Additive Interaction of Hyperglycemia and Albuminuria on Risk of Ischemic Stroke in Type 2 Diabetes

Hong Kong Diabetes Registry

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OBJECTIVE — The study aims to test whether biological interaction between hyperglycemia and albuminuria can explain the inconsistent findings from epidemiological studies and clinical trials about effects of hyperglycemia on stroke in type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 6,445 Hong Kong Chinese patients with type 2 diabetes and free of stroke at enrollment were followed up for a median of 5.37 years. Spline Cox proportional hazard regression was used to obtain hazard ratio curves, which were used to identify cutoff points of A1C and spot urinary albumin–to–creatinine ratio for increased ischemic stroke risk. The identified cutoff point of A1C was used to check biological interaction between A1C and albuminuria (micro- and macroalbuminuria). The biological interaction was estimated using relative excess risk due to interaction (RERI), attributable proportion due to interaction (AP), and synergy index.

RESULTS — During the follow-up period, 4.45% (n = 287) of patients developed ischemic stroke. A1C was associated with increased hazard ratios of ischemic stroke in a near-linear manner except for two points—6.2 and 8.0%—where the slope between these two points accelerated. For A1C values <6.2%, the presence of micro/macroalbuminuria did not confer additional risk, while significant biological interaction between A1C and micro/macroalbuminuria for values ≥6.2% was observed (RERI 0.92, 95% CI 0.16–1.68, and AP 0.40, 0.01–0.78).

CONCLUSIONS — A1C ≥6.2% and micro/macroalbuminuria interact to markedly increase the ischemic stroke risk, which explains a large proportion of risk in patients with type 2 diabetes harboring both risk factors.

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Several large cohort studies have demonstrated that hyperglycemia or type 2 diabetes is associated with an elevated risk in stroke (1) and cardiovascular death (2). The Diabetes Control and Complications Trial (DCCT) verified that glycemic control in type 1 diabetes reduced the incidence rate of cardiovascular disease, including stroke (3). However, in type 2 diabetes, neither individual randomized clinical trials nor meta-analysis of published randomized controlled trials could convincingly and consistently demonstrate the beneficial effects of glucose lowering on reducing stroke incidence (4). Somewhat paradoxically, the UK Prospective Diabetes Study (UKPDS) even reported a nonsignificant increase in stroke incidence in the intensive treatment arm (5).

There are two possible reasons for these inconsistent findings. One is the target of glycemia is not low enough to reduce stroke risk. In this regard, the recent premature discontinuation of the intensive treatment arm of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study, in which there is an excessive number of deaths, largely due to sudden death, in the intensive treatment arm with a target A1C level <6% further complicates the picture (6). The second is whether hyperglycemia has biological interaction with other important risk factors such as hypertension or albuminuria to give sufficient "causes" for stroke. According to the Rothman model, there should be sufficient "causes" and component "causes" in disease development (7). In this regard, biological interaction indicates that two risk factors are involved in the same sufficient "cause" of disease, or pathway toward disease (8,9).

Albuminuria was a strong predictor of stroke (10), cardiovascular death (11), and all-cause death (12). Previously, we have developed a hazard ratio (HR) curve method to examine full-range relationships between risk factors and outcomes (13,14). In this analysis, we hypothesize that hyperglycemia interacts with albuminuria, both being potent risk factors, to increase stroke risk in type 2 diabetes. We tested this hypothesis by applying the HR curve (13,14) and biological interaction (8,9) to ascertain the optimal target of glycemia and its interaction with albuminuria on ischemic stroke risk.

RESEARCH DESIGN AND METHODS

— Detailed description of the cohort has been published previously (12). Briefly, the Hong Kong Diabetes Registry was established at the Prince of Wales Hospital, which served a catch-

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ment area of 1.2 million residents, in 1995. Patients came from general practitioners, community clinics, and other specialty clinics and also included patients discharged from the Prince of Wales Hospital or other hospitals. Enrolled patients with hospital admissions within 6–8 weeks before assessment accounted for <10% of all referrals. The patients underwent a 4-h comprehensive assessment, which was modified from the European DIABCARE protocol (15) as part of a quality improvement program of the Prince of Wales Hospital Diabetes Centre. Once a diabetic subject was enrolled, he or she will be observed until time of death. Hong Kong has a heavily subsidized health care system. The Hospital Authority is the governing body of all 42 public hospitals, 45 specialist outpatient clinics, and 74 general outpatient clinics and provides over 95% of acute and chronic care to the 6.8 million population. Ethics approval was obtained from the Chinese University of Hong Kong Clinical Research Ethics Committee. Written informed consent was obtained from all patients for data analysis and research purpose upon enrollment.

