Meta-Analysis: Glycosylated Hemoglobin and Cardiovascular Disease in Diabetes Mellitus

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Background: In persons with diabetes, chronic hyperglycemia (assessed by glycosylated hemoglobin level) is related to the development of microvascular disease; however, the relation of glycosylated hemoglobin to macrovascular disease is less clear.

Purpose: To conduct a meta-analysis of observational studies of the association between glycosylated hemoglobin and cardiovascular disease in diabetic persons.

Data Sources: Search of the MEDLINE database by using Medical Subject Heading search terms and key words related to glycosylated hemoglobin, diabetes, and cardiovascular disease.

Study Selection: Prospective cohort studies with data on glycosylated hemoglobin levels and incident cardiovascular disease.

Data Extraction: Relative risk estimates were derived or abstracted from each cohort study that met the inclusion criteria.

Data Synthesis: Adjusted relative risk estimates for glycosylated hemoglobin (total glycosylated hemoglobin, hemoglobin A1c levels, or hemoglobin A1c levels) and cardiovascular disease events (coronary heart disease and stroke) were pooled by using random-effects models. Three studies involved persons with type 1 diabetes (n = 1688), and 10 studies involved persons with type 2 diabetes (n = 7435). The pooled relative risk for cardiovascular disease was 1.18; this represented a 1-percentage point increase in glycosylated hemoglobin level (95% CI, 1.10 to 1.26) in persons with type 2 diabetes. Results in persons with type 1 diabetes were similar but had a wider CI (pooled relative risk, 1.15 [CI, 0.92 to 1.43]).

Limitations: This review largely reflects the limitations of the literature. Important concerns were residual confounding, the possibility of publication bias, the small number of studies, and the heterogeneity of study results.

Conclusions: Pending confirmation from large, ongoing clinical trials, this analysis shows that observational studies are consistent with limited clinical trial data and suggests that chronic hyperglycemia is associated with an increased risk for cardiovascular disease in persons with diabetes.

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Persons with diabetes mellitus are at an increased risk for cardiovascular disease; they have more than a 2-fold increased risk for cardiovascular death compared with persons without diabetes (1–3). Cardiovascular death accounts for more than 75% of all deaths among persons with diabetes mellitus (3, 4). Because this excess risk is only partially explained by traditional risk factors, such as obesity, dyslipidemia, and hypertension, diabetes is often considered an independent risk factor for cardiovascular disease.

A strong body of evidence links chronic hyperglycemia to microvascular complications, such as retinopathy, neuropathy, and nephropathy, in persons with diabetes (5–10). In randomized clinical trials, improving glycemic control substantially reduces the incidence of microvascular disease in persons with diabetes (5, 6, 11). However, few randomized trials have specifically been designed to examine the influence of glycemic control on macrovascular complications, such as coronary heart disease, stroke, and peripheral arterial disease. Results from clinical trials that collected information on cardiovascular outcomes have been equivocal. In interpreting recent clinical trial data in a position statement, the American Diabetes Association stated that “the role of hyperglycemia in cardiovascular complications is still unclear” (12).

Fasting blood glucose levels in diabetic and nondiabetic persons have been linked to an excess risk for cardiovascular disease (13–15); this link suggests an association between glycemic control and cardiovascular risk. A meta-regression analysis that combined data from more than 95 000 persons without diagnosed diabetes found a graded relationship between fasting and postprandial blood glucose levels and subsequent risk for a cardiovascular event (15). An important clinical question is whether improving long-term glycemic control in persons with diabetes reduces the risk for cardiovascular disease events.

Glycosylated hemoglobin reflects long-term glycemic control and is a more accurate and stable measure than fasting blood glucose levels (16). It tracks well over time in persons with diabetes and has less measurement error than fasting blood glucose (17–20). Glycosylated hemoglobin is at the center of the clinical management of hyperglycemia in persons with diabetes. However, clinical guidelines for glycosylated hemoglobin levels are based on cut-points relevant for the prevention of microvascular complications (21). The relationship between glycosylated hemoglobin and cardiovascular disease, the most deadly complication of diabetes mellitus, has not been adequately characterized.

We performed a systematic review to characterize the risk relation between long-term glycemic control, as measured by glycosylated hemoglobin, and cardiovascular end points (peripheral arterial disease, coronary heart disease, and cerebrovascular disease) in persons with type 1 and type 2 diabetes mellitus.
Context
The relationship between glycosylated hemoglobin and cardiovascular disease in diabetic persons is less clear than its relationship with microvascular disease.

