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Title	Effect of Multifactorial Treatment Targets and Relative Importance of Hemoglobin A1c, Blood Pressure, and Low Density Lipoprotein Cholesterol on Cardiovascular Diseases in Chinese Primary Care Patients With Type 2 Diabetes Mellitus: A Population Based Retrospective Cohort Study
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Effect of Multifactorial Treatment Targets and Relative Importance of Hemoglobin A1c, Blood Pressure, and Low-Density Lipoprotein-Cholesterol on Cardiovascular Diseases in Chinese Primary Care Patients With Type 2 Diabetes Mellitus: A Population-Based Retrospective Cohort Study

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Background—The relative effect of hemoglobin A1c, blood pressure, and low-density lipoprotein-cholesterol (LDL-C) ("ABC" factors) on the prevention of cardiovascular diseases (CVD) among patients with type 2 diabetes mellitus is poorly understood. This study aimed to evaluate the association of key clinical parameters on CVD risk using a multifactorial optimal control approach in Chinese primary care patients with type 2 diabetes mellitus.

Methods and Results—A population-based retrospective cohort study was conducted on 144 271 Chinese type 2 diabetes mellitus primary care patients, aged 18 to 79 and without prior clinical diagnosis of CVD in 2008–2011. Cox regressions were conducted to examine the association between the combinations of ABC targets (hemoglobin A1c <7%, blood pressure <130/90 mm Hg, and LDL-C <2.6 mmol/L) and risks of CVD (overall), coronary heart disease, stroke, and heart failure. Achieving more ABC targets incrementally reduced the incidence of total CVD and individual disease including coronary heart disease, stroke, and heart failure, irrespective of other patient characteristics. Compared with suboptimal control in all ABC levels, achieving any 1, 2, and all 3 ABC targets reduced the relative risk of CVD by 13% to 42%, 31% to 52%, and 55%, respectively. Among those achieving only 1 ABC target, LDL-C reduction was associated with the greatest CVD risk reduction (42%), followed by blood pressure reduction (18%), and hemoglobin A1c reduction (13%).

Conclusions—To achieve the greatest risk reduction for the incidence of CVD, the ultimate goal of treatment should be to achieve target control of hemoglobin A1c, blood pressure, and LDL-C. If it is not possible to achieve all 3 targets, efforts should be prioritized on treating the LDL-C to minimize CVD risk. (***J Am Heart Assoc***. 2017;6:e006400. DOI: 10.1161/JAHA.117.006400.)

Key Words: blood pressure • cardiovascular disease • diabetes mellitus • hemoglobin A1c • lipids

D iabetes mellitus (DM) remains a growing global health challenge. There are currently 415 million patients with DM worldwide, and this figure is predicted to increase to 642 million by 2040.[1] Cardiovascular diseases (CVD) are the

dominant cause of mortality in diabetic populations, contributing to 70% of deaths.[2] The International Diabetes Federation and the American Diabetes Association strongly recommend maintaining optimal hemoglobin A1c (HbA1c), blood pressure (BP), and low-density lipoprotein-cholesterol (LDL-C) ("ABC") levels for the primary prevention of CVD.[3,4] Unfortunately, achieving target levels of all ABC risk factors remains a significant challenge as has been reported in Canada, the United States, the United Kingdom, and Europe.[5–8] The benefits of CVD risk reduction through better control of all 3 factors is beyond doubt, but little is known about the relative effects of controlling individual or various combinations of these risk factors in diabetic populations.

To date, there have only been a few studies that have explored the association between multifactorial risk factors and CVD.[9–12] These studies have typically examined the number of factors controlled as none, any 1, any 2, or all 3

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Clinical Perspective

What Is New?

- In Chinese primary care type 2 diabetes mellitus patients, attainment of all 3 ABC targets (hemoglobin A1c <7%, blood pressure <130/90 mm Hg, and low-density lipoprotein-C <2.6 mmol/L) was achieved in only one tenth of patients.
- Achieving a greater number of ABC targets, irrespective of the patient's characteristics, incrementally reduced the risk of total cardiovascular disease (CVD) and all its subtypes including coronary heart disease, stroke, and heart failure.
- The relative importance of ABC control for the primary prevention of CVD was found to be target low-density lipoprotein-C, followed by target blood pressure, followed by target hemoglobin A1c.
- Patients benefitted the most from attaining all 3 ABC targets compared with those with suboptimal levels in all 3 ABC in the duration of diabetes mellitus <1 year group.

What Are the Clinical Implications?

- To achieve the greatest risk reduction for the incidence of CVD, the ultimate goal of treatment should be to achieve target control of hemoglobin A1c, blood pressure, and low-density lipoprotein-C.
- If it is not possible to achieve all 3 targets, efforts should be prioritized on treating the low-density lipoprotein-C to minimize CVD risk.
- Our findings highlight the importance of optimal control of multifactorial risk factors at an earlier disease stage, and the need to promote and educate clinicians and patients of the importance of target control of the modifiable risk factors for the primary prevention of CVD.

risk factors, but the relative importance of these 3 risk factors remains unclear. In clinical practice, physicians need to understand the relative importance of treating individual factors to help them prioritize the treatment goals in patients who may not be able to tolerate treatment of all 3 conditions synchronously such as those who may be at increased risk of adverse effects, those with excessive polypharmacy, or to help minimize treatment burden.[13,14] Evidence on the relative importance of treating each factor or combinations of factors can help clinicians make the most informed decisions and can also be used for shared decision making in diabetic patients with multimorbidity. Previous studies included both type 1 diabetes mellitus (DM) and type 2 DM (T2DM) subjects, have included patients recruited from hospital-based settings, have had inadequate sample sizes to observe sufficient end-point events, or have been performed under very structured but artificial settings such as randomized clinical trials.[9–12] Given the potential difference in pathophysiology of CVD in type 1 DM and T2DM,[15] and difference in disease severity in

hospital-based patients and primary care patients, findings from these previous studies may not be applicable to T2DM patients managed in a real-world primary care outpatient setting. This is important given recent trends to shift delivery of diabetic care away from hospitals to primary care settings in most developed countries.[16] Also, most previous studies have only considered baseline ABC measurements, ignoring the changes that may occur during the follow-up period, and have not shown the results of subgroup analyses describing the association of multifactorial risk factors control on CVD in different higher-risk subgroups such as smokers or those who are obese, which is an area where more knowledge is needed.