From 1995 to 2005, 7,920 diabetic patients were enrolled in this registry. Patients excluded from this analysis included 332 patients with type 1 diabetes (defined as acute presentation with diabetic ketoacidosis, heavy ketonuria [>3+], or continuous requirement of insulin within 1 year of diagnosis), 5 with uncertain type 1 diabetes status, 61 with non-Chinese or unknown nationality, and 329 with past history of stroke, including cardioembolism, ischemic, and hemorrhagic stroke. Another 765 patients with missing values on the variables used in the analysis were excluded, and eventually 6,445 patients with complete data were used in the analysis.

Clinical measurements

Assessment methods, definitions, and laboratory assays have been reported previously (6–8). Briefly, clinical examination and laboratory investigations were performed after at least 8 h of fasting. A sterile, random spot urine sample was used to measure albumin-to-creatinine ratio (ACR). Microalbuminuria was defined as ACR ≥2.5 and <25 mg/mmol in men and ≥3.5 and <25 mg/mmol in women. Macroalbuminuria was defined as ACR ≥25 mg/mmol in both sexes. The abbreviated Modification of Diet in Renal Disease (MDRD) formula recalibrated for Chinese (16) was used to estimate glomerular filtration rate (eGFR) expressed in ml/min per 1.73 m^2:

$$\text{eGFR} = 186 \times [\text{SCR} \times 0.011]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if female}] \times 1.233$$

where SCR is serum creatinine expressed as μmol/l (originally expressed as mg/l, now converted to μmol/l) and 1.233 is the adjusting coefficient for Chinese.

Outcome measures

Details of hospital admissions were retrieved from the Hong Kong Hospital Authority Central Computer System, which records admissions to all public hospitals in Hong Kong. These databases were matched by a unique identification number, the Hong Kong Identity Card number, which is compulsory for all residents in Hong Kong. Hospital discharge diagnoses coded by the *International Classification of Diseases, Ninth Revision (ICD-9)*, were used to identify ischemic stroke defined as nonfatal ischemic stroke (ICD-9 code 432–434, 436) or deaths from ischemic stroke (ICD-9 code 432–438). Ischemic stroke events from enrollment up to 30 July 2005 were recorded or otherwise censored on 30 July 2005. All diagnoses of ischemic stroke were confirmed by the attending physician on discharge based on clinical findings and ascertained by computed tomography of brain in accordance with the Hospital Authority clinical guidelines. Transient ischemic attack and asymptomatic stroke were not included in both the definition of ischemic stroke end point and stroke history at baseline.

Statistical analysis

The Statistical Analysis System (Release 9.10) was used to perform the statistical analysis (SAS Institute, Cary, NC). Cox proportional hazard regression was used to obtain HRs of A1C and ACR for ischemic stroke while controlling for covariates. Restricted cubic spline is piecewise cubic polynomials that are connected across different intervals of a continuous variable (17). It can fit sharply curving shapes with the additional advantage that only k-1 parameters must be estimated (*k* is the number of knots, which are used to divide the covariate into piecewise cubic polynomials) (17). We have developed an HR curve method to examine full-range associations between risk factors and all-cause death (14) and interrelationships of risk factors for the risk of coronary heart disease (CHD) (13). In this analysis, we used the same method to examine full-range association between A1C, ACR, and ischemic stroke and to choose cutoff points if indicated and their interrelationship for ischemic stroke risk (13,14,17). Use of the selected cutoff points, A1C and ACR, was initially stratified into two levels. Then, recoding was performed according to the requirements for calculation of biological interaction (8,9). Three measures to examine biological interaction (or additive interaction) are *1*) relative excess risk due to interaction (RERI), *2*) attributable proportion due to interaction (AP), and *3*) synergy index (S). The RERI is the excess risk due to interaction relative to the risk without exposure. AP refers to the attributable proportion of disease that is due to interaction among individuals with both exposures. S is the excess risk from exposure (to both exposures) when there is interaction relative to the risk from exposure (to both exposures) without interaction (18). RERI >0, AP >0, and S >1 indicate biological interaction. However, the RERI is the best choice of measures using a proportional hazards model (19).