Contribution
This meta-analysis of 13 observational studies estimates that, for every 1–percentage point increase in glycosylated hemoglobin, the relative risk for any cardiovascular disease event is 1.18 for patients with type 2 diabetes mellitus and 1.15 for patients with type 1 diabetes mellitus.

Cautions
Although this analysis suggests that improvements in glycosylated hemoglobin level might translate into reductions in cardiovascular events, confirmation from randomized trials is necessary.

METHODS
Study Design
We systematically reviewed prospective cohort studies of glycosylated hemoglobin and cardiovascular disease in persons with diabetes mellitus. This study was part of a larger project commissioned by the Agency for Healthcare Research and Quality, which was conducted by the Johns Hopkins Evidenced-based Practice Center (22).

Study Selection
We searched the MEDLINE database for articles published in English from 1966 to July 2003 by using Medical Subject Heading terms and text words related to cardiovascular disease (coronary heart disease, peripheral arterial disease, or cerebrovascular disease), diabetes mellitus, glycemic control, and glycosylated hemoglobin (the Appendix [available at www.annals.org] contains the full text of the search string). We reviewed all abstracts obtained from our search for relevance. We manually reviewed bibliographies and review articles for additional citations and obtained the full text of all potentially relevant articles. We also queried experts to identify any additional studies.

Our prespecified inclusion criteria were as follows: 1) prospective cohort studies that examined the cardiovascular outcomes of interest (peripheral arterial disease, coronary heart disease, and stroke) and 2) studies that reported a measure of glycosylated hemoglobin and that were conducted in samples that included persons with type 1 or type 2 diabetes. Persons described as having insulin-dependent diabetes mellitus or younger- or juvenile-onset diabetes were classified as having type 1 diabetes. Individuals described as having non–insulin-dependent diabetes mellitus or older-onset diabetes were classified as having type 2 diabetes. We excluded studies if they 1) had no original data, 2) did not address persons with diabetes, 3) involved nonprospective studies (for example, cross-sectional and retrospective case-control studies), 4) had less than 1 year of follow-up, 5) assessed the effect of glycemic control on cardiovascular outcomes after admission to a hospital or after surgery, and 6) involved only patients receiving dialysis or transplants. We excluded 1 additional study (23) in which the outcome was self-reported and the authors did not use standard definitions for classifying cardiovascular outcomes.

When several, sequentially published studies were performed in the same sample, the publication with the longest follow-up was selected for inclusion in our analysis. For multiple studies of the same sample with equivalent follow-up, the most recent publication was selected.

Data Abstraction
Two investigators independently reviewed each article that met the selection criteria and abstracted the data by using standardized data abstraction forms. Discrepancies were resolved by consensus. Data abstracted were age, percentage of male and female study participants, sample size, outcome or outcomes, duration of follow-up, method of measuring glycosylated hemoglobin, main results, statistical methods, number of study participants included in the final analysis, and variables included in the adjusted model or models.

For each prospective cohort study that met our inclusion criteria, we abstracted adjusted effect estimates (odds ratios, relative risks, or relative hazards) for the association between cardiovascular risk (based on incident events during follow-up) and baseline or updated mean glycosylated hemoglobin values. Standard errors for the estimates were abstracted or derived by using data reported in the manuscript.

The cardiovascular disease end points, defined a priori, were fatal and nonfatal coronary heart disease (myocardial infarction, angina, and ischemic heart disease); cerebrovascular disease (fatal and nonfatal stroke); peripheral arterial disease (lower-extremity peripheral arterial disease, amputation, and claudication); and a combined cardiovascular disease outcome that included studies of coronary heart disease and stroke (but not peripheral arterial disease). We conducted separate analyses for each cardiovascular end point and for samples of persons with type 1 and type 2 diabetes. Studies using a combined outcome that included both coronary heart disease and stroke (24–26) were excluded from the pooled effect estimates for stroke alone and coronary heart disease alone but were included in the combined coronary heart disease and stroke subgroup.

Statistical Analysis
We conducted separate meta-analyses of the prospective cohort studies for study samples of persons with type 1 and type 2 diabetes and for the different cardiovascular outcomes. Most studies reported glycosylated hemoglobin as percentage hemoglobin A1c or its equivalent, although some studies (27–32) measured hemoglobin A1c, and 1 study (33) measured total glycosylated hemoglobin. Al-
though the American Diabetes Association advises that all measurements of glycosylated hemoglobin be reported as percentage hemoglobin A1c or its equivalent (16), there are direct linear relationships between glycosylated hemoglobin subfractions (34); therefore, we did not consider the measured subfraction to be an important source of heterogeneity across studies.