This study aimed to address some of the gaps in the existing literature by examining the association and relative importance of achieving target control for individual and combinations of ABC risk factors on CVD risk reduction among Chinese primary care patients with T2DM and to perform subgroup analyses to examine which patient characteristics are associated with CVD risk.

Methods

Study Design

This was a retrospective cohort study. All subjects were Chinese, aged from 18 to 79 years old, were clinically diagnosed with T2DM as identified by the International Classification of Primary Care-2 (ICPC-2) code of "T90," without any CVD event before baseline, and were receiving health services for DM in 1 of the 74 general outpatient clinics of the Hong Kong Hospital Authority (HA). The HA is the government organization coordinating all public-sector hospitals and primary care clinics in Hong Kong. Clinical records between August 1, 2008 and December 31, 2011 on all subjects meeting the inclusion criteria were retrieved through the HA's administrative database. For each patient, the date of the first time having the ABC value recorded was defined as their baseline and they were followed up until the date of occurrence of an outcome event, death, or last follow-up as of the censoring date (November 30, 2015), whichever occurred first.

Consent of participants was not necessary as all data were anonymous and were extracted through the computerized administrative system of the HA. Ethics approval was received from all the regional Institutional Review Boards of the Hong Kong HA. The reported investigations have been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2008.

CVD Identification

Outcomes of interest included the following 4 events:

1. CVD event including coronary heart disease (CHD), stroke, or heart failure;
2. CHD included ischemic heart disease, myocardial infarction, coronary death, and sudden death as identified using ICPC-2 K74 to K76 or *International Classification of Diseases, Ninth Edition, Clinical Modification 410.x to 414.x, 798.x*;
3. Stroke including fatal and nonfatal was identified using ICPC-2 K89 to K91 or *International Classification of Diseases, Ninth Edition, Clinical Modification of 430.x to 438.x*; and
4. Heart failure was identified using ICPC-2 K77 or *International Classification of Diseases, Ninth Edition, Clinical Modification 428.x*.

Achieved ABC and Baseline Covariates

The achieved ABC value was defined as the average of annual ABC measurements from baseline to the date of last follow-up. For instance, if the follow-up period was 4 years, then the achieved mean value was calculated by averaging the baseline, 1-, 2-, 3-, and 4-year ABC values. Achieved values are commonly used to evaluate the association between clinical parameters and the incidence of morbidity.[17–19] According to local guidelines, the recommended target values for HbA1c, BP, and LDL-C were <7%, <130/80 mm Hg, and <2.6 mmol/L, respectively.[20] All study subjects were stratified into 1 of the following 8 groups according to whether achieved ABC values achieved target or not (Group 1: none achieved the targets; Group 2: only HbA1c achieved the targets; Group 3: only BP achieved the targets; Group 4: only LDL-C achieved the targets; Group 5: only HbA1c and BP achieved the targets; Group 6: only HbA1c and LDL-C achieved the targets; Group 7: only BP and LDL-C achieved the targets; Group 8: all achieved the targets). For example, if a patient had achieved HbA1c of 8%, BP of 125/75 mm Hg, and LDL-C of 2.5 mmol/L, then this patient was stratified into Group 7.

The baseline covariates comprised the following:

1. Patient's sociodemographics: sex, age, and smoking status;
2. Laboratory results: lipid profile (LDL-C and total cholesterol to high-density lipoprotein-cholesterol ratio), triglyceride, urine albumin-to-creatinine ratio, and estimated glomerular filtration rate.
3. Clinical characteristics: body mass index (BMI), Charlson's Index, treated hypertension defined as ICPC-2 code of "K86" or "K87," self-reported duration of DM, and family history of DM.
4. Treatment modalities: use of insulin, metformin, sulfonylurea, other oral antidiabetic drugs, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other antihypertensive drugs, and statins.

All laboratory assays were performed in accredited laboratories by the College of American Pathologists, the Hong Kong Accreditation Service, or the National Association of Testing Authorities, Australia.

Data Analysis

Multiple imputation was adopted to deal with missing data for all baseline covariates other than ABC.[21] This approach can effectively reduce unnecessary biases,[21,22] raise the power of the analysis, and produce more reliable and applicable models.[23–25] In this study, each missing value was imputed 5 times by the chained equation method. The same analysis was performed for each of the 5 imputed data sets, and the 5 sets of results were combined using Rubin's rules.[26]

Descriptive statistics for the baseline covariates of each group were displayed after multiple imputation. Univariable linear (for continuous variables) or logistic (for binary variables) regressions were used to test whether there was any significant difference in baseline covariates across the groups. The incidence rate was estimated by an exact 95% CI based on a Poisson distribution for each group.[27] The differences of the incidence of CVD across the 8 groups were examined using multivariable Cox proportional hazards regression models with the adjustment of all baseline covariates as shown above. The proportional hazards assumption was checked by examining plots of the scaled Schoenfeld residuals against time for the covariates. All models in the study satisfied the proportional hazards assumptions and showed no presence of multicollinearity. To avoid the association of specific standard target for ABC levels and potential bias because of severe disease at baseline, 3 sensitivity analyses: (1) changing HbA1c and BP targets to 7.5% and 140/90 mm Hg, respectively; (2) changing HbA1c and BP targets to 8% and 140/90 mm Hg, respectively; and (3) excluding subjects with follow-up period less than 1 year were also conducted. Subgroup analyses were performed subsequently by stratifying sex, age groups (<65 years; ≥65 years), duration of DM (<1 year; ≥1 year), smoking status (smokers; nonsmokers), and BMI groups (<23 kg/m²; 23–24.9 kg/m²; BMI ≥25 kg/m²).

All significance tests were 2-tailed and those with $P<0.05$ were considered statistically significant. Statistical analyses were performed in STATA Version 13.0.

