Type 2 Diabetes Mellitus and Risk of Incident Atrial Fibrillation in Women

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Objectives

The purpose of this study was to assess whether changes of major atrial fibrillation (AF) risk factors and/or intercurrent cardiovascular events could explain the relationship between type 2 diabetes mellitus (T2D) and incident AF.

Background

Previous studies found an increased risk of incident AF among individuals with T2D, but few, if any, of these studies took into account changes of AF risk factors over time.

Methods

A total of 34,720 female health professionals who participated in the Women’s Health Study, and who were free of cardiovascular disease and AF at baseline were followed for a median of 16.4 years. Cox proportional-hazards models were constructed to assess the relationship between T2D and incident AF, using either information at baseline or time-varying covariates for both T2D and potential confounders.

Results

At baseline, 937 (2.7 %) women had T2D. Compared with women without T2D, women with T2D had an age-adjusted hazard ratio (HR) for new-onset AF of 1.95 (95% confidence interval [CI]: 1.49 to 2.56; p < 0.0001). In multivariable analyses adjusting for baseline confounders, this HR was substantially attenuated, but baseline T2D remained a significant predictor of incident AF (HR: 1.37; 95% CI: 1.03 to 1.83; p = 0.03). In time-updated models that adjusted for changes in AF risk factors and intercurrent cardiovascular events, the HR for T2D was attenuated further and became nonsignificant (HR: 1.14; 95% CI: 0.93 to 1.40; p = 0.20).

Conclusions

Although this study confirms a significant relationship between baseline T2D and incident AF, our data suggest that the increased risk associated with T2D is mainly mediated by changes of other AF risk factors. (J Am Coll Cardiol 2012;60:1421–8) © 2012 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population (1), and its prevalence is projected to increase substantially over the next decades (2). Individuals with AF have an increased risk of major complications, including death, stroke, and congestive heart failure, even after adjustment for relevant comorbidities (3–8), such that defining and treating risk factors for AF occurrence is a major public health priority.

Several prospective studies evaluated the relationship between type 2 diabetes (T2D) and incident AF, and discrepant findings were reported (9–15). A recent meta-analysis found a modest, but statistically significant increased risk of new-onset AF among individuals with T2D (summary relative risk: 1.34 [95% confidence interval (CI): 1.07 to 1.68]) (16). However, significant between-study heterogeneity was observed, part of which might be explained by the fact that studies with more extensive multivariable adjustment were associated with smaller relative risk estimates than studies with less extensive adjustments (p for heterogeneity = 0.053) (16).

Given the close relationship of T2D with obesity and hypertension (17), which are 2 of the strongest risk factors for new-onset AF (15,18–20), adequate adjustment in the evaluation of the association between T2D and AF is a relevant issue. The observed association between baseline T2D and AF may be due to differential changes of these risk factors in diabetic compared with nondiabetic subjects, because of the increased risk of weight gain and hypertension among patients with established T2D (21–23).

Few if any studies on the association between T2D and AF have taken into account changes of risk factors over time after the development of T2D (9–15,24,25). Because detailed

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knowledge of these relationships is important to optimize measures for AF disease prevention in the population, the primary aim of this study was to prospectively examine whether changes of major AF risk factors over time and intercurrent cardiovascular events may explain the previously observed association between T2D and AF.

Methods

Study participants. All study subjects participated in the WHS (Women's Health Study), a completed randomized trial among 39,876 women evaluating benefits and risks of low-dose aspirin (100 mg every other day) and vitamin E (600 IU every other day) in the primary prevention of cardiovascular disease and cancer, using a randomized, double-blind, placebo-controlled study design. Details about the conduct of the study have been previously published (26–28).

Participants were female health professionals in the United States, age ≥45 years and free of cardiovascular disease, cancer, or other major illnesses at study entry. Randomized treatment ended on March 31, 2004, and all women were invited to participate in continued observational follow-up, which for the present analysis was truncated on March 2, 2011. Of the original cohort, we excluded 897 women (2.2%) with a history of AF at baseline and 54 (0.1%) women with a confirmed cardiovascular event (stroke, heart failure, or myocardial infarction) before study entry. In addition, 4,205 (10.5%) women did not participate in the observational follow-up, leaving 34,720 participants for the present analysis. The study was approved by the institutional review board of Brigham and Women’s Hospital, Boston, and was monitored by an external data and safety monitoring board.