A structured adjustment scheme was used to control for covariates. Besides age, sex, smoking status, and hypertension status, we also adjusted for BMI, LDL and HDL cholesterol, duration of diabetes, eGFR, and baseline drug use variables, including lipid-lowering drugs, oral antidiabetic drugs, and insulin. Further adjustment using spline terms of continuous variables was also performed. The proportional hazards assumption was checked.

RESULTS

Characteristics of study patients

At enrollment, the median age of the cohort was 57 years (interquartile range 46–67 years), with a median duration of diabetes of 5 years (interquartile range 1–10 years). During a median follow-up period of 5.37 years (interquartile range 2.89–7.75 years), 4.45% (n = 287) of ischemic stroke events were recorded, giving an incidence rate of 8.36 (95% CI 7.40–9.33) per 1,000 person-years. Patients who developed ischemic stroke had significantly higher A1C and ACR than patients who remained free of ischemic stroke during the follow-up period (Table 1). Patients with ischemic stroke were older, were more likely to be smokers,

Table 1—*Baseline clinical and biochemical characteristics of the study cohort of type 2 diabetic patients*

	Nonischemic stroke	Ischemic stroke	*P*
n	6,158	287	—
Age (years)	56 (46–67)	68 (60–73)	<0.0001*
Male sex	45.3	48.4	0.3012‡
BMI (kg/m^2)	24.7 (22.4–27.3)	24.7 (22.4–26.9)	0.8339*
Smoking			0.0003‡
Former smokers	13.9	19.5	
Current smokers	18.9	24.7	
Duration of diabetes (years)	5 (1–10)	9 (3–15)	<0.0001*
Systolic blood pressure (mmHg)	133 (120–147)	144 (130–160)	<0.0001*
Diastolic blood pressure (mmHg)	76 (69–83)	77 (70–85)	0.0364*
Hypertension	57.6	78.4	<0.0001‡
A1C (%)	7.3 (6.4–8.5)	7.9 (6.8–9.2)	<0.0001*
A1C ≥6.2%	81.0	90.9	<0.0001‡
LDL cholesterol (mmol/l)	3.10 (2.50–3.80)	3.30 (2.70–4.00)	0.0002*
HDL cholesterol (mmol/l)	1.26 (1.07–1.50)	1.21 (1.03–1.46)	0.0096*
Triglyceride (mmol/l)	1.33 (0.94–1.95)	1.40 (0.98–2.05)	0.1051*
Total cholesterol (mmol/l)	5.10 (4.5–5.83)	5.30 (4.70–5.09)	0.0044*
ACR (mg/mmol)	1.79 (0.73–9.27)	9.03 (1.83–62.49)	<0.0001*
Microalbuminuria	25.1	31.7	<0.0001‡
Macroalbuminuria	15.3	34.8	
eGFR (ml/min per 1.73 m^2)	106.1 (85.6–127.7)	89.3 (67.1–109.1)	<0.0001*
Retinopathy	25.3	42.5	<0.0001‡
Sensory neuropathy	25.2	40.4	<0.0001‡
Peripheral arterial disease	5.3	12.2	<0.0001‡
History of CHD	5.4	12.9	<0.0001‡
History of cancer	2.2	0.7	0.0773‡
Drug use at baseline			
Lipid-lowering drugs	13.4	13.2	0.958‡
ACE inhibitors/angiotensin II receptor blockers	20.6	23.7	0.2050‡
Other antihypertensive drugs	34.2	46.0	<0.0001‡
Oral antidiabetic drugs	62.4	59.6	0.3317‡
Insulin	17.3	25.4	0.0004‡
Aspirin§	8.3	12.3	0.0345*
Other aspirin-containing drugs§	0.1	0.0	1.0†
Antiplatelet drugs§	8.5	13.1	0.0166*
Anti-arrhythmic drugs§	0.3	0.4	0.5448†
Glucocorticoid§	1.6	0.0	0.051†
Non-steroidal anti-inflammatory drugs§	2.4	1.3	0.2751*