Results

In total, there were 162 589 subjects who were Chinese, aged between 18 and 79 years old, clinically diagnosed with

Table 1. Baseline Characteristics of Subjects

Factor	Total (N=144 271)	Group 1 (N=29 507)	Group 2 (N=22 382)	Group 3 (N=13 656)	Group 4 (N=21 270)	Group 5 (N=13 999)	Group 6 (N=18 337)	Group 7 (N=11 659)	Group 8 (N=13 461)	P Value
Sociodemographic, % (n)										
Male	47.4% (68 360)	46.0% (13 559)	45.2% (10 122)	45.2% (6175)	50.2% (10 677)	43.3% (6063)	51.7% (9474)	48.8% (5694)	49.0% (6596)	<0.001*
Age (mean±SD), y	61.63±10.02 (144 271)	60.91±10.05 (29 507)	63.62±9.72 (22 382)	58.59±9.86 (13 656)	61.63±10.00 (21 270)	61.05±9.84 (13 999)	64.26±9.56 (18 337)	59.42±9.94 (11 659)	61.86±9.89 (13 461)	<0.001*
Smoker	11.7% (16 884)	12.4% (3654)	9.2% (2055)	16.0% (2182)	12.0% (2546)	10.5% (1467)	9.4% (1730)	15.5% (1805)	10.7% (1446)	<0.001*
Laboratory results, mean±SD										
TC/HDL-C ratio	4.32±1.25 (144 271)	4.80±1.23 (29 507)	4.60±1.22 (22 382)	4.69±1.29 (13 656)	4.01±1.15 (21 270)	4.51±1.18 (13 999)	3.84±1.13 (18 337)	3.91±1.10 (11 659)	3.77±1.07 (13 461)	<0.001*
Triglyceride, mmol/L	1.62±0.91 (144 271)	1.72±0.91 (29 507)	1.58±0.81 (22 382)	1.61±0.84 (13 656)	1.71±1.05 (21 270)	1.51±0.78 (13 999)	1.56±0.92 (18 337)	1.60±1.02 (11 659)	1.49±0.89 (13 461)	<0.001*
BMI, kg/m^2	25.60±3.92 (144 271)	26.13±4.03 (29 507)	25.84±3.89 (22 382)	24.91±3.69 (13 656)	26.11±4.12 (21 270)	24.93±3.69 (13 999)	25.80±3.93 (18 337)	24.91±3.79 (11 659)	24.93±3.77 (13 461)	<0.001*
Urine ACR, mg/mmol	7.14±55.71 (144 271)	9.46±44.27 (29 507)	7.75±38.34 (22 382)	5.59±51.78 (13 656)	8.09±37.27 (21 270)	5.18±28.64 (13 999)	7.26±40.46 (18 337)	5.14±28.42 (11 659)	4.74±31.79 (13 461)	<0.001*
Follow-up measurements, mean±SD										
Number of HbA1c	4.98±1.26 (144 271)	4.88±1.41 (29 507)	4.77±1.37 (22 382)	5.05±1.27 (13 656)	5.15±1.16 (21 270)	4.91±1.25 (13 999)	4.97±1.17 (18 337)	5.24±1.06 (11 659)	5.05±1.09 (13 461)	<0.001*
Mean HbA1c, %	7.21±0.99 (144 271)	7.95±0.97 (29 507)	6.48±0.38 (22 382)	7.86±0.93 (13 656)	7.83±0.80 (21 270)	6.46±0.39 (13 999)	6.47±0.40 (18 337)	7.74±0.79 (11 659)	6.44±0.41 (13 461)	<0.001*
Mean HbA1c, mmol/mol	55.24±10.87 (144 271)	63.43±10.64 (29 507)	47.31±4.19 (22 382)	62.37±10.20 (13 656)	62.03±8.77 (21 270)	47.08±4.26 (13 999)	47.20±4.33 (18 337)	61.11±8.64 (11 659)	46.90±4.49 (13 461)	<0.001*
Number of BP	5.32±1.23 (144 271)	5.13±1.42 (29 507)	5.26±1.32 (22 382)	5.32±1.26 (13 656)	5.35±1.19 (21 270)	5.41±1.16 (13 999)	5.41±1.11 (18 337)	5.46±1.03 (11 659)	5.48±1.01 (13 461)	<0.001*
Mean SBP, mm Hg	132.52±11.41 (144 271)	139.70±9.39 (29 507)	138.65±8.45 (22 382)	121.55±6.52 (13 656)	138.46±8.45 (21 270)	121.62±6.48 (13 999)	137.71±7.83 (18 337)	121.82±6.39 (11 659)	121.87±6.29 (13 461)	<0.001*
Mean DBP, mm Hg	74.14±7.57 (144 271)	77.34±7.65 (29 507)	75.59±7.71 (22 382)	70.90±5.56 (13 656)	76.65±7.39 (21 270)	70.06±5.88 (13 999)	75.10±7.52 (18 337)	70.78±5.68 (11 659)	69.86±5.87 (13 461)	<0.001*
Number of LDL-C	4.74±1.29 (144 271)	4.57±1.43 (29 507)	4.65±1.38 (22 382)	4.77±1.31 (13 656)	4.79±1.21 (21 270)	4.81±1.26 (13 999)	4.79±1.20 (18 337)	4.89±1.12 (11 659)	4.90±1.13 (13 461)	<0.001*
Mean LDL-C, mmol/L	2.71±0.59 (144 271)	3.15±0.48 (29 507)	3.11±0.44 (22 382)	3.10±0.44 (13 656)	2.23±0.30 (21 270)	3.06±0.41 (13 999)	2.22±0.31 (18 337)	2.23±0.30 (11 659)	2.22±0.31 (13 461)	<0.001*
Clinical characteristics, % (n)										
Duration of T2DM, y	6.22±6.33 (144 271)	6.97±6.77 (29 507)	4.95±5.62 (22 382)	6.56±6.29 (13 656)	7.82±6.89 (21 270)	4.78±5.51 (13 999)	5.45±6.00 (18 337)	7.38±6.62 (11 659)	5.32±5.67 (13 461)	<0.001*
Treated hypertension	67.3% (97 104)	70.3% (20 739)	79.3% (17 746)	43.3% (5914)	73.1% (15 555)	58.8% (8226)	80.4% (14 735)	49.3% (5744)	62.7% (8445)	<0.001*
Family history of DM	43.6% (62 940)	45.7% (13 481)	37.7% (8447)	49.9% (6814)	46.3% (9851)	42.8% (5992)	38.4% (7045)	49.6% (5780)	41.1% (5530)	<0.001*
eGFR <60 mL/min per 1.73 m^2	3.3% (4704)	3.4% (1006)	4.1% (907)	2.2% (296)	3.6% (764)	2.6% (362)	3.8% (698)	2.3% (273)	3.0% (397)	<0.001*
Charlson's Index	1.09±0.37 (144 271)	1.08±0.35 (29 507)	1.09±0.38 (22 382)	1.07±0.33 (13 656)	1.08±0.36 (21 270)	1.09±0.40 (13 999)	1.10±0.41 (18 337)	1.08±0.37 (11 659)	1.10±0.42 (13 461)	<0.001*
Treatment modalities, % (n)										
Use of insulin	1.3% (1872)	2.0% (587)	0.5% (105)	1.6% (221)	2.3% (482)	0.4% (56)	0.7% (129)	1.8% (207)	0.6% (85)	<0.001*
Use of metformin	71.1% (102 513)	76.3% (22 521)	57.1% (12 778)	75.9% (10 366)	83.3% (17 711)	56.8% (7947)	67.8% (12 440)	82.0% (9563)	68.2% (9187)	<0.001*
Use of sulfonylurea	53.1% (76 548)	64.3% (18 968)	37.7% (8435)	61.1% (8344)	70.3% (14 945)	33.5% (4683)	43.4% (7967)	67.1% (7828)	40.0% (5378)	<0.001*
Use of other oral diabetic drugs	1.6% (2357)	2.4% (714)	0.5% (123)	2.0% (274)	3.0% (639)	0.5% (68)	0.8% (152)	2.4% (279)	0.8% (108)	<0.001*
Use of ACEI/ARB	31.8% (45 860)	35.5% (10 476)	33.5% (7487)	21.5% (2931)	39.7% (8445)	22.7% (3175)	36.5% (6701)	26.0% (3030)	26.9% (3615)	<0.001*