Study variables. Mailed questionnaires were used to collect information on baseline characteristics. To obtain information on study outcomes, changes in covariates, and other information, follow-up questionnaires were sent to all participants every 6 months during the first year and every 12 months thereafter. Covariates of interest included age, hypertension, body mass index (BMI) (weight in kilograms divided by height in meters squared), hypercholesterolemia, physical exercise, self-reported race/ethnicity, highest education level, smoking, and alcohol consumption.

Ascertainment of incident type 2 diabetes. Details regarding the ascertainment of incident T2D in the WHS have been previously reported (29). Briefly, participants were asked annually whether and when they had been diagnosed with diabetes since baseline. Confirmation of T2D was conducted using American Diabetes Association diagnostic criteria (30). Self-reported cases were investigated by either telephone interview conducted by a physician or a self-administered supplemental questionnaire that inquired about symptoms, diagnostic testing, and use of diabetes medications. In a validation study (31), the self-administered questionnaire proved highly accurate for confirmation of clinical diabetes compared with medical record review. Thus, since 1999, confirmation of T2D has relied upon supplemental questionnaires. Overall, in 95% of all post-randomization self-reported diabetes, sufficient information for confirmation or disconfirmation of the endpoint was obtained. In addition, among women with available baseline levels of hemoglobin A1c (HbA1c) and without a baseline diagnosis of T2D, the prevalence of HbA1c >6.5% was only 0.5%. Only confirmed cases of incident T2D were included in this study.

Ascertainment of incident atrial fibrillation. Details about AF endpoint confirmation have been previously published (18,32). Briefly, participating women were asked about incident AF diagnoses at baseline, after 48 months, and annually thereafter. Women who participated in the continued observational follow-up who indicated the occurrence of an incident AF event on ≥1 yearly questionnaires were sent a supplemental questionnaire to collect additional information and to obtain written informed consent for medical record review. For all deceased participants who reported AF during the trial and extended follow-up period, family members were contacted to obtain consent and additional relevant information. An endpoint committee of cardiovascular physicians reviewed medical records for reported events according to predefined criteria. An AF event was confirmed if there was electrocardiographic evidence of AF or if a medical report clearly indicated a personal history of AF. Only confirmed AF events were included in the present study.

Ascertainment of incident cardiovascular events. Collection of cardiovascular endpoints occurred through questionnaires, letters, and phone calls, as described previously (8,26). A blinded endpoint committee of physicians adjudicated all events according to predefined criteria (26). Information on stroke and myocardial infarction was collected from the beginning of the study. Incident diagnoses of congestive heart failure were reported for the first time at the 48-month questionnaire. Heart failure was confirmed if participants met either the Framingham Heart Study (33) or the Cardiovascular Health Study (34) criteria for the presence of heart failure, and both definite and probable cases were included in the analysis.

Measurement of HbA1c levels. Blood samples at study entry were obtained from 28,345 women. Levels of HbA1c were estimated using the Tina-Quant turbidimetric inhibition immunoassay on a Hitachi 911 (Roche Diagnostics, Indianapolis, Indiana) autoanalyzer using packed red blood cells (35). The assay is specific for HbA1c, standardized against the approved International Federation of Clinical Chemists reference method, and traceable to the Diabetes Control and Complications Trial by use of a conversion factor. Values of HbA1c presented in this study are Diabetes
Control and Complications Trial aligned. The coefficient of variation for HbA1c computed from blinded simultaneously analyzed quality controls was 7.2%.

Statistical analysis. Wilcoxon rank-sum tests for continuous variables and chi-square tests for categorical variables were used to compare baseline characteristics of women with and without T2D at study entry. Person-years of follow-up were calculated from the date of return of the baseline questionnaire to the first occurrence of new-onset AF, death, loss to follow-up, or March 2, 2011.

Cox proportional hazards models were constructed to calculate hazard ratios (HRs) and 95% CIs for incident AF and to adjust for potential confounders. Age-adjusted models were further adjusted for adult height, smoking, exercise, alcohol consumption, education, race/ethnicity, and hypercholesterolemia. Because of the close relationship among BMI, hypertension, and T2D (17), these variables were added in separate steps to the multivariable models.

To evaluate the influence of covariate changes over time, we then constructed multivariable Cox models where T2D and all other covariates were updated during follow-up whenever follow-up values were available. We adjusted these multivariable models according to the same previously described pre-specified order, but added a final step where we additionally adjusted for intercurrent cardiovascular events, defined as stroke, myocardial infarction, or congestive heart failure. Finally, to assess the potential bidirectional nature of the relationship between T2D, hypertension, and BMI, we constructed a similar series of multivariable Cox models for BMI and hypertension, where T2D was added as a covariate in a separate step.