For 4 studies (27, 30–32) that reported relative risk estimates for participants in the highest tertile of glycosylated hemoglobin compared with participants in the 2 lowest tertiles, we assumed a normal distribution for glycosylated hemoglobin values and used the reported mean and SD to estimate the 33rd and 83rd percentiles of glycosylated hemoglobin (corresponding to the midpoints of the 2 lowest and the highest tertiles, respectively). Then, we divided the log relative risk by the difference of these 2 values to estimate the effect of a 1-unit change in glycosylated hemoglobin but calculated the 25th and 75th percentiles and divided the log relative risk by the difference of these 2 values. One study (29) did not report relative risks or odds ratios but reported the mean and SD of glycosylated hemoglobin in persons with and without cardiovascular disease events. In this case, we estimated the odds ratio and its 95% CI on the basis of a linear discriminant function model. This model estimates the log odds ratio for a 1-unit change in glycosylated hemoglobin, assuming that the distribution of glycosylated hemoglobin in cases and noncases follows a multivariate normal distribution (35).

We based the meta-analytic comparison on the adjusted summary relative risk estimate from each cohort study. All relative risk estimates included in the pooled analyses were from the most fully adjusted multivariable model. The relative risk estimate from each cohort study was converted to reflect a 1-unit increase in percentage glycosylated hemoglobin (35). Because of substantial qualitative and quantitative heterogeneity across studies, a random-effects model was used to pool the effect estimates

### Table 1. Design Characteristics of Prospective Cohort Studies of Glycosylated Hemoglobin and Cardiovascular Disease*

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Maximum Follow-up Time, y</th>
<th>Sample Size at Baseline, n</th>
<th>Mean Age at Baseline, y</th>
<th>Men, %</th>
<th>Country</th>
<th>Source of Participants</th>
<th>Cardiovascular Disease End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1 diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lehto et al., 1999 (27)</td>
<td>7</td>
<td>177</td>
<td>55</td>
<td>50</td>
<td>Finland</td>
<td>Population registry, East and West Finland</td>
<td>CHD</td>
</tr>
<tr>
<td>Moss et al., 1994 (44)</td>
<td>10</td>
<td>1210</td>
<td>29</td>
<td>51</td>
<td>United States</td>
<td>Primary care (WESDR)</td>
<td>CHD, stroke</td>
</tr>
<tr>
<td>Moss et al., 1999 (33)</td>
<td>14</td>
<td>996</td>
<td>28</td>
<td>50</td>
<td>United States</td>
<td>Primary care (WESDR)</td>
<td>PAD</td>
</tr>
<tr>
<td>Olson et al., 2002 (28)</td>
<td>10</td>
<td>658</td>
<td>27</td>
<td>51</td>
<td>United States</td>
<td>Children’s Hospital (Pittsburgh EDC)</td>
<td>PAD</td>
</tr>
<tr>
<td>Orchard et al., 2003 (29)</td>
<td>10</td>
<td>658</td>
<td>27</td>
<td>51</td>
<td>United States</td>
<td>Children’s Hospital (Pittsburgh EDC)</td>
<td>CHD</td>
</tr>
<tr>
<td><strong>Type 2 diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Adler et al., 2002 (42)</td>
<td>6</td>
<td>3834</td>
<td>60</td>
<td>60</td>
<td>United Kingdom</td>
<td>UKPDS</td>
<td>PAD</td>
</tr>
<tr>
<td>Agewall et al., 1997 (52)</td>
<td>7.7</td>
<td>94</td>
<td>67</td>
<td>100</td>
<td>Sweden</td>
<td>Hypertension intervention trial</td>
<td>CVD</td>
</tr>
<tr>
<td>Florkowski et al., 1998 (24)</td>
<td>6</td>
<td>447</td>
<td>62</td>
<td>47</td>
<td>New Zealand</td>
<td>Christchurch Hospital Diabetes Center</td>
<td>CHD</td>
</tr>
<tr>
<td>Gall et al., 1995 (25)</td>
<td>5</td>
<td>328</td>
<td>54</td>
<td>56</td>
<td>Denmark</td>
<td>Hvidore Hospital</td>
<td>CVD</td>
</tr>
<tr>
<td>Kuusisto et al., 1994 (36)</td>
<td>3.5</td>
<td>229</td>
<td>69</td>
<td>32</td>
<td>Finland</td>
<td>Population registry, East Finland</td>
<td>CHD</td>
</tr>
<tr>
<td>Lehto et al., 1996 (30)</td>
<td>7</td>
<td>1044</td>
<td>58</td>
<td>55</td>
<td>Finland</td>
<td>Population registry, East and West Finland</td>
<td>PAD</td>
</tr>
<tr>
<td>Lehto et al., 1996 (31)</td>
<td>7</td>
<td>1059</td>
<td>58</td>
<td>55</td>
<td>Finland</td>
<td>Population registry, East and West Finland</td>
<td>Stroke</td>
</tr>
<tr>
<td>Lehto et al., 1997 (32)</td>
<td>7</td>
<td>1059</td>
<td>58</td>
<td>55</td>
<td>Finland</td>
<td>Population registry, East and West Finland</td>
<td>CHD</td>
</tr>
<tr>
<td>Mattock et al., 1998 (53)</td>
<td>7</td>
<td>146</td>
<td>59</td>
<td>56</td>
<td>United Kingdom</td>
<td>London diabetes clinic</td>
<td>CHD</td>
</tr>
<tr>
<td>Moss et al., 1994 (44)</td>
<td>10</td>
<td>1780</td>
<td>67</td>
<td>46</td>
<td>United States</td>
<td>Primary care (WESDR)</td>
<td>CHD, stroke</td>
</tr>
<tr>
<td>Moss et al., 1999 (33)</td>
<td>14</td>
<td>1370</td>
<td>64</td>
<td>44</td>
<td>United States</td>
<td>Primary care (WESDR)</td>
<td>PAD</td>
</tr>
<tr>
<td>Roselli della Rovere et al., 2003 (54)</td>
<td>9</td>
<td>120</td>
<td>67</td>
<td>44</td>
<td>Italy</td>
<td>Diabetic outpatient clinic</td>
<td>CVD</td>
</tr>
<tr>
<td>Standl et al., 1996 (26)</td>
<td>10</td>
<td>290</td>
<td>65</td>
<td>36</td>
<td>Germany</td>
<td>Munich General Practitioner Project</td>
<td>CVD</td>
</tr>
<tr>
<td>Stratton et al., 2000 (40)</td>
<td>10</td>
<td>5102</td>
<td>53</td>
<td>60</td>
<td>United Kingdom</td>
<td>UKPDS</td>
<td>CHD, stroke</td>
</tr>
</tbody>
</table>