ORIGINAL RESEARCH

Table 1. Continued

Factor	Total (N=144 271)	Group 1 (N=29 507)	Group 2 (N=22 382)	Group 3 (N=13 656)	Group 4 (N=21 270)	Group 5 (N=13 999)	Group 6 (N=18 337)	Group 7 (N=11 659)	Group 8 (N=13 461)	P Value
Use of β-Blocker	25.7% (37 056)	25.0% (7385)	31.2% (6982)	16.3% (2226)	27.8% (5906)	22.4% (3138)	32.1% (5889)	18.5% (2159)	25.0% (3371)	<0.001*
Use of CCB	38.6% (55 645)	37.6% (11 105)	46.1% (10 325)	23.8% (3256)	39.7% (8438)	36.9% (5167)	48.1% (8820)	27.2% (3172)	39.8% (5362)	<0.001*
Use of diuretic	9.8% (14 094)	10.6% (3125)	11.7% (2623)	6.4% (871)	10.8% (2304)	8.4% (1172)	11.3% (2073)	7.3% (850)	8.0% (1076)	<0.001*
Use of other antihypertensive drugs	8.5% (12 259)	7.7% (2258)	10.7% (2389)	4.7% (643)	8.9% (1896)	7.3% (1018)	11.6% (2127)	5.9% (688)	9.2% (1240)	<0.001*
Use of statin	9.7% (14 024)	6.1% (1810)	7.2% (1610)	6.3% (861)	12.2% (2591)	7.2% (1012)	14.4% (2632)	12.7% (1477)	15.1% (2031)	<0.001*

ACEI indicates angiotensin-converting enzyme inhibitor; ACR, albumin–creatinine ratio; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CCB, calcium channel blocker; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Group 1, no targets achieved; Group 2, only HbA1c target achieved; Group 3, only BP target achieved; Group 4, only LDL-C target achieved; Group 5, only HbA1c and BP targets achieved; Group 6, only HbA1c and LDL-C targets achieved; Group 7, only BP and LDL-C targets achieved; Group 8, all targets achieved; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein–cholesterol; LDL-C, low-density lipoprotein–cholesterol; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol.

*Significant at 0.05 level by univariate linear or logistic regression, as appropriate.

T2DM, with valid ABC measurement, and received their DM care in primary care clinics of HA between August 1, 2008 and December 31, 2011. After excluding 18 318 subjects with prior history of CVD history or without follow-up after baseline, 144 271 T2DM patients were included in the main analysis. Data completion rates for each baseline covariate were >95%.

Table 1 shows the baseline characteristics for the overall cohort and for each of the groups after multiple imputation. In general, there were slightly more females (53%) than males (47%), mean age was 61.6 years (SD: 10.0 years), and the mean duration of DM was 6.2 years (SD: 6.3 years). In the study cohort, 40%, 31%, and 9% achieved 1, 2, and all 3 ABC targets, respectively; 47%, 37%, and 45% met the target levels for HbA1c, BP, and LDL-C.

The number, unadjusted incidence rate, and hazard ratio of various CVD events for each group are shown in Table 2. The incidence rates of CVD ranged between 10.9 and 25.7 per 1000 person-years among all groups during a median follow-up period of 63.5 to 68.5 months. In general, the more ABC targets achieved, the lower the CVD risk. Compared with Group 1 (no targets achieved), achieving only 1 of the ABC targets (Groups 2–4), any 2 of the ABC targets (Groups 5–7), and all 3 ABC targets (Group 8) were associated with 13% to 42%, 31% to 52%, and 55% reduction in the incidence of CVD, respectively. Among Groups 2 to 4, achieving LDL-C target only (Group 4) was associated with the largest reduction in CVD risk of 42% compared with Group 1. The relative CVD risk reduction for achieving LDL-C and BP targets (Group 7) decreased further by 52% compared with Group 1. Similar results were obtained for CHD, stroke, and heart failure. The sensitivity analyses were conducted after changing the target for ABC levels and the exclusion of subjects with a follow-up period of <1 year. The results were almost identical to the main analysis and the pattern was even more obvious for less stringent treatment targets.

Similar analyses were conducted on the following 11 subgroups: (1) females, (2) males, (3) age <65 years, (4) age ≥65 years, (5) duration of DM <1 year, (6) duration of DM ≥1 year, (7) smokers, (8) nonsmokers, (9) BMI <23 kg/m², (10) BMI between 23 and 24.9 kg/m² and (11) BMI ≥25 kg/m² and the corresponding adjusted hazard ratios for the incidence of each outcome event were plotted against the 7 groups (using Group 1 as the reference group) in Figure 1. A similar pattern was observed for incidence of total CVD, CHD, heart failure, and stroke and the deviation from the overall cohort was small for each of the 11 subgroups. Among all subgroups, the largest relative risk reduction in CVD was 69% when all 3 targets were achieved compared with none in the group with duration of DM <1 year.