To gain further insights on the role of glucose homeostasis in AF development, we assessed the relationship between approximate quartiles of HbA1c levels and incident AF in age- and multivariable-adjusted Cox models among women with available HbA1c levels at baseline. Tests for linear trend were performed by assigning all women the quartile-specific median HbA1c value. To evaluate the effect of elevated HbA1c values, we repeated the same analyses after dichotomizing HbA1c levels at the 95th percentile. Finally, we also specifically assessed the association between HbA1c and incident AF among women with baseline T2D.

Categorical variables were entered into the Cox models using binary indicator variables. Multiplicative interaction terms between T2D and several baseline characteristics were evaluated in the fully adjusted baseline models using likelihood ratio tests. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina). A 2-tailed p value <0.05 was pre-specified to indicate statistical significance.

Results

Baseline characteristics. Baseline characteristics stratified by the presence or absence of T2D are presented in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Baseline T2D (N = 34,720)</th>
<th>Baseline T2D (n = 937)</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>52.8 (48.9–58.7)</td>
<td>55.5 (50.0–62.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.9 (22.5–28.3)</td>
<td>30.0 (26.3–34.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Adult height, cm</td>
<td>165 (160–168)</td>
<td>165 (160–170)</td>
<td>0.23</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>8,586 (25.4%)</td>
<td>589 (62.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of hypercholesterolemia</td>
<td>10,041 (29.7%)</td>
<td>443 (47.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>4,179 (12.4%)</td>
<td>127 (13.6%)</td>
<td>0.49</td>
</tr>
<tr>
<td>Past</td>
<td>12,139 (35.9%)</td>
<td>343 (36.6%)</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>17,439 (51.6%)</td>
<td>467 (49.8%)</td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely/never</td>
<td>14,706 (43.5%)</td>
<td>655 (69.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1–3 drinks/month</td>
<td>4,463 (13.2%)</td>
<td>122 (13.0%)</td>
<td></td>
</tr>
<tr>
<td>3–6 drinks/week</td>
<td>11,052 (32.7%)</td>
<td>124 (13.2%)</td>
<td></td>
</tr>
<tr>
<td>1+ drinks/day</td>
<td>3,552 (10.5%)</td>
<td>36 (3.8%)</td>
<td></td>
</tr>
<tr>
<td>Highest education level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than a bachelor’s degree</td>
<td>18,438 (54.6%)</td>
<td>599 (63.9%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bachelor’s degree</td>
<td>7,900 (23.4%)</td>
<td>190 (20.3%)</td>
<td></td>
</tr>
<tr>
<td>Master’s degree or doctorate</td>
<td>6,876 (20.4%)</td>
<td>127 (13.6%)</td>
<td></td>
</tr>
<tr>
<td>Exercise, times/wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rarely/never</td>
<td>12,646 (37.4%)</td>
<td>446 (47.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>&lt; 1</td>
<td>6,693 (19.8%)</td>
<td>187 (20.0%)</td>
<td></td>
</tr>
<tr>
<td>1–3</td>
<td>10,734 (31.8%)</td>
<td>229 (24.4%)</td>
<td></td>
</tr>
<tr>
<td>≥ 4</td>
<td>3,695 (10.9%)</td>
<td>75 (8.0%)</td>
<td></td>
</tr>
</tbody>
</table>

Values are median (interquartile ranges) or counts (percentages). Number of observations across categories may not sum to the given number because of missing data. *Based on Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables.

T2D = type 2 diabetes.
At study entry, 937 women (2.7%) had T2D. Women with T2D were significantly older, had a higher BMI, a higher prevalence of hypertension, a lower educational level, and exercised less frequently compared with women without T2D (all p < 0.0001).

**Baseline T2D and new-onset AF.** During a median follow-up of 16.4 years (interquartile range: 15.6 to 16.8 years), 1,079 (3.1%) women developed incident AF. The age-adjusted incidence rate for new-onset AF was 3.97 and 1.99 per 1,000 person-years of follow-up among women with and without baseline T2D, respectively (Table 2, upper section). Accordingly, in Cox proportional-hazards models, the age-adjusted HR for women with baseline T2D was 1.95 (95% CI: 1.49 to 2.56; p < 0.0001). Multivariable adjustment for established cardiovascular risk factors, but not BMI and hypertension, had little effect on this risk estimate (HR: 1.87; 95% CI: 1.41 to 2.47; p < 0.0001). Although additional adjustment for hypertension and BMI substantially attenuated this relationship, a significant effect of baseline T2D persisted in the fully adjusted model (HR: 1.95; 95% CI: 1.49 to 2.56; p = 0.03). BMI and hypertension were strongly associated with incident AF in all models and the effect of adding T2D to these models was small (Online Tables 1 and 2).