*CHD = coronary heart disease; CVD = cardiovascular disease; EDC = Epidemiology of Diabetic Complications cohort; PAD = peripheral arterial disease; UKPDS = United Kingdom Prospective Diabetes Study; WESDR = Wisconsin Epidemiologic Study of Diabetic Retinopathy.
We obtained pooled estimates of risk by combining the separate estimates of inverse variance–weighted log risk ratio estimates from each study by using a random-effects model.

We assessed publication bias by using the Begg and Egger tests and funnel plots, which graphically display the magnitude of the effect estimate by the inverse variance of the study. Sensitivity analyses assessed the relative influence of each study in each subgroup analysis by omitting 1 study at a time to assess the influence of any single study on the pooled estimate. All statistical analyses were conducted by using Stata software, version 8.0 (Stata Corp., College Station, Texas) (38).

Role of the Funding Source

The funding source had no role in the design, conduct, or reporting of the study or in the decision to submit the manuscript for publication.

**Data Synthesis**

**Search Results**

Our search identified 694 published articles; we retrieved the full text of 69 and reviewed them to assess whether they provided information on glycosylated hemoglobin and cardiovascular risk. Five studies were prospective reanalyses of data from the United Kingdom Prospective Diabetes Study (UKPDS) and were designed to assess the relationship between glycosylated hemoglobin levels and cardiovascular outcomes after controlling for other relevant variables (39–43). We included only the most recently published manuscripts on coronary heart disease, stroke, and peripheral arterial disease outcomes in the UKPDS (40, 42). We identified multiple studies from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (4, 33, 44–46) and the Pittsburgh Epidemiology of Diabetic Complications (28, 29, 47, 48) cohorts; in our analysis, we included only the most recent manuscripts reporting the longest follow-up (28, 29, 33, 44). Four studies of glucose control and heart disease used the same data from Kupio County, eastern Finland (36, 49–51). In 3 of these (49–51), hemoglobin A1c levels measured only at the 5- or 10-year intervals were considered in the analyses; however, all incident events over the 10- or 15-year intervals of follow-up were assessed, indicating that some events may have occurred before measurement of hemoglobin A1c. These 3 studies cannot truly be considered “prospective,” and temporality of the association is uncertain. Thus, we excluded these 3 studies from this review. Only 1 prospective analysis of data from this population, which had 3.5 years of follow-up, was included (36).