Table 2. Number, Incidence Rate, and Hazard Ratio of CVD Events

	Group 1 (N=29 507)	Group 2 (N=22 382)	Group 3 (N=13 656)	Group 4 (N=21 270)	Group 5 (N=13 999)	Group 6 (N=18 337)	Group 7 (N=11 659)	Group 8 (N=13 461)
CVD								
Cumulative cases with event	4033	2823	1248	1870	1168	1643	680	794
Cumulative incidence rate	13.7%	12.6%	9.1%	8.8%	8.3%	9.0%	5.8%	5.9%
Person-years	156 871	117 803	74 577	114 118	75 529	95 935	62 651	70 798
Median follow-up, months	68.5	66.5	68.5	66.5	67.5	63.5	65.5	63.5
Incidence rate (95% CI)*	25.71 (24.93, 26.51)	23.96 (23.10, 24.86)	16.73 (15.83, 17.69)	16.39 (15.66, 17.15)	15.46 (14.60, 16.38)	17.13 (16.32, 17.97)	10.85 (10.07, 11.70)	11.22 (10.46, 12.02)
Hazard ratio[†] (95% CI)	Reference group	0.87[‡] (0.83, 0.92)	0.82[‡] (0.77, 0.87)	0.58[‡] (0.55, 0.62)	0.69[‡] (0.65, 0.74)	0.57[‡] (0.54, 0.61)	0.48[‡] (0.44, 0.52)	0.45[‡] (0.42, 0.49)
CHD								
Cumulative cases with event	2078	1377	690	851	602	749	361	362
Cumulative incidence rate	7.0%	6.2%	5.1%	4.0%	4.3%	4.1%	3.1%	2.7%
Person-years	162 587	121 877	76 106	116 540	77 032	97 995	63 398	71 782
Median follow-up, months	70.5	68.5	69.5	67.5	67.5	64.5	65.5	63.5
Incidence rate (95% CI)*	12.78 (12.24, 13.34)	11.30 (10.72, 11.91)	9.07 (8.41, 9.77)	7.30 (6.83, 7.81)	7.81 (7.21, 8.46)	7.64 (7.12, 8.21)	5.69 (5.14, 6.31)	5.04 (4.55, 5.59)
Hazard ratio[†] (95% CI)	Reference group	0.87[‡] (0.81, 0.94)	0.86[‡] (0.78, 0.94)	0.54[‡] (0.50, 0.59)	0.71[‡] (0.65, 0.78)	0.56[‡] (0.51, 0.61)	0.50[‡] (0.45, 0.56)	0.43[‡] (0.38, 0.48)
Stroke								
Cumulative cases with event	1734	1202	514	801	498	677	270	347
Cumulative incidence rate	5.9%	5.4%	3.8%	3.8%	3.6%	3.7%	2.3%	2.6%
Person-years	163 018	121 998	76 490	116 537	77 183	98 082	63 582	71 734
Median follow-up, months	70.5	68.5	70.5	67.5	68.5	64.5	65.5	63.5

Continued

Table 2. Continued

	Group 1 (N=29 507)	Group 2 (N=22 382)	Group 3 (N=13 656)	Group 4 (N=21 270)	Group 5 (N=13 999)	Group 6 (N=18 337)	Group 7 (N=11 659)	Group 8 (N=13 461)
Incidence rate (95% CI)*	10.64 (10.15, 11.15)	9.85 (9.31, 10.43)	6.72 (6.16, 7.33)	6.87 (6.41, 7.37)	6.45 (5.91, 7.04)	6.90 (6.40, 7.44)	4.25 (3.77, 4.78)	4.84 (4.35, 5.37)
Hazard ratio† (95% CI)	Reference group	0.87‡ (0.79, 0.97)	0.80‡ (0.69, 0.92)	0.64‡ (0.58, 0.72)	0.59‡ (0.51, 0.69)	0.58‡ (0.52, 0.66)	0.48‡ (0.40, 0.58)	0.41‡ (0.35, 0.49)
Heart failure								
Cumulative cases with event	982	699	252	495	215	405	141	156
Cumulative incidence rate	3.3%	3.1%	1.8%	2.3%	1.5%	2.2%	1.2%	1.2%
Person-years	165 903	124 023	77 344	117 414	77 990	98 846	63 938	72 244
Median follow-up, months	70.5	69.5	70.5	67.5	68.5	64.5	65.5	64.5
Incidence rate (95% CI)*	5.92 (5.56, 6.30)	5.64 (5.23, 6.07)	3.26 (2.88, 3.69)	4.22 (3.86, 4.60)	2.76 (2.41, 3.15)	4.10 (3.72, 4.52)	2.21 (1.87, 2.60)	2.16 (1.85, 2.53)
Hazard ratio† (95% CI)	Reference group	0.84‡ (0.77, 0.90)	0.79‡ (0.71, 0.87)	0.59‡ (0.54, 0.64)	0.67‡ (0.61, 0.74)	0.54‡ (0.49, 0.59)	0.44‡ (0.39, 0.51)	0.45‡ (0.40, 0.51)

CHD indicates coronary heart disease; CVD, cardiovascular disease; Group 1, no target achieved; Group 2, only hemoglobin A1c (HbA1c) target achieved; Group 3, only blood pressure (BP) target achieved; Group 4, only low-density lipoprotein cholesterol (LDL-C) target achieved; Group 5, only HbA1c and BP targets achieved; Group 6, only HbA1c and LDL-C targets achieved; Group 7, only BP and LDL-C targets achieved; Group 8, all targets achieved.

*Incidence rate (cases / 1000 person-years) with 95% CI based on Poisson Distribution.

†Hazard ratios were adjusted by age, sex, smoking status, total cholesterol/high-density lipoprotein cholesterol ratio, triglyceride, body mass index, urine albumin–creatinine ratio, duration of type 2 diabetes mellitus, diagnosed hypertension, family history of diabetes mellitus, estimated glomerular filtration rate, Charlson's Index, use of insulin, metformin, sulfonylurea, other oral diabetic drugs, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other antihypertensive drugs, and statin, calcium channel blocker, diuretic, other antihypertensive drugs, and statin.

