

Effects of Treatment Targets on Subsequent Cardiovascular Events in Chinese Patients With Type 2 Diabetes

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OBJECTIVE — International guidelines recommend optimal control of risk factors in diabetes to prevent cardiovascular events. We examined risk associations between achieving treatment targets for glycemia, blood pressure and lipid control, and other risk factors on subsequent cardiovascular events in Chinese patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — Between 1995 and 2005, 6,386 Chinese type 2 diabetic patients without a history of coronary heart disease (CHD) or stroke were recruited. They were classified according to the number of treatment targets attained at baseline, and their cardiovascular outcomes were compared. Treatment targets were defined as A1C <7.0%, blood pressure <130/80 mmHg, and LDL cholesterol <2.6 mmol/l.

RESULTS — After a median follow-up of 5.7 years, cumulative incidence of CHD or stroke ($n = 749$) increased with decreasing numbers of treatment targets attained at baseline. Attainment of two or more targets at baseline was associated with reduced risk of CHD compared with those with no target achieved (hazard ratio 0.69 [95% CI 0.50–0.94], $P = 0.020$). However, the association lost its significance after adjustment for urinary albumin-to-creatinine ratio, estimated glomerular filtration rate, and hemoglobin.

CONCLUSIONS — Reaching more treatment targets was associated with reduced risk of new onset of CHD in Chinese patients with type 2 diabetes.

Diabetes Care 30:953–959, 2007

According to the World Health Organization, 5% of global deaths are directly attributable to diabetes (1). In India and China, 3 million people die from cardiovascular disease every year (2). More than 50% of these cardiovascular deaths were related to chronic diseases such as diabetes. Optimal control of blood glucose, blood pressure, blood lipids, and use of renin angiotensin system

blockers such as ACE inhibitors (ACEIs) or angiotensin-II receptor blockers (ARBs) reduce the risk of new onset of cardiovascular complications in type 2 diabetic patients (3–8).

Both international and regional guidelines recommend treatment targets for diabetes management. However, national audits reported low rates of adherence to monitoring processes and poor attain-

ment of these targets in diabetic patients (9,10). Apart from this chasm between evidence and practice, the impacts of failure to attain treatment targets on clinical outcomes in a nontrial setting remains uncertain. Against this background, we hypothesize that achieving treatment targets will be associated with a better cardiovascular outcome on long term follow-up.

In this observational study, we examined risk associations between attainment of treatment goals and other risk factors, as well as incident cardiovascular events in a consecutive cohort of Chinese type 2 diabetic patients without a history of coronary heart disease (CHD) or stroke at baseline.

RESEARCH DESIGN AND METHODS

Since 1995, diabetic patients attending medical clinics at the Prince of Wales Hospital can be referred to the Diabetes Centre for comprehensive assessment based on the European DIABCARE protocol (11). Once these patients have undergone assessments, their outcomes are monitored until time of death. The Prince of Wales Hospital is a regional hospital that serves a population of 1.2 million. The study has been approved by the Chinese University of Hong Kong Clinical Research Ethics Committee. Informed consent was obtained from all patients.

Figure 1 summarizes the number of patients recruited and reasons for exclusion in this analysis. From the original cohort of 7,920 patients, 6,386 with type 2 diabetes were included in the present analysis. Patients with type 1 diabetes ($n = 332$), defined as acute presentation with diabetic ketoacidosis, heavy ketonuria (more than three), or continuous requirement for insulin within 1 year of diagnosis (12), were excluded from the analysis. Five subjects with uncertain typing of diabetes, 49 non-Chinese subjects, and 792 subjects with CHD and/or stroke were also excluded.

Patients were stratified according to the number of targets achieved at enrollment: A1C <7.0%, blood pressure <130/80 mmHg, and LDL cholesterol <2.6 mmol/l (13). Linked by the Hong

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Received for publication 30 November 2006 and accepted in revised form 11 January 2007.

Published ahead of print at <http://care.diabetesjournals.org> on 26 January 2007. DOI: 10.2337/dc06-2443.