After we applied all exclusion and inclusion criteria, 17
**Figure 2.** Relative risk (RR) estimates and 95% CIs for glycosylated hemoglobin (per 1–percentage point increase) and incident cardiovascular disease in persons with type 2 diabetes.

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Events/Patients, n/n*</th>
<th>RR (95% CI)</th>
<th>Covariates in Multivariable Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular disease (coronary heart disease + stroke)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roselli della Rovere et al., 2003 (54)</td>
<td>22/113</td>
<td>2.56 (1.10–5.98)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Florkowski et al., 1998 (24)</td>
<td>92/422</td>
<td>1.43 (1.02–2.00)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Agewalt et al., 1997 (52)</td>
<td>21/94</td>
<td>1.54 (1.14–2.09)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Kuusiisto et al., 1994 (36)</td>
<td>33/229</td>
<td>1.29 (0.98–1.70)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Mattock et al., 1998 (53)</td>
<td>20/138</td>
<td>1.25 (1.01–1.55)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Gall et al., 1995 (25)</td>
<td>29/321</td>
<td>1.30 (1.10–1.60)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Standl et al., 1996 (26)</td>
<td>58/223</td>
<td>1.18 (1.02–1.35)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Lehto et al., 1997 (32)</td>
<td>256/1059</td>
<td>1.03 (0.96–1.15)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Stratton et al., 2000 (40)</td>
<td>606/3642</td>
<td>1.16 (1.09–1.27)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Moss et al., 1994 (44)</td>
<td>241/1194</td>
<td>1.10 (1.04–1.17)</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Pooled</td>
<td>1376/7435</td>
<td>1.18 (1.10–1.26)</td>
<td>X X X X X X</td>
</tr>
</tbody>
</table>

| **Coronary heart disease (fatal and nonfatal)** | | | |
| Florkowski et al., 1998 (24) | 92/422 | 1.43 (1.02–2.00) | X X X X X X |
| Kuusiisto et al., 1994 (36) | 33/229 | 1.29 (0.98–1.70) | X X X X X X |
| Mattock et al., 1998 (53) | 20/138 | 1.25 (1.01–1.55) | X X X X X X |
| Lehto et al., 1997 (32) | 256/1059 | 1.03 (0.96–1.15) | X X X X X X |
| Stratton et al., 2000 (40) | 606/3642 | 1.16 (1.09–1.27) | X X X X X X |
| Moss et al., 1994 (44) | 241/1194 | 1.10 (1.04–1.17) | X X X X X X |
| Pooled | 1248/6684 | 1.13 (1.06–1.20) | X X X X X X |

| **Fatal coronary heart disease** | | | |
| Kuusiisto et al., 1994 (36) | 15/229 | 1.62 (1.03–2.54) | X X X X X X |
| Florkowski et al., 1998 (24) | 92/422 | 1.43 (1.03–2.00) | X X X X X X |
| Mattock et al., 1998 (53) | 20/138 | 1.25 (1.01–1.55) | X X X X X X |
| Lehto et al., 1997 (32) | 158/1059 | 1.12 (1.00–1.25) | X X X X X X |
| Moss et al., 1994 (44) | 241/1194 | 1.10 (1.04–1.17) | X X X X X X |
| Pooled | 526/3042 | 1.16 (1.07–1.26) | X X X X X X |

| **Stroke** | | | |
| Lehto et al., 1996 (31) | 125/1059 | 1.17 (1.03–1.34) | X X |
| Stratton et al., 2000 (40) | 212/3642 | 1.14 (1.01–1.28) | X X X X X X |
| Moss et al., 1994 (44) | 59/1261 | 1.17 (1.05–1.30) | X X X X X X |
| Pooled | 396/5962 | 1.17 (1.09–1.25) | X X X X X X |

Boxes are the relative risk estimates from each study; the horizontal bars are 95% CIs. The size of the box is proportional to the weight of the study in the pooled analysis. The studies are sorted by weight in the plot. Diamonds represent pooled random-effect estimates (per 1–percentage point higher glycosylated hemoglobin level). The vertical line at 1.0 indicates no effect of glycosylated hemoglobin on cardiovascular risk. The table on the right side of the graph indicates whether the study relative risk estimate was adjusted for relevant covariates. BMI = body mass index; DM = diabetes mellitus; WHR = waist-to-hip ratio. *Sample size of final multivariable analysis may differ from the sample size at baseline reported in Table 1. †Represents any measure of glycemic control, other than glycosylated hemoglobin, that was simultaneously included in the multivariable model (fasting blood glucose level or random blood glucose level).
reports that presented results of prospective cohort studies were included in this review. The prospective cohort studies represented 13 unique study samples (10 groups of type 2 diabetic persons and 3 groups of type 1 diabetic persons).