‡Significant difference (P<0.05) by multivariable Cox proportional hazards regression.
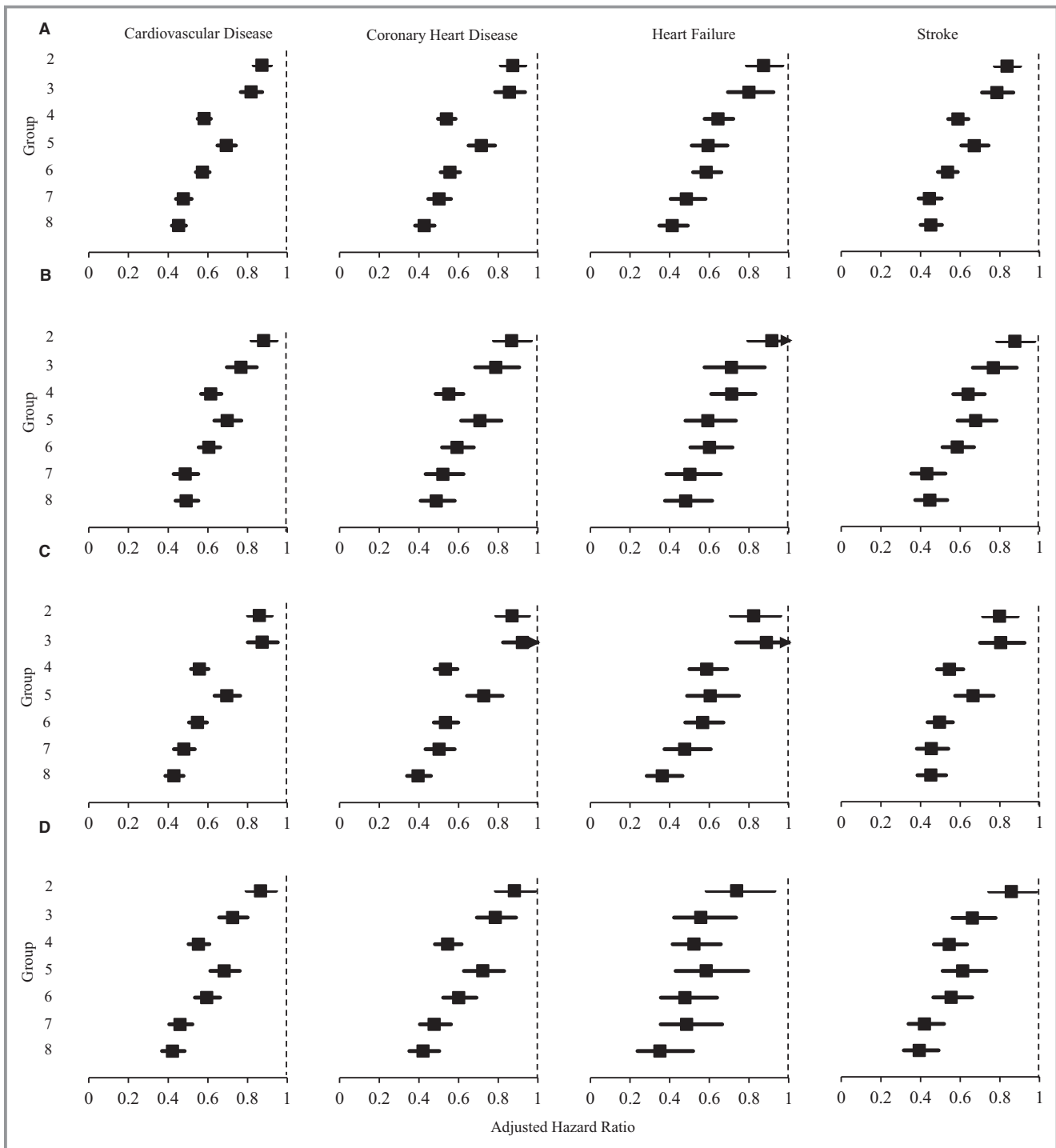
Figure. Adjusted hazard ratios for incidence of cardiovascular diseases among (A) all participants, (B) female, (C) male (D), age <65 years old, (E) age ≥65 years old, (F) duration of diabetes mellitus (DM) <1 year, (G) duration of DM ≥1 year, (H) smoker, (I) nonsmoker, (J) body mass index (BMI) <23 kg/m^2, (K) BMI 23 to 25 kg/m^2, and (L) BMI ≥25 kg/m^2 by multivariable Cox proportional hazards regressions. Hazard ratios were adjusted by age, sex, smoking status, total cholesterol to high-density lipoprotein cholesterol ratio, triglyceride, BMI, urine albumin-to-creatinine ratio, self-reported duration of DM, diagnosed hypertension, family history of DM, estimated glomerular filtration rate, Charlson Index and the use of insulin, metformin, sulfonylurea, other oral diabetic drugs, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, β-blocker, calcium channel blocker, diuretic, other antihypertensive drugs, and statin at baseline. Group 1 (no target achieved) was used as reference group; Group 2: only HbA1c (hemoglobin A1c) target achieved; Group 3: only blood pressure (BP) target achieved; Group 4: only low-density lipoprotein-cholesterol (LDL-C) target achieved; Group 5: only HbA1c and BP targets achieved; Group 6: only HbA1c and LDL-C targets achieved; Group 7: only BP and LDL-C targets achieved; Group 8: all targets achieved.
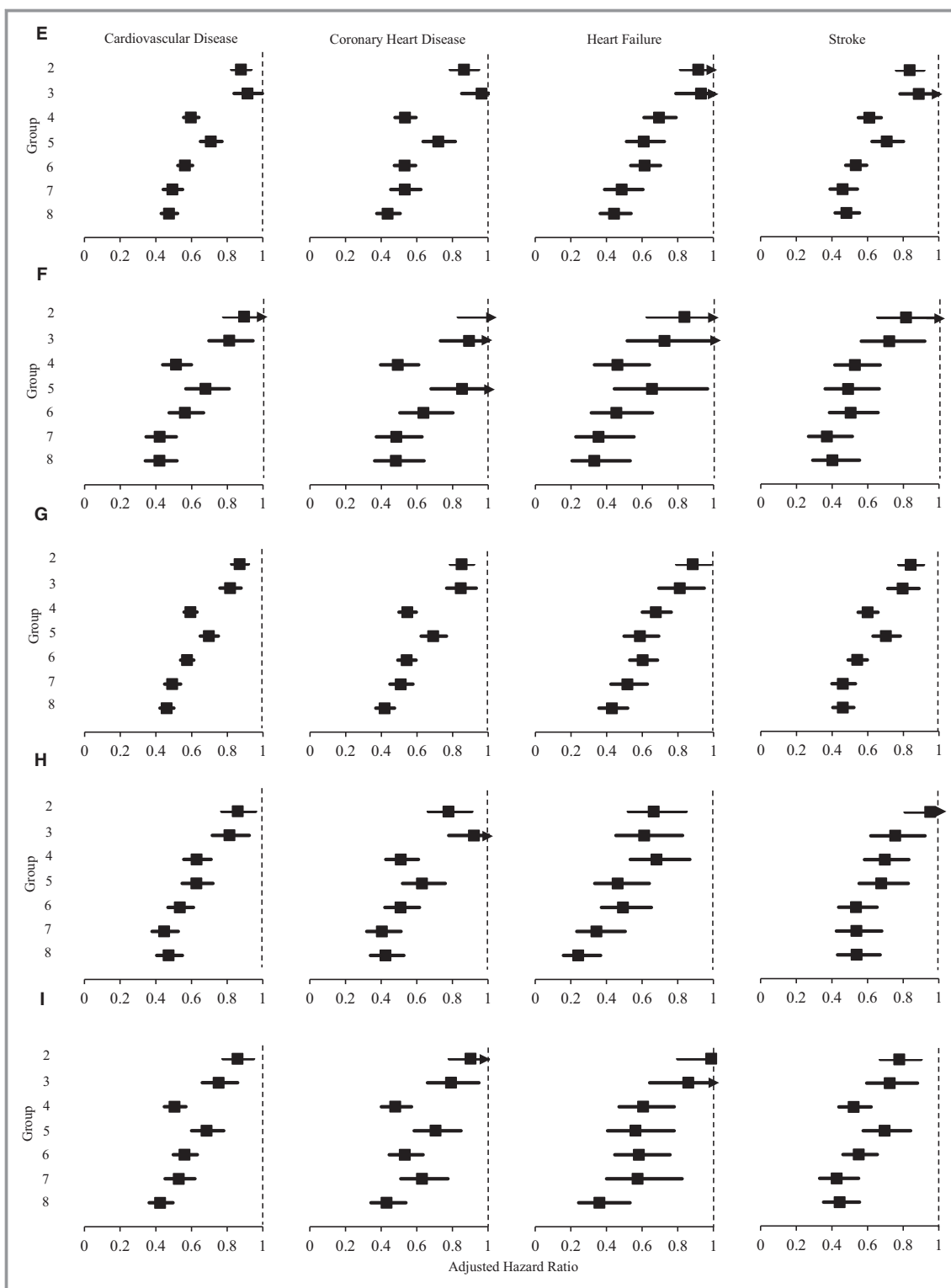
Figure. Continued.