**Models with time-updated covariates.** Among women without T2D at baseline, 2,730 (7.9%) developed new-onset T2D during follow-up. Sixty-eight (2.5%) of these women had a subsequent diagnosis of new-onset AF, which corresponded to an age-adjusted incidence rate of 3.62 events per 1,000 person-years among women with new-onset T2D, as shown in Table 2. In multivariable models that did not adjust for hypertension and BMI, T2D was significantly associated with incident AF (HR: 1.58; 95% CI: 1.30 to 1.93; p < 0.0001) (Table 2, lower section). When BMI and hypertension were added to this model, the association between T2D and new-onset AF was weakened and no longer statistically significant (HR: 1.19; 95% CI: 0.97 to 1.45; p = 0.10).

Among women with T2D, significantly more AF events were preceded by a cardiovascular event compared with women without T2D (16 of 124 [12.9%] vs. 39 of 955 [4.1%]; p < 0.001). After additional adjustment for these intercurrent events, the multivariable adjusted relative risk was further attenuated (HR: 1.14; 95% CI: 0.93 to 1.40; p = 0.20), as shown in Table 2. Again, BMI and hypertension were strongly associated with incident AF in all models and adding T2D only minimally altered these results (Online Tables 1 and 2).

**Subgroup analyses.** Subgroup analyses are displayed in Table 3. The relationship between baseline T2D and incident AF was stronger among women age <65 years (HR: 1.54; 95% CI: 1.13 to 2.11) than among women age ≥65 years (HR: 0.85; 95% CI: 0.42 to 1.74) (p for interaction = 0.01). Again, in women age <65 years, the effect of T2D on incident AF was attenuated in fully adjusted time-updated Cox models (HR: 1.24; 95% CI 0.99 to 1.63).

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**Table 2 Risk of Incident AF According to the Presence or Absence of T2D**

<table>
<thead>
<tr>
<th>Models With Baseline Characteristics Only</th>
<th>No T2D at Baseline (n = 33,783)</th>
<th>T2D at Baseline (n = 937)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events/person-years</td>
<td>1,023/528,106</td>
<td>56/13,192</td>
<td>—</td>
</tr>
<tr>
<td>Age-adjusted incidence rate</td>
<td>1.99</td>
<td>3.97</td>
<td>—</td>
</tr>
<tr>
<td>Age-adjusted model</td>
<td>Referent</td>
<td>1.95 (1.49–2.56)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable-adjusted model†‡</td>
<td>Referent</td>
<td>1.87 (1.41–2.47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>Referent</td>
<td>1.62 (1.22–2.14)</td>
<td>0.0008</td>
</tr>
<tr>
<td>BMI‡</td>
<td>Referent</td>
<td>1.47 (1.11–1.96)</td>
<td>0.008</td>
</tr>
<tr>
<td>Hypertension and BMI‡</td>
<td>Referent</td>
<td>1.37 (1.03–1.83)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Models Using Time–Updated Covariates</th>
<th>Never T2D (n = 31,053)</th>
<th>Baseline or Incident T2D (n = 3,667)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events/person-years</td>
<td>955/507,851</td>
<td>124/33,448</td>
<td>—</td>
</tr>
<tr>
<td>Age-adjusted incidence rate</td>
<td>1.98</td>
<td>Baseline T2D: 3.97</td>
<td>Incident T2D: 3.62</td>
</tr>
<tr>
<td>Age-adjusted model</td>
<td>Referent</td>
<td>1.63 (1.35–1.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Multivariable-adjusted model†‡</td>
<td>Referent</td>
<td>1.58 (1.30–1.93)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension†</td>
<td>Referent</td>
<td>1.42 (1.16–1.73)</td>
<td>0.0005</td>
</tr>
<tr>
<td>BMI‡</td>
<td>Referent</td>
<td>1.24 (1.01–1.53)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hypertension and BMI‡</td>
<td>Referent</td>
<td>1.19 (0.97–1.45)</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypertension, BMI, and intercurrent cardiovascular events‡</td>
<td>Referent</td>
<td>1.14 (0.93–1.40)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Values are counts, rates per 1,000 person-years of follow-up, or hazard ratios (95% confidence intervals) as appropriate. †Adjusted for age, smoking, exercise, alcohol consumption, education, race/ethnicity, hypercholesterolemia, and adult height. ‡These models were based on 1,040 events in 33,757 women because of missing data. These models were based on 1,027 events in 33,372 women because of missing data. 