Abbreviations: ACEI, ACE inhibitor; ACR, albumin-to-creatinine ratio; ARB, angiotensin-II receptor blocker; CHD, coronary heart disease; GFR, glomerular filtration rate; IQR, interquartile range.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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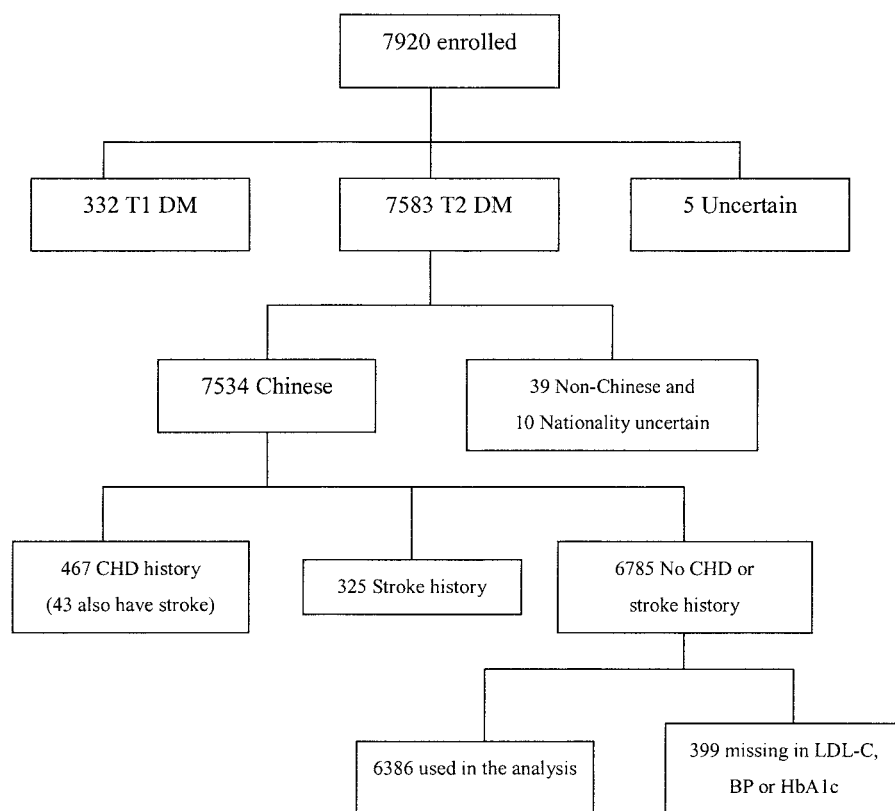


Figure 1—Study profile. Between 1995 and 2005, 7,920 diabetic patients were recruited consecutively for comprehensive assessment. Among them, 7,585 had type 2 diabetes (T2DM), 332 had type 1 diabetes (T1DM), and 5 had uncertain disease classification; 49 had non-Chinese or uncertain ethnicity, 467 had a history of CHD, and 325 had a history of stroke (including 43 having both); and 399 had missing data in LDL cholesterol (LDL-C), blood pressure (BP), or A1C. After excluding these subjects, 6,386 were included in the analysis with data censored by 31 July 2005.

Kong Identity Card number, the Hospital Authority Central Computer System and Hong Kong Death Registry were used to retrieve causes of hospital admissions and death, censored on 31 July 2005. Cardiovascular event was defined as CHD and/or stroke. Using the ICD-9 codes, CHD was defined as first incidence of 1) acute myocardial infarction (code 410) and coronary death (codes 410, 411–414, and 428), 2) nonfatal ischemic heart disease (codes 411–414), 3) nonfatal heart failure (code 428), and 4) coronary revascularization (procedure code 36) and percutaneous transluminal coronary angioplasty or coronary atherectomy (procedure code 00.66). Stroke was defined as first incidence of stroke (codes 430–434 and 436) or death from stroke (codes 430–438). Diabetic nephropathy was defined as diabetes with 1) fatal and nonfatal renal manifestations (code 250.4), chronic kidney disease (code 585), or unspecified renal failure (code 586) and 2) dialysis (ICD-9 procedure

code 39.95) or peritoneal dialysis (ICD-9 procedure code 54.98). Cancer was defined as first incident cancer or death due to cancer (codes 140–149, 150–159, 160–165, 170–176, 179–189, 190–199, and 200–208).