Discussion

This is the first study to evaluate the relative association of target control of individual and combinations of ABC risk factors on the reduction of CVD among Chinese primary care patients with T2DM. In our study population, attainment of all 3 ABC targets was achieved in only one tenth of patients. Achieving a greater number of ABC targets, irrespective of the
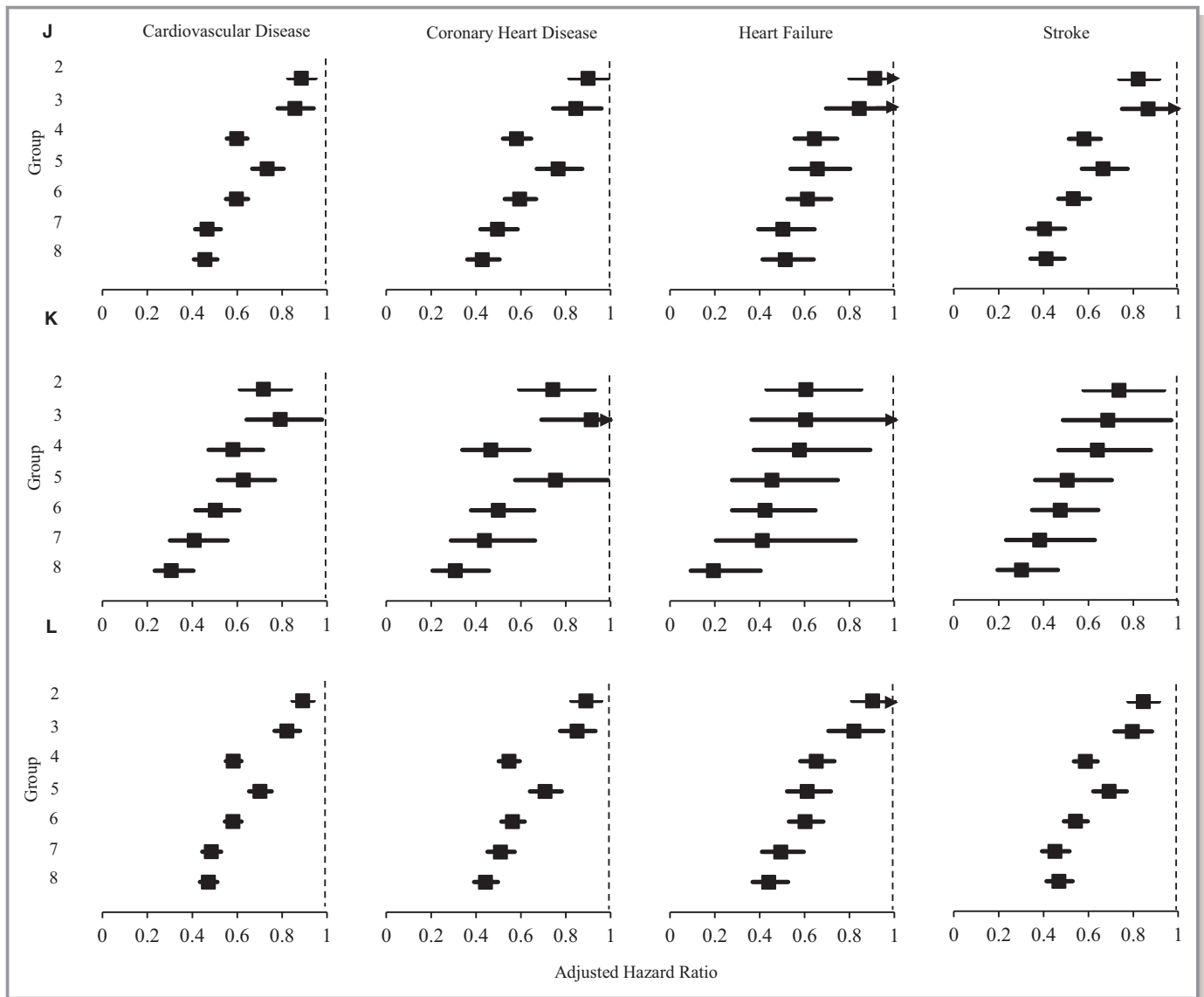
Figure. Continued.

patient's characteristics, incrementally reduced the risk of total CVD and all its subtypes including CHD, stroke, and heart failure. Achieving target control of LDL-C was associated with the most significant reduction of CVD risk, suggesting that the relative importance of attaining ABC targets for the primary prevention of CVD should be LDL-C first, BP second, and HbA1c third. Among all subgroups, patients benefitted the most from attaining all 3 ABC targets compared with those with suboptimal levels in all 3 ABC in the group with duration of DM <1 year, suggesting that early optimization of the ABC risk factor control in earlier disease stage is important.