Qualitative Summary

Table 1 summarizes the characteristics of all studies included in our analysis. The studies were geographically heterogeneous. Study samples were from the United States, United Kingdom, Italy, New Zealand, Sweden, Germany, Finland, and Denmark. Sample sizes ranged from fewer than 100 participants to more than 5000 in the largest study. Most studies had primary care or clinic-based patient populations. All studies described basic inclusion and exclusion criteria for study participants.

The method of measurement of glycosylated hemoglobin varied across studies. Most studies used high-performance liquid chromatography (28, 29, 36, 40, 42). Lehto and colleagues (27, 30–32) used affinity chromatography. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (33, 44) used a microcolumn technique; 1 study (24) used an automated furfural method; 1 study (25) used a thin isoelectric focusing method; and 1 study (53) used electroendosmosis. Two studies did not specify the method used to measure glycosylated hemoglobin (26, 52).

Table 2. Comparison of the Relative Risk Estimates and 95% CIs for Glycosylated Hemoglobin (per 0.9–Percentage Point Decrease) in the United Kingdom Prospective Diabetes Study Trial Results and the Meta-Analysis of Prospective Cohort Studies*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS Trial Results†</td>
<td>Meta-Analysis Pooled Estimate Including UKPDS Observational Studies</td>
</tr>
<tr>
<td>Coronary heart disease and myocardial infarction (fatal and nonfatal)</td>
<td>0.84 (0.71–1.00)</td>
</tr>
<tr>
<td>Fatal coronary heart disease and myocardial infarction</td>
<td>0.94 (0.68–1.30)</td>
</tr>
<tr>
<td>Stroke (fatal and nonfatal)</td>
<td>1.11 (0.81–1.51)</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>0.65 (0.36–1.18)</td>
</tr>
</tbody>
</table>

* UKPDS = United Kingdom Prospective Diabetes Study.
† Primary results from the UKPDS trial (expressed per 0.9–percentage point decrease in glycosylated hemoglobin, the difference observed in the intensive vs. conventionally treated groups) were abstracted directly from Figure 4 in the UKPDS 33 (5).
‡ Pooled estimates excluded the prospective reanalyses of UKPDS observational data (40, 42).
§ Stratton and colleagues (40) did not report a separate relative risk estimate for fatal coronary heart disease alone. Thus, this pooled estimate is the same as the pooled estimate for fatal coronary heart disease and myocardial infarction, including the UKPDS observational data.
Most studies used standard definitions, such as World Health Organization criteria or International Classification of Diseases, Ninth Revision, codes to define the cardiovascular outcome. For outcome assessment, they used standard methods, such as reviews of medical records or death certificates. Most studies modeled the effect of baseline glycated hemoglobin measurements on the risk for incident cardiovascular disease events; however, 1 study (40), a reanalysis of data from the UKPDS trial, used updated mean hemoglobin A1c levels and modeled hemoglobin A1c as a time-dependent variable in the multivariable models.

The extent of adjustment for potential confounding factors in the relationship between cardiovascular disease and glycated hemoglobin varied considerably across studies (Figures 1 to 3). Approximately half of the studies (25, 26, 28, 29, 33, 44, 53, 54) used automatic (stepwise) selection methods to determine covariates for the multivariable models. Only 3 studies (24, 27, 40) simultaneously adjusted for known risk factors for cardiovascular disease, including age, sex, lipids, blood pressure, and smoking status.

Quantitative Summary

Type 1 Diabetes

Figure 1 presents results for all analyses of persons with type 1 diabetes. The pooled relative risk for the 3 prospective studies of glycated hemoglobin and coronary heart disease in persons with type 1 diabetes was 1.15 (95% CI, 0.92 to 1.43) for each 1–percentage point increase in glycated hemoglobin. For the 2 studies of glycated hemoglobin and incident peripheral arterial disease in persons with type 1 diabetes, the pooled relative risk was 1.32 (CI, 1.19 to 1.45). No studies estimated the risk for stroke by level of glycated hemoglobin in persons with type 1 diabetes.