Data are medians (25th to 75th) or %, unless otherwise indicated. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or using ACE inhibitors, angiotensin II receptor blockers, or other antihypertensive drugs. Microalbuminuria was defined as ACR ≥2.5 and <25 mg/mmol in men and ≥3.5 and <25 mg/mmol in women; macroalbuminuria was defined as ACR ≥25 mg/mmol in both sexes. *Derived from the χ^2 test. †Derived from Fisher's exact test. ‡Derived from the Wilcoxon two-sample test. §Only in 5,362 patients who were enrolled in the cohort after 1 December 1996.

had longer duration of diabetes, had poorer metabolic profile, and were more likely to have complications and to use antihypertensive drugs, insulin, aspirin, and antiplatelet drugs (Table 1).

A1C and albuminuria as risk factors of ischemic stroke

Both A1C and ACR were risk factors of ischemic stroke. A1C was associated with HR in a nearly linear manner. Nevertheless, two points where the slopes of the curves sharply changed, 6.2 and 8.0%, were identifiable. The two A1C curves with and without adjustment for ACR started to separate from 6.2% onward with marked divergence from 8.0% (Fig. 1*A*).

ACR was associated with ischemic stroke roughly in a linear manner from 0 to 100 mg/mmol and from 150 mg/mmol upwards. The two ACR curves with and without adjustment for A1C started to separate at a very low level, roughly at the level of microalbuminuria. The separation of the two curves widened progressively with increasing ACR (Fig. 1*B*). Using A1C and ACR as categorical variables, either A1C ≥6.2% or albuminuria was significantly, and by itself independently, associated with increased risk of ischemic stroke (Table 2).

In multivariable models, cancer history ($P = 0.3654$) was not significant as a covariate for ischemic stroke. Use of ACE inhibitors or angiotensin II receptor blockers was also nonsignificant in a separate multivariable model (1.03, 95% CI 0.76–1.40, $P = 0.8548$). Additionally, aspirin ($P = 0.4716$), antiplatelets ($P = 0.3958$), antiarrhythmic drugs ($P = 0.7724$), glucocorticoids ($P = 0.9625$),