The key finding of this study was understanding that not all ABC risk factors are of equal importance in the reduction of CVD risk in diabetic patients. Among Chinese primary care

patients with T2DM, the relative importance of ABC control for the primary prevention of CVD was found to be target lipid levels, followed by target BP, followed by target HbA1c. As earlier studies had only focused on the association of achieving target control for individual risk factors or number of risk factors, this study helps to fill a gap in the literature by providing information on the relative importance of achieving individual ABC targets or combinations of targets. A study comparing the effectiveness of lowering ABC levels by combining findings from epidemiological data and meta-analyses found that the numbers needed to treat for the prevention of 1 CVD event over 5 years were 119 for 0.9% reduction in HbA1c, 44 for 1 mmol/L reduction in LDL-C, and 34 for 10 mm Hg reduction in systolic blood pressure or 5 mm Hg reduction in diastolic blood pressure, and

concluded that addressing lipid and BP control had much larger benefits on the prevention of CVD than glycemic control.[28] In terms of the tolerability and safety of pharmacological treatments, glucose-lowering therapies, in particular intensive glycemic control, can increase the risk of severe hypoglycemia and severe adverse events resulting in hospitalization or significant disability.[29] In contrast, lowering of blood pressure or lipid levels can be achieved with drugs that have relatively less dangerous side effects.[30–32] A recent review highlighted that effective low-cost statin regimens (generic atorvastatin 40 mg daily costs around USD 2.6 per month) can reduce at least 2 mmol/L in patients with LDL-C of 4 mmol/L or above, and lowering by 2 mmol/L reduces CVD risks by 45%.[30] Weighing the benefits and risks of ABC factors based on current evidence, it appears that targeting lipid control should be prioritized if all 3 cannot be achieved.

Our findings were consistent with the results of the Steno-2 randomized clinical trial, which also concluded the crucial importance of multifactorial interventions for established risk factors in DM management.[12] Another recent study conducted in the United States demonstrated that diabetic patients achieving 1, 2, and all 3 ABC targets incrementally reduced CVD risk by 36%, 52%, and 62%, respectively, with similar associations observed in CHD risk.[9] A large population-based study also pointed out that 34.1%, 38.4%, 36.2%, and 29.3% of new onset of CVD, CHD, stroke, and heart failure events could be prevented with adequate control of risk factors in American diabetic patients.[10] Another simulation study projected that 38.3% of CHD events were prevented by controlling all risk factors by applying the United Kingdom Prospective Diabetes Study Risk Engine.[11] We found that patients with newly diagnosed DM received the greatest benefit from attaining all 3 ABC targets compared with those with suboptimal levels in all 3 ABC targets. Several previous studies also found that treatments were more effective for diabetic patients in an earlier disease stage, highlighting the importance of early optimal risk factor control to delay or reduce complications.[33–35]

Similar to other countries, it was observed that only a small proportion of Chinese diabetic patients achieve all 3 ABC targets. The local prevalence of 9% for 3-factor target control is slightly lower than rates reported in other countries, where 41% (27% for age <40), 14.3%, 12.0%, 6.5% in the United Kingdom, the United States, Canada, and 8 European countries, respectively, achieved 3-factor control. Clinical inertia has been postulated to be the main reason underlying the low prevalence of multitarget control. Clinical inertia refers to a failure or reluctance to initiate or intensify therapies when clinically indicated.[36,37] The causes for clinical inertia can be complex and multifactorial involving both clinician and patient barriers.[36,37] At the clinician level, barriers include time constraints for consultation, concern

about the potential risk of harm, and lack of information and training needed to achieve therapeutic goals. At the patient level, barriers include anxieties about side effects of treatments, difficulties with adhering to treatment regimens, costs of medications, and other factors that contribute to excessive treatment burden. Regardless of the reason, while risk factor control remains suboptimal there is an urgent need to understand how to best manage patients in a real-world setting where 3-factor control may be the goal but is often not feasible.

There were several strengths to this study. First, a comprehensive evaluation on the association between ABC targets and CVD with subgroup analyses was able to be performed because of the large population-based sample. Second, repeated measurements of ABC increased the reliability of the findings. Third, all data were extracted from a computerized administrative database, which helps assure data accuracy.

There were also several limitations. First, this was a retrospective cohort study, which can only provide associations but not causation. However, an identical conclusion was obtained in the sensitivity analysis, which minimized reverse causation. A further randomized clinical trial would be required to reappraise our results. Second, the clinical diagnosis of CVD depended on the ICPC-2 and International Classification of Diseases, Ninth Edition, Clinical Modification coding from the database, which might be subject to misclassification bias. While there were no studies to audit the accuracy and completeness of diagnostic coding in this database, previous studies demonstrated a nearly excellent data completeness for drug prescription (99.98%), and all clinicians are needed to provide accurate coding for each episode of care in routine clinical practice in the HA.[38,39] Third, the specific optimal targets for ABC levels in this study were selected based on the current local guidance for the management of DM in effect at the time of the subject included. Although some international guidelines changed the BP target from 130/80 to 140/90 mm Hg recently, there is currently no consensus among international guidelines on the optimal targets. Similar results in the sensitivity analyses after changing to less stringent treatment targets were also obtained. Fourth, lifestyle factors such as diet and exercise were not available in the current study, but most of key factors such as laboratory and drug data could reflect the lifestyle and disease severity. Last, the current cohort only comprised Chinese patients with local target protocols. An external validation should be warranted to validate our model by using a Chinese population in other regions.

In T2DM primary care patients, regardless of other patient characteristics, achieving more ABC targets incrementally reduced the risk of CVD. These findings support current recommendations that control of all 3 ABC factors to target

should be the ultimate goal for treatment. However, if it is not possible to achieve target control of all 3 parameters, efforts could be prioritized to achieving target LDL-C levels. Among all subgroups, patients with newly diagnosed DM received the most benefit from attaining target control of all 3 ABC factors. These findings highlight the importance of optimal control of multifactorial risk factors at an earlier disease stage, and the need to promote and educate clinicians and patients about the importance of target control of the modifiable risk factors for the primary prevention of CVD.

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Disclosures

None.

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Effect of Multifactorial Treatment Targets and Relative Importance of Hemoglobin A1c, Blood Pressure, and Low−Density Lipoprotein−Cholesterol on Cardiovascular Diseases in Chinese Primary Care Patients With Type 2 Diabetes Mellitus: A Population−Based Retrospective Cohort Study

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