Type 2 Diabetes

Figure 2 summarizes the results of all analyses of persons with type 2 diabetes. The pooled relative risk for total cardiovascular disease in persons with type 2 diabetes (combining 10 independent studies of coronary heart disease alone, stroke alone, and stroke and coronary heart disease combined) was 1.18 (CI, 1.10 to 1.26) for each 1–percentage point increase in glycated hemoglobin. The pooled relative risk of the 5 independent studies that examined glycated hemoglobin and the risk for coronary heart disease in persons with type 2 diabetes was 1.13 (CI, 1.06 to 1.20) for each 1–percentage point increase in glycated hemoglobin. The pooled relative risk combining 5 studies of fatal coronary heart disease was 1.16 (CI, 1.07 to 1.26). Only 3 independent studies examined glycated hemoglobin and risk for stroke in persons with type 2 diabetes; the pooled relative risk for these 3 studies was 1.17 (CI, 1.09 to 1.25). The pooled relative risk for the 3 studies of glycated hemoglobin and peripheral arterial disease in persons with type 2 diabetes was 1.28 (CI, 1.18 to 1.39).

Sensitivity analyses indicated that all of the studies included in the pooled estimates seemed to contribute relatively equally to the estimate (no single study had substantial influence). Some evidence of publication bias was seen in these cohort studies. The larger, more precise studies tended to show smaller relative risk estimates (Figures 1 to 3). Both the Begg and the Egger tests were significant (P < 0.05) for the largest subgroup analysis (coronary heart disease and stroke combined). The small number of independent studies, however, limits our ability to draw conclusions regarding publication bias.

We also observed significant heterogeneity among the studies of cardiovascular disease in persons with type 2 diabetes. To evaluate potential sources of heterogeneity, we conducted subgroup analyses that compared the relative risk estimates for studies including an additional measure of glycemic control in the multivariable model with those that did not (relative risk, 1.37 vs. 1.15; P > 0.2); studies that simultaneously adjusted for age, sex, blood pressure, and lipids with those that did not (relative risk, 1.19 vs. 1.20; P > 0.2); and studies that used step-wise regression with those that did not (relative risk, 1.19 vs 1.19; P > 0.2). No significant differences were observed; however, the small number of studies limited our ability to identify important sources of heterogeneity.

DISCUSSION

These data support a moderate increase in cardiovascular risk with increasing levels of glycated hemoglobin in persons with diabetes mellitus. This association seems to be similar in persons with type 1 and type 2 diabetes and is present across diverse geographic populations. In some studies, this association seems to be independent of other known risk factors for cardiovascular disease. The magnitude of the effect for total cardiovascular disease, fatal and nonfatal coronary heart disease, and stroke was similar. Compared with coronary heart disease and stroke, the pooled results of the few studies on glycated hemoglobin and peripheral arterial disease in persons with type 1 and type 2 diabetes suggest the possibility of a stronger association between glycated hemoglobin levels and this outcome (pooled risk estimates were 1.32 and 1.28 in persons with type 1 and type 2 diabetes, respectively). However, all pooled relative risk estimates reported here are based on small numbers of studies.

The UKPDS (5) was the only large trial specifically designed to address the hypothesis that glucose-lowering therapies may reduce the risk for cardiovascular morbidity or death in persons with type 2 diabetes. For cardiovascular outcomes, this trial is largely considered negative by the medical community. However, results from the UKPDS and other smaller trials are consistent with moderate reductions in cardiovascular risk and improvements in glycemic
control. Table 2 compares the results of the UKPDS trial with those of our meta-analysis by converting our pooled results to reflect a 0.9-unit decrease in percentage glycosylated hemoglobin (the difference between the intensively treated and conventionally treated groups in the UKPDS trial). Table 2 reveals that while the UKPDS results are not strictly statistically significant at the usual 0.05 level, they are generally consistent with a moderate decrease in cardiovascular risk, except for stroke. This table includes a column that reports our pooled meta-analysis estimates after exclusion of prospective observational reanalyses of UKPDS data (40, 42). Excluding the reanalyses from the pooled estimates did not appreciably alter the results.

A previous meta-analysis (55) of glucose-lowering therapies in persons with type 2 diabetes compared risk for cardiovascular death in intensively treated groups with risk in control groups. A fixed-effects model was used for the comparison, which included the UKPDS and 4 of the other largest trials (those with >100 patients) of glucose-lowering therapies. The meta-analysis reported a nonsignificant pooled incidence rate ratio for cardiovascular mortality of 0.89 (CI, 0.74 to 1.08). However, this null result is not surprising given that this analysis combined trials that showed nonsignificant but protective effects of glycemic control (5, 11, 56, 57) with a trial (the Veterans Affairs Diabetes Feasibility Trial) that showed an increased risk for cardiovascular events in the intensively treated group (58). In the Veterans Affairs Feasibility Trial, which was a pilot study for a larger, ongoing trial, cardiovascular morbidity or mortality did not differ significantly between the 2 treatment groups; however, patients with lower hemoglobin A1c levels had an increase in cardiovascular events. The authors advised that “this finding should be interpreted with great caution” because of the short follow-up and small number of events.