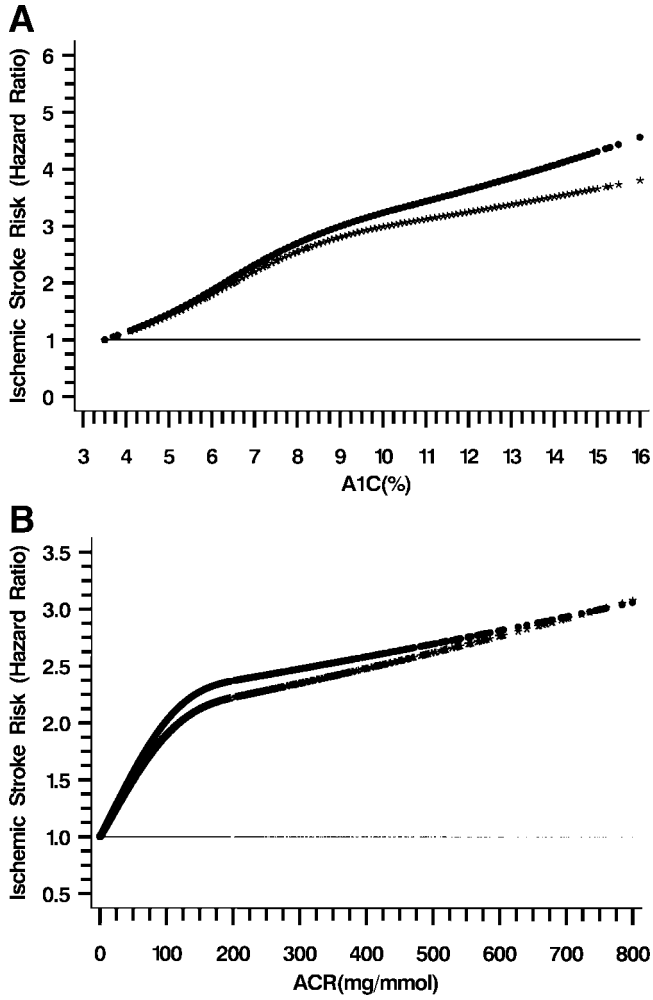

Figure 1—*Hazard ratio of hyperglycemia and albuminuria for ischemic stroke in type 2 diabetes. The multivariable models are adjusted for sex, smoking status (current and ex), hypertension (defined as systolic/diastolic blood pressure ≥140/90 mmHg, on ACE inhibitors/angiotensin II receptor blockers, or on other antihypertensive drugs), use of drugs at baseline (lipid-lowering drugs, oral antidiabetic drugs, and insulin), and spline functions of systolic blood pressure, BMI, HDL cholesterol, estimated glomerular filtration rate, and duration of diabetes.* A*: Dotted [upper] line represents the multivariable model, not adjusted for ACR. Starred [lower] line represents the multivariate model, adjusted for ACR.* B*: Dotted [upper] line represents the multivariable model, not adjusted for A1C. Starred [lower] line represents the multivariate model, adjusted for A1C.*

and nonsteroidal anti-inflammatory drugs ($P = 0.6473$) were all nonsignificant for ischemic stroke in 5,362 patients who were enrolled on or after 1 December 1996 and whose additional drug use data were available.

Interactive effects of hyperglycemia and albuminuria

Separate models testing micro- and macroalbuminuria showed that albuminuria was a significant risk factor for ischemic stroke for all A1C levels except when A1C was <6.2% (Table 2). A1C ≥6.2% and albuminuria were significantly and independently associated with increased stroke risk after adjusting for other covariates. When A1C and albuminuria were put together in an interaction model, the risk association only persisted in coexistence of A1C ≥6.2% and albuminuria (Table 2), which greatly increased stroke risk, even after adjustment for all covariates or their spline terms (Table 2). Measure of biological interaction between A1C ≥6.2% and albuminuria was tested positive for RERI and AP but not significant for S (Table 3).

Associations between albuminuria and traditional risk factors

Additional analysis using logistic procedure shows that baseline albuminuria was associated with hypertension (odds ratio: 2.77 [95% CI 2.44–3.16]), A1C (1.17 per % [1.14–1.21]), LDL cholesterol (1.09 per mmol/l [1.03–1.16]), and BMI (1.04 per kg/m^2, 1.03–1.06) after adjusting for age, duration of diabetes, baseline drug use, and other covariates.

CONCLUSIONS — Based on relatively novel analysis, we have answered two important questions: *1*) A1C needs to be lowered to <6.2% to reduce the incidence rate of ischemic stroke substantially and *2*) there is biological interaction between A1C ≥6.2% and albuminuria; put in another way, these two risk factors interact to substantially increase ischemic stroke risk in type 2 diabetes, an effect that is more than summation. Based on these findings, we infer that stroke risk can be substantially reduced by lowering A1C to <6.2% or by substantially reducing albuminuria if A1C cannot be reduced effectively and safely to <6.2%.

A meta-analysis of cohort studies showed that every 1% increase in A1C was associated with a 1.17-fold risk of stroke (1). We have reported a 1.49-fold increased risk of ischemic stroke per 1% increase in A1C in Chinese patients with type 2 diabetes (20). These increased risks may be attributable to the high prevalence of albuminuria in our population—estimated at 50–60%—that has also been reported in other Asian populations (21). In the landmark DCCT involving 1,441 patients with type 1 diabetes followed up for 17 years (3), microalbuminuria was more prevalent (13 vs. 7%, $P < 0.01$) and A1C was higher (9.1 vs. 7.4%, $P < 0.01$) in the conventional treatment group than the intensive insulin treatment group, with the latter conferring 42% risk reduction in any cardiovascular events. In the UKPDS, which consists of 3,867 newly diagnosed type 2 diabetes patients followed up for 10 years (22), a 0.9% difference in achieved A1C between the intensive and conventional treatment groups was associated with nonsignificantly higher stroke risk (relative risk 1.11, $P = 0.52$). Our findings may provide an explanation for these discrepant findings between type 1 and type 2 diabetes. In the UKPDS, over a 10-year period, A1C in the intensive treatment group was significantly lower than that in the conventional treatment group ($P < 0.0001$). However, A1C level in the intensive treatment remained high (median: 7%, interquartile range: 6.2–8.2%). Given the near-linear relationship between A1C and stroke rate and that many type 2 diabetic patients may have coexisting albuminuria, it is conceivable that the