BMI = body mass index; other abbreviations as in Table 1.
to 1.55). Consistent findings with nonsignificant interaction tests were obtained for all other subgroups assessed.

**HbA1c levels and new-onset AF.** Among 28,345 women with available blood samples at baseline, 25,290 were eligible for the present analysis, of whom 24,890 (98%) had a valid HbA1c measurement. In this subcohort, 835 confirmed incident AF events occurred. HbA1c at study entry was not significantly associated with incident AF. The age- and multivariable-adjusted models for quartiles of HbA1c are shown in Table 4, and the p values for linear trend across quartiles were nonsignificant. When extreme levels above the 95th percentile (i.e., >5.6%) were examined, the age-adjusted association was significant (HR: 1.53; 95% CI: 1.20 to 1.96), but was highly attenuated and became nonsignificant after multivariable adjustment (HR: 1.13; 95% CI: 0.87 to 1.48). Finally, stratifying women by the presence or absence of T2D at baseline provided similar results. Among the 647 women with T2D at baseline, the multivariable HR for each 1% increase in HbA1c was 1.09 (95% CI: 0.93 to 1.27). The corresponding HR among the nondiabetic women was 0.87 (95% CI: 0.71 to 1.07).

**Discussion**
In this large, prospective cohort of initially healthy middle-aged women, baseline T2D was a modest, but statistically significant risk factor of incident AF after multivariable adjustment.
adjustment. Similar to previous studies on this issue, we
found that the risk of incident AF among women with T2D
was increased approximately 2-fold after adjustment for age,
and that this risk was attenuated to about 1.4 after more
extensive multivariable adjustment for baseline risk factors
(9,12,14,16). The present study added to this literature by
showing that much of the remaining association between
T2D and AF in these previous studies could be accounted
for by the development over time of hypertension, obesity,
and cardiovascular disease. We also found that the effect
of T2D on incident AF was stronger in younger women (p for
interaction = 0.01). The reason for this finding was unclear,
but it might suggest that environmental factors leading to
hypertension and obesity are less important in younger
individuals with T2D.

Our data suggested that the adiposity and hypertension
associated with T2D were more important for AF develop-
ment than glucose homeostasis, a concept that was sup-
ported by at least 2 lines of evidence. First, we found no
relationship between HbA1c levels and incident AF in
women with and without established T2D who had avail-
able blood samples. However, a recent study found that
elevated HbA1c levels were associated with an increased risk
of AF occurrence in the subgroup of participants with
established T2D (25). The reasons for these differential
findings were unclear, but might be related to the fact that
a more severe endpoint (AF hospitalizations) was assessed
in the earlier study or that a different sample population was
evaluated (community-based cohort vs. initially healthy
female health professionals). Alternatively, the relatively
small subgroup of women with T2D and available HbA1c
levels in our study might have limited our power to detect
such an association. The upper limit of the 95% CI in our
analysis suggested that our study could not exclude an
increased risk of incident AF up to 27% for each 1% increase
in HbA1c among women with T2D, an order of magnitude
well in line with the risk estimate of the previous analysis
(25). In contrast, the tight 95% CIs (HR: 0.87; 95% CI:
0.71 to 1.07) for HbA1c in the much larger group of
nondiabetic women did confidently rule out even a modest
increase in risk. Second, recent data from the Framingham
Heart Study investigators showed that insulin resistance did
not independently increase the risk of incident AF, with a
multivariable adjusted HR for new-onset AF associated
with insulin resistance of 1.03 (95% CI: 0.72 to 1.46) (36).