Clinical measurements

Details of assessment methods and definitions have been previously described (14,15). Measured parameters include BMI, waist circumference, sitting blood pressure (after 5 min of rest using Dinamapp machine), and visual acuity. Fundoscopy through dilated pupils and foot examination using monofilament and graduated tuning fork were performed by trained personnel. Retinopathy was defined as typical changes due to diabetes or a history of vitrectomy or laser therapy. Sensory neuropathy was defined by any two of three findings: 1) typical symptoms affecting the extremities, 2) graduated tuning fork <4/8 for subjects aged ≥ 65 years or <6/8 for subjects aged <65 years, and 3) reduced sensation to mono-

filament in any part of the sole or dorsum of the feet with normal skin. Peripheral arterial disease was defined by an ankle-to-brachial ratio <0.90 as detected by Doppler ultrasound examination.

Fasting blood was taken for measurement of plasma glucose, lipids (total cholesterol, HDL cholesterol, and triglycerides), renal and liver function, complete blood count, and A1C. A random spot urinary albumin-to-creatinine ratio (ACR) was measured after exclusion of urinary tract infection, followed by a timed collection (4 or 24 h) for albumin excretion rate. Using ACR from these two samples, normoalbuminuria was defined as a mean ACR <3.5 mg/mmol. Microalbuminuria was defined as ACR ≥ 3.5 mg/mmol and macroalbuminuria as ≥ 25 mg/mmol. Glomerular filtration rate (GFR) was estimated using the abbreviated Modification of Diet in Renal Disease formula: estimated GFR = $186 \times [\text{SCR} \times 0.011] - 1.154 \times [\text{age}] - 0.203 \times [0.742 \text{ if female}]$, where SCR is serum creatinine expressed as $\mu\text{mol/l}$ (original mg/dl converted to $\mu\text{mol/l}$) (16,17).

Laboratory assays

Complete blood picture was measured using an automated cell counter (GEN-S; Beckman Coulter, Miami, FL). Plasma glucose was measured by a hexokinase method (Hitachi 911 automated analyzer; Boehringer Mannheim, Mannheim, Germany). A1C was measured by an automated ion-exchange chromatographic method (Bio-Rad Laboratory, Hercules, CA) (reference range 5.1–6.4%). Inter- and intra-assay coefficient of variation (CV) for A1C was $\leq 3.1\%$ at values <6.5%. Total cholesterol, triglycerides, and HDL cholesterol were measured by enzymatic methods on a Hitachi 911 automated analyzer (Boehringer Mannheim) using reagent kits supplied by the manufacturer of the analyzer. LDL cholesterol was calculated by Friedewald's equation (18). The precision performance of these assays was within the manufacturer's specifications. Urinary creatinine (Jaffe's kinetic method) and albumin (immunoturbidimetry) were also measured using a Hitachi 911 analyzer and reagent kits supplied by the manufacturer. The interassay precision CV was 12.0% and 2.3% for urinary albumin concentrations of 8.0 and 68.8 mg/l, respectively. The lowest detection limit was 3.0 mg/l. Serum creatinine (Jaffe's kinetic method)

Table 1—Clinical profile, patterns of drug use, and clinical end points in 6,386 Chinese type 2 diabetic patients without a history of CHD or stroke divided according to number of attained treatment targets at baseline

