup in our study, did not observe significant reductions in cardiovascular event risk until 10 years after the trial (9).

The diminished potential of tight glycemic control to reduce cardiovascular events in patients with high TIBI scores is probably due to a combination of limited life expectancy and the complexities of managing these very sick patients. The association between the TIBI score and risk for death or incident cardiovascular events persisted when we rescored the TIBI to exclude items that assessed previous cardiac disease. These findings suggest that noncardiac comorbid conditions, such as pulmonary dysfunction, gastrointestinal disease, and arthritis, may independently diminish a patient's potential to benefit from intensive glycemic control.

Our study has limitations. First, this is an observational study. We cannot establish causal links between high levels of comorbidity and diminished benefit from tight glycemic control. We also did not have information on clinical management during the 5-year observational period. However, these results lend support to the importance of comorbidity in identifying which patients may benefit from attaining intensive glycemic control. Evidence for this conclusion would be strengthened by a prospective, randomized, controlled trial designed to study the benefits of intensive glycemic control with a priori specified subgroups of patients with varying levels of comorbidity.

Second, multiple comparisons that consider variables other than TIBI score to define subgroups may affect the interpretation of *P* values. Third, our study includes only 1 sample of patients in 1 country with minimal ethnic and racial diversity, which may limit the generalizability of findings. Finally, we did not test other measures of comorbidity derived from other data sources (21), but we would expect them to produce similar results (22).

The results of our 5-year observational study suggest that any reduction of risk for cardiovascular events associated with tight glycemic control may not be uniform across patient subgroups. Only clinical trials that include relatively young and healthy diabetic patients can causally demonstrate that patients with low levels of comorbidity can benefit from attaining tight glycemic control. However, our study suggests that intensive glucose control may not have the expected protective effect on cardiovascular event risk for a substantial group of patients with type 2 diabetes who have high levels of comorbidity. Comorbidity may be an important consideration when tailoring glucose-lowering therapy in patients with type 2 diabetes.

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