In contrast to these negative findings, the strong and
independent relationships of obesity and elevated blood
pressure, 2 important T2D-related comorbidities (17), with
AF development were demonstrated in several independent
studies (18–20,37). These relationships persisted in models
that took into account changes of covariates over time
(18,19), and were only minimally affected in the present
study by adding T2D to the models. Population attributable
risks around 20% for overweight and obesity (19,37), and up
to 25% for elevated blood pressure (37), further highlighted
the importance of overweight and elevated blood pressure as
AF risk factors. Because patients with T2D are more likely
to have additional weight gain and increases in blood
pressure, taking into account changes in these risk factors
over time was important to isolate any residual association
attributable to diabetes independent of these factors. Inter-
estingly, obesity, hypertension, T2D, and AF were all
strongly related to blood levels of inflammatory biomarkers
in earlier studies, such that inflammation might be an important
pathophysiological link between these variables (19,38,39).
With regard to clinical implications, our data suggest that
prevention of AF among individuals with T2D should focus
on the strict control of body weight and blood pressure (40).

The occurrence of cardiovascular events is a strong risk
factor for incident AF (14,37) and an important determin-
ant of an adverse outcome in AF patients (8). Because
patients with T2D have an increased risk of developing
cardiovascular events (41), we hypothesized that intercur-
rent cardiovascular events could also mediate AF risk in
these patients. However, although significantly more AF
events were preceded by a cardiovascular event in women
with T2D, the majority of AF events occurred indepen-
dently of an overt cardiovascular event also among individ-
uals with T2D. Accordingly, our multivariable models
suggested that once changes in blood pressure and body
weight were taken into account, only a small part of the
relationship between baseline T2D and new-onset AF
might be mediated by nonfatal cardiovascular events.

### Table 4

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>p Value for Trend*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events/participants</td>
<td>170/6,275</td>
<td>181/6,149</td>
<td>235/6,293</td>
<td>249/6,173</td>
<td>—</td>
</tr>
<tr>
<td>Age-adjusted incidence rate</td>
<td>2.05</td>
<td>1.99</td>
<td>2.33</td>
<td>2.37</td>
<td>—</td>
</tr>
<tr>
<td>Age-adjusted model Referent</td>
<td>0.97 (0.79–1.20)</td>
<td>1.12 (0.92–1.37)</td>
<td>1.12 (0.91–1.37)</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Multivariable-adjusted model†‡ Referent</td>
<td>0.99 (0.80–1.22)</td>
<td>1.07 (0.87–1.31)</td>
<td>1.11 (0.90–1.36)</td>
<td>0.22</td>
<td></td>
</tr>
<tr>
<td>Hypertension and BMI§ Referent</td>
<td>0.95 (0.76–1.17)</td>
<td>0.97 (0.79–1.19)</td>
<td>0.99 (0.73–1.11)</td>
<td>0.35</td>
<td></td>
</tr>
</tbody>
</table>

Data are counts, rates per 1,000 person-years of follow-up, or hazard ratios (95% CIs) as appropriate. *p value for trend across quartiles of HbA1c using quartile-specific medians of HbA1c. †Adjusted for age, smoking, exercise, alcohol consumption, education, race/ethnicity, hypercholesterolemia, and adult height. ‡These models were based on 794 events in 24,194 women because of missing data. §These models were based on 794 events in 23,921 women because of missing data.

HbA1c = glycated hemoglobin; other abbreviations as in Tables 2 and 3.
Strengths and limitations. Strengths of the present study included the prospective design, the large sample size, and complete long-term follow-up with a large number of events confirmed by medical record review and regular covariate update. Potential study limitations should also be considered. First, most participants of the present study were Caucasian women, and generalization of our findings to different populations should be done cautiously. Second, some AF cases might have been undetected because of asymptomatic AF episodes. The only way to obtain a true picture of the AF prevalence would be by long-term continuous Holter monitoring, which unfortunately is not feasible in large long-term cohort studies of this type. Third, defining the onset of the initial AF episode might be challenging. Fourth, underdiagnosis of T2D might have occurred, given the lack of systematic T2D screening. Fifth, subclinical hyperthyroidism was repeatedly associated with an increased risk of AF and might also be related to T2D (42,43). Because information on thyroid function was not available in this study, we were unable to assess its role in the relationship between T2D and incident AF.

Conclusions

In this large cohort of initially healthy women, T2D at study entry was associated with a modest increase in risk of incident AF. Most of this increased risk seemed to be mediated through excess weight gain and a higher prevalence of hypertension among individuals with T2D, such that the impact of diabetes beyond these risk factors was less important. Therefore, strategies for AF prevention in diabetic patients should focus on the control of T2D-associated comorbidities, in particular weight maintenance and blood pressure control.

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REFERENCES


**Key Words:** atrial fibrillation • blood pressure • cardiovascular disease • obesity • prospective cohort study • type 2 diabetes • women.

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**APPENDIX**

For supplemental tables, please see the online version of this article.