	Targets achieved			P
	2–3	1	0	
n	1,970	2,618	1,798	
Baseline profiles				
Male sex	45.5	45.7	43.1	0.142*
Age (years)	52.3 ± 0.3	56.6 ± 0.3	58.8 ± 0.3	0.023†
Duration of diabetes (years)	5.5 ± 0.1	6.8 ± 0.1	8.2 ± 0.2	<0.001†
Current smoker	21.1	19.8	20.9	0.847*
Ex-smoker	12.4	13.3	14.0	0.152*
Sensory neuropathy	21.5	25.3	29.9	<0.001*
Retinopathy	17.5	26.2	34.9	<0.001*
Peripheral arterial disease	3.4	5.7	7.4	<0.001*
BMI (kg/m ²)	24.6 ± 0.1	25.2 ± 0.1‡	25.4 ± 0.1‡	<0.001†
Waist circumference (cm)	83.9 ± 0.2	86.0 ± 0.2	87.4 ± 0.2	<0.001†
Systolic BP (mmHg)	123 ± 0.4	136 ± 0.4	146 ± 0.4	<0.001†
Diastolic BP (mmHg)	71 ± 0.2	76 ± 0.2	83 ± 0.2	<0.001†
A1C (%)	6.60 ± 0.04	7.65 ± 0.03	8.01 ± 0.04	<0.001†
Total cholesterol (mmol/l)	4.58 ± 0.02	5.35 ± 0.02	5.81 ± 0.02	<0.001†
Triglyceride (mmol/l)	1.14 (0.89)	1.38 (0.98)	1.51 (1.06)	<0.001§
HDL cholesterol (mmol/l)	1.30 (0.46)	1.25 (0.44)	1.24 (0.42)	<0.001§
LDL cholesterol (mmol/l)	2.75 ± 0.03	3.33 ± 0.02	3.70 ± 0.02	<0.001†
ACR (mg/mmol/l)	1.11 (3.43)	1.83 (8.01)	3.71 (21.17)	<0.001§
eGFR (ml/min per 1.73m ²)	90.8 ± 3.2‡	91.1 ± 2.7‡	85.3 ± 3.3‡	0.347†
With eGFR <60	12.2	16.4	19.0	<0.001*
Hemoglobin (g/dl)	13.5 ± 0.0	13.8 ± 0	14.1 ± 0	<0.001*
Diet treatment	16.5	10.0	4.9	<0.001*
Oral antidiabetes drugs	55.4	60.9	64.9	<0.001*
Insulin	12.7	17.5	20.9	<0.001*
Antihypertensive drugs	26.6	34.1	34.6	<0.001*
ACEIs or ARBs	16.5	19.8	21.5	<0.001*
Use of LLD	12.1	11.6	10.1	0.047*
End points				
CHD	4.1	7.9	10.7	<0.001*
Stroke	2.9	4.9	6.8	<0.001*
Diabetic nephropathy	4.3	9.7	13.9	<0.001*
Cancer	5.0	5.8	5.2	0.759*
All-cause death	7.0	9.1	11.5	<0.001*

Data are percent, mean ± SE, or median (IQR). *Mantel-Haenszel χ^2 . †Derived from ANOVA, and P values are for trend. ‡Two means with ‡ are not significant at 5% of level, using Bonferroni test for multiple comparisons and all other pairwise comparisons of means are significant at 5% of level. §Derived from Kruskal-Wallis test, and no multiple comparison made. BP, blood pressure; eGFR, estimated GFR; LLD, lipid-lowering drugs.

was measured on a Dimension AR system (Dade Behring, Deerfield, IL), which is compatible with the Modification of Diet in Renal Disease methodology. All laboratory assays were performed in the Department of Chemical Pathology, which is externally accredited by the Australian Quality Assurance Program.

Statistical analyses

All analyses were performed using SAS release 9.10 (SAS Institute, Cary, NC). All data were expressed as means ± SD or median (interquartile range [IQR]) or percentages, as appropriate. HDL cholesterol, triglycerides, and ACR were loga-

rithmically transformed due to skewed distributions. Mantel-Haenszel χ^2 test was used to test trend of rates among the four groups (0, 1, 2, and 3 targets). A general linear model was used to perform unbalanced ANOVA and to compare mean values among the four groups, adjusted by Bonferroni's test for post hoc multiple comparisons. In the case of logarithmically transformed variables, the Kruskal-Wallis was used to test the difference among the four groups with medians plus IQR reported. The Cox proportional hazard regression was used to obtain hazard ratios (HRs) and 95% CIs for effects of composite targets achieved and individ-