Table 2—*Hazard ratios for the risk of ischemic stroke in relation to A1C and albuminuria*

Exposure	Number at risk	Hazard ratio	95% CI	*P*
Basic models				
Basic model 1*				
A1C (per %)	6,445	1.10	1.03–1.17	0.0039
Albuminuria				
Microalbuminuria vs. normoalbuminuria	1,635	1.43	1.06–1.94	0.0182
Macroalbuminuria vs. normoalbuminuria	1,042	2.13	1.54–2.95	<0.0001
Hypertension: yes vs. no	3,776	1.50	1.10–2.06	0.0113
Glomerular filtration rate (per 10 ml/min per 1.73 m^2)	6,445	0.97	0.93–1.02	0.2341
Basic model 2*				
A1C ≥6.2 vs. <6.2%	5,555	1.73	1.15–2.60	0.0084
Micro/macroalbuminuria vs. normoalbuminuria	2,677	1.74	1.33–2.27	<0.0001
Hypertension: yes vs. no	3,776	1.53	1.12–2.08	0.0075
Glomerular filtration rate, per 10 ml/min per 1.73 m^2	6,445	0.96	0.92–1.00	0.0627
Basic model 3 (four individual models)‡				
Micro/macroalbuminuria vs. normoalbuminuria in A1C <6.2%	1,194	1.25	0.56–2.76	0.5846
Micro/macroalbuminuria vs. normoalbuminuria in A1C 6.2–6.9%	1,422	2.16	1.23–3.80	0.0078
Micro/macroalbuminuria vs. normoalbuminuria in A1C 7.0–10.0%	3,129	1.81	1.28–2.56	0.0009
Micro/macroalbuminuria vs. normoalbuminuria in A1C ≥10.0%	700	2.22	1.05–4.70	0.0376
Interaction models				
Interaction model 1†				
A1C ≥6.2% and normoalbuminuria vs. others	2,974	1.66	0.93–2.98	0.0889
A1C <6.2% and micro/macroalbuminuria vs. others	400	2.18	1.01–4.70	0.0474
A1C ≥6.2% and micro/macroalbuminuria vs. others	2,277	5.11	2.91–8.70	<0.0001
Interaction model 2*				
A1C ≥6.2% and normoalbuminuria vs. others	2,974	1.35	0.75–2.44	0.3130
A1C <6.2% and micro/macroalbuminuria vs. others	400	1.17	0.54–2.56	0.6888
A1C ≥6.2% and micro/macroalbuminuria vs. others	2,277	2.46	1.38–4.39	0.0024
Interaction model 3§				
A1C ≥6.2% and normoalbuminuria vs. others	2,974	1.30	0.72–2.35	0.3807
A1C <6.2% and micro/macroalbuminuria vs. others	400	1.10	0.50–2.40	0.8090
A1C ≥6.2% and micro/macroalbuminuria vs. others	2,277	2.32	1.30–4.16	0.0046

Microalbuminuria was defined as ACR ≥2.5 and <25 mg/mmol in men and ≥3.5 and <25 mg/mmol in women; macroalbuminuria was defined as ACR ≥25 mg/mmol in both sexes. *Adjusted for traditional risk factors including age, sex, smoking status (current and former), hypertension (defined as systolic/diastolic blood pressure ≥140/90 mmHg or on ACE inhibitors/angiotensin II receptor blockers or other antihypertensive drugs), BMI, HDL cholesterol, duration of diabetes, estimated glomerular filtration rate, and use of drugs at baseline (lipid-lowering drugs, oral anti-diabetic drugs, and insulin). †Not adjusted for other covariates. ‡Adjusted for age, sex, current smoking status, and hypertension. §Adjusted for covariates listed in *, but spline was used for all the continuous covariates.

interactive effects of suboptimal glycemic control and albuminuria may explain the failure to reduce the stroke rate.