Several plausible biological mechanisms have been proposed to explain a possible direct relationship between chronically elevated blood glucose levels and coronary heart disease (59). Glucose can react with many different proteins, causing structural alterations and subsequently impaired protein and tissue function. Such alterations, including the formation of advanced glycation end products, may contribute to long-term complications in diabetes as well as to endothelial dysfunction, changes in arterial distensibility, plaque formation, and atherosclerosis (60–64). The hypothesized physiologic processes by which hyperglycemia contributes to cardiovascular disease are probably gradual and cumulative, occurring during decades of exposure to chronically elevated blood glucose levels. This possibility suggests that most previous studies, including clinical trials, may have had insufficient follow-up to detect a moderate (approximate 10% to 20%) increase in risk. In addition, the glucose-lowering drugs used in trials may actually have adverse cardiovascular effects, which would attenuate macrovascular benefits of improved glycemic control (65).

Our meta-analysis expands on previous nonsystematic reviews of the literature on cardiovascular disease and glycosylated hemoglobin (66–68) and on reviews that have focused on fasting and postprandial blood glucose levels (69, 70) or populations of nondiabetic persons (15). Of note, a recent study in persons with type 1 diabetes showed that intensive glucose-lowering slows the progression of atherosclerosis (71). Four prospective epidemiologic studies in persons without diagnosed diabetes also provide evidence that the association between glycosylated hemoglobin and risk for cardiovascular disease risk may extend below the diagnostic threshold for diabetes (72–75).

Our systematic review highlights important weaknesses in the literature. Several of the studies (24, 32, 44, 52) included random or fasting blood glucose levels and the use of diabetic medications in the model with glycosylated hemoglobin; this might be considered “over-adjustment” and probably underestimates the “true” effect of glycemic control (as measured by glycosylated hemoglobin) on the risk for cardiovascular disease. It is also unclear to what extent certain biases and methodologic limitations, such as residual confounding and selection bias, might exist in these studies. Many of the studies included in our analysis used automatic or semi-automatic selection strategies, such as step-wise regression, to select the covariates included in the multivariable analyses. Such selection methods rely on arbitrary statistical cut-points for model building, rather than on clinical or pathophysiologic reasoning. These methods are known to result in biased estimates of effect and P values (76, 77). Our analysis also reveals the paucity of independent, methodologically rigorous studies that examine the effect of glycosylated hemoglobin on cardiovascular outcomes, particularly in persons with type 1 diabetes.

Our analysis has several limitations. We may not have identified all of the relevant literature on this topic. However, our process of literature identification was comprehensive, capturing many of the published studies on the relation between glycosylated hemoglobin and incident cardiovascular disease events in persons with type 1 and type 2 diabetes. We also cannot exclude the possibility that the observed association is a result of publication bias. There was evidence that smaller studies with more positive results may be more likely to be published. In addition, our analyses assumed a linear increase in glycosylated hemoglobin with cardiovascular risk. Whether this is correct is unclear. We also observed substantial qualitative and quantitative heterogeneity across the studies, but we could not thoroughly explore possible sources of this variability because of the severe constraints of sample size.

To date, randomized, controlled trials have not answered one of the most important questions in diabetes treatment: What is the relationship of glycemic control to cardiovascular risk? Our meta-analysis suggests that hyperglycemia is associated with an increased risk for cardiovascular disease in persons with diabetes. One advantage of
pooling data from prospective cohort studies to investigate this important clinical issue is better generalizability because this analysis combines data from heterogeneous populations. The lengthy follow-up and comprehensive surveillance in many of the cohorts and the large number of events also afforded us power to detect relatively modest increases in risk.

PENDING confirmation from large, ongoing clinical trials, our findings suggest that improvements in glycemic control may lower the risk for cardiovascular disease in persons with diabetes. Because cardiovascular disease is the most common cause of death in persons with diabetes mellitus, additional studies are needed to decipher the independent effect of glycated hemoglobin in predicting cardiovascular disease outcomes in persons with diabetes.

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APPENDIX: SEARCH STRING


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