ual targets achieved on incident CHD, stroke, diabetic nephropathy, cancer, total death, cardiovascular disease (i.e., CHD and/or stroke)-specific death, and cancer-specific death, using three adjustment schemes: 1) age and sex; 2) age, sex, duration of diabetes, BMI, waist circumference, \log_{10} (triglycerides), \log_{10} (HDL cholesterol), current smoker, ex-smoker, peripheral arterial disease, neuropathy, retinopathy, and treatment profile at baseline, including diet (received dietary reinforcement from dietitians: yes = 1, no = 0), oral antidiabetes drugs, antihypertensive drugs, ACEIs/ARBs, and lipid-lowering drugs; and 3) all of the above

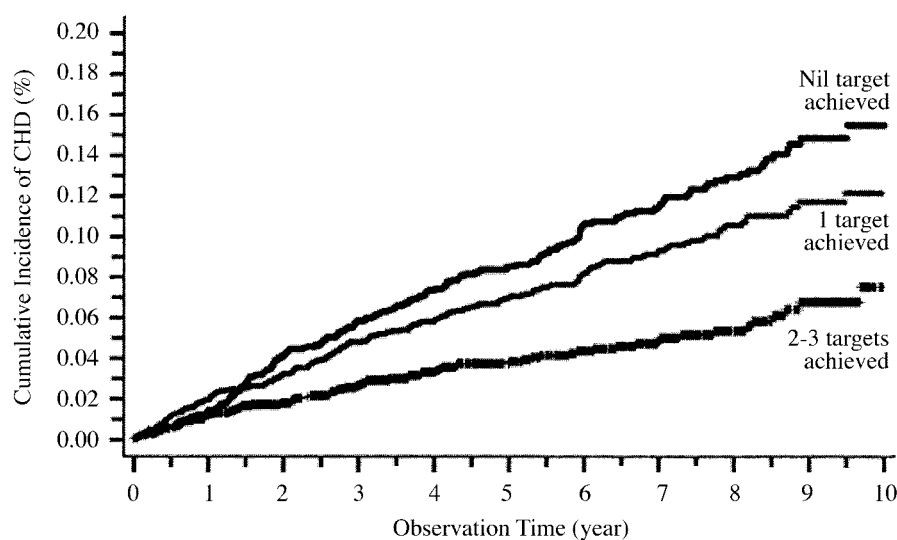


Figure 2—Cumulative incidence of CHD or stroke stratified by the number of targets achieved at baseline in Chinese type 2 diabetic patients. The curves from top to bottom: nil target achieved, one target achieved, two targets achieved, and three targets achieved. *P* value for log-rank test <0.0001.

variables plus blood hemoglobin, \log_{10} (ACR), and estimated GFR. In the analysis using the Cox regression, only those whose time-to-event was at least 1 year were used.

Kaplan Meier estimator is not valid in the presence of competing risk, i.e., deaths not due to cardiovascular diseases (19). Hence, the cumulative incidences of cardiovascular diseases in different groups were calculated to indicate the probability of the end point over time as described by Gooley et al. (19). A *P* value <0.05 (two tailed) was considered statistically significant.

RESULTS— The median age of the cohort was 56 years (IQR 46–67), and the median duration of disease was 5 years (1–10). The median follow-up period was 5.70 years (3.04–7.94; by death or censoring date). Table 1 summarizes their baseline characteristics. At the time of enrollment, 30.9% had attained two or three targets (6.3% attained all three targets), while 28.2% did not attain any target, 36.7% reached the blood pressure goal, 28.6% reached the LDL cholesterol goal, and 43.7% reached the A1C goal.

Failure to attain treatment targets at baseline was associated with older age, longer disease duration, higher BMI and waist circumference, more microvascular complications, and peripheral arterial disease (Table 1). In the prospective analysis, the more treatment targets achieved at baseline, the lower the incidence of clinical end points including CHD,

stroke, diabetic nephropathy, and all-cause deaths (Table 1). Figure 2 shows the probability of CHD with decreasing numbers of attained treatment targets at baseline (*P* < 0.001).