Given the powerful risk associations between microalbuminuria and cardiovascular complications in type 2 diabetes and the lack of effective therapy to reduce hyperglycemia without causing hypoglycemia, our data strongly support the aggressive reduction of albuminuria to compensate for our inability to reduce A1C to <6.2% safely. To this end, we further confirm that albuminuria is a marker of multiple risk factors, especially remediable risk factors, including hypertension, hyperglycemia, high BMI, and high LDL cholesterol. Our findings are particularly intriguing, since in the ADVANCE (Preterax and Diamicron Modified Release Controlled Evaluation) study, the use of the ACE inhibitor perindopril in the intensive treatment arm based on gliclazide and other sulfonylureas, aiming at a target of ≤6.5%, may have enhanced the vasculoprotective effect of glycemic control by reducing albuminuria (23). The Heart Outcomes Prevention Evaluation (HOPE) study (24) also reported that ramipril, an ACE inhibitor, helped lower the risk of stroke by 33%, cardiovascular death by 37%, and total mortality by 24%, an effect beyond that due to a decrease in blood pressure. Of note, in the HOPE study, ramipril treatment led to a lower ACR at 1 year and 4 years of study.

Our study has several limitations. First, the cutoff points of A1C, 6.2 and 8.0%, were chosen based on visual observation of characteristics of the hazard ratio curve of A1C for ischemic stroke. Second, only one measurement of ACR and A1C was available for this analysis. Third, this cohort was a clinic-based rather than population-based cohort. However, Hong Kong does not have a comprehensive health insurance policy and integrated primary health care system. Thus, the majority of patients with chronic illnesses are managed in public hospitals more for financial reasons than disease severity. In Hong Kong, 90% of patients diagnosed with diabetes were treated in the public health sector (12). An annualized rate of 16.43 per 1,000 person-years for mortality and 14.08 per 1,000 person-years for incident CHD in the cohort were similar to those reported in other community-based databases

Table 3—*Biological interactions between A1C and albuminuria*

Measures of biological interaction	
Interaction model 1†	
RERI	2.27 (0.67–3.87)*
AP	0.44 (0.17–0.72)*
S	2.23 (0.97–5.15)
Interaction model 2‡	
RERI	0.93 (0.12–1.74)*
AP	0.38 (0.01–0.75)*
S	2.77 (0.31–24.33)
Interaction model 3¶	
RERI	0.92 (0.16–1.68)*
AP	0.40 (0.01–0.78)*
S	3.78 (0.19–56.11)

Data are estimates (95% CI). *Statistically significant with RERI >0, AP >0, and S >1, indicating biological interaction. †Not adjusted for other covariates. ‡Adjusted for traditional risk factors including age, sex, smoking status (current and former), hypertension (defined as systolic/diastolic blood pressure ≥140/90 mmHg or on ACE inhibitors/angiotensin II receptor blockers, or on other antihypertensive drugs), BMI, HDL cholesterol, duration of diabetes, estimated glomerular filtration rate, and use of drugs at baseline (lipid-lowering drugs, oral anti-diabetic drugs, and insulin). ¶Adjusted for the covariates listed for interaction model 1, but spline was used for all the continuous covariates.

(12). Fourth, a small number of ischemic events might not have been identified, notably due to emigration to other countries. However, this number is likely to be few, since lack of insurance coverage is likely to reduce the likelihood of emigration or acceptance of these high-risk patients by other countries as permanent residents. Fifth, only baseline measurements of risk factors such as A1C, ACR, lipids, and drug use were available for the present analysis. Metabolic profile may deteriorate over time and, as a result, drug use may increase substantially during the long follow-up period. Sixth, we did not have information on atrial fibrillation or inflammatory or immunological disorder conditions. However, use of antiarrhythmic drugs, glucocorticoids, and nonsteroidal anti-inflammatory drugs in the cohort was very low and not significant for ischemic stroke. Thus, these medical conditions may not have major impacts on the findings of the study.

In conclusion, based on a large prospective cohort of patients with type 2 diabetes, we confirmed the marked increase in the risk of ischemic stroke when A1C ≥6.2% and albuminuria coexist. These findings have important therapeutic implications given our current armamentarium in lowering blood glucose. Until safe and effective agents become available to lower A1C to <6.2%, reducing albuminuria by aggressive control of multiple risk factors, notably blood pressure and inhibition of the renin-angiotensin system, is of critical importance to reduce the risk of stroke in type 2 diabetes.

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