During this follow-up period, 7.53% (*n* = 481; HR 14.08 [95% CI 12.83–15.33]) per 1,000 person-years developed CHD and 4.81% (*n* = 307; 8.88 [7.89–9.87] per 1,000 person-years) developed stroke. Excluding those with GFR <60 ml/min per 1.73 m² and missing data, 4.73% (*n* = 254; 8.38 [7.35–9.41] per 1,000 person-years) developed diabetic nephropathy and 4.85% (*n* = 303; 8.82 [7.83–9.81] per 1,000 person-years) developed cancer. There were a total of 580 deaths (16.43 [15.10–17.76] per 1,000 person-years).

After adjustment for potential confounding factors, including age, sex, duration of diabetes, smoking status, BMI, waist circumference, triglyceride and HDL cholesterol levels, baseline peripheral arterial disease, microvascular complications, and treatment modalities, attainment of two or three treatment targets at enrollment was significantly associated with lower risk of developing CHD compared with those with no target achieved (Table 2). Development of stroke was not associated with number of treatment targets.

The risk association of CHD with treatment targets was attenuated after adjustment for renal parameters including urinary ACR, estimated GFR, and hemoglobin. Higher urinary ACR, lower hemo-

globin, and estimated GFR were all significantly associated with increased risk of incident CHD. Higher urinary ACR was also predictive of stroke (Table 2).

For individual treatment goals, stroke was predicted by reaching A1C goal, while CHD was predicted by reaching blood pressure and A1C goals after adjustment for age and sex. These effects were attenuated after adjustment of other potential confounding factors (Table 2).

CONCLUSIONS— The results of this study highlight the importance of achieving recommended treatment targets in predicting subsequent development of CHD in type 2 diabetes. These beneficial effects might be in part mediated through renal function as evidenced by the prognostic significance of urinary ACR, estimated GFR, and hemoglobin at baseline. Higher urinary ACR level was associated with a nearly twofold increased risk of CHD. Compared with Caucasian counterparts, Asian diabetic subjects have high prevalence of albuminuria for similar duration of disease and risk factor control (20). Albuminuria is now recognized as a renal expression of endothelial dysfunction and a powerful risk factor for atherosclerosis and cardiovascular events (21–23). In the natural clinical course of diabetic nephropathy, microalbuminuria precedes the decline in GFR. Both albuminuria and reduced GFR are independently associated with increased occurrence of micro- and macrovascular complications in diabetic patients (14).

Anemia is now increasingly recognized as a risk factor for development of CHD in diabetic populations (24). Chronic kidney disease-associated anemia can lead to increased cardiac output, maladaptive left ventricular hypertrophy, and increased cardiovascular risk (24–27). In a separate analysis of a subset of this registry, blood hemoglobin even within the normal range was found to be an independent predictor for CHD in a stepwise manner (28). These results were replicated in this expanded dataset emphasizing the importance of monitoring blood hemoglobin in diabetes management. There are now ongoing studies to examine the effects of correcting anemia on cardiovascular outcomes in patients with diabetes (29).

Randomized controlled trials have confirmed the importance of optimal glycemic, blood pressure, and lipid control in improving the outcome of di-

Table 2—Risk association of treatment targets (A1C <7.0%, blood pressure <130/80 mmHg, and LDL cholesterol <2.6 mmol/l) and CHD and stroke expressed as HRs in Hong Kong Chinese type 2 diabetic patients after a median follow-up period of 5.7 years

	CHD*		Stroke*	
	HR (95% CI)	P	HR (95% CI)	P
Composite target, model 1†				
2–3 targets achieved	0.54 (0.40–0.74)	<0.001	0.80 (0.56–1.14)	0.208
1 target achieved	0.79 (0.63–0.98)	0.034	0.90 (0.69–1.19)	0.476
Composite target, model 2‡				
2–3 targets achieved	0.69 (0.50–0.94)	0.020	0.93 (0.64–1.34)	0.689
1 target achieved	0.88 (0.70–1.10)	0.261	0.98 (0.74–1.31)	0.913
Composite target, model 3§				
2–3 targets achieved	0.83 (0.57–1.20)	0.324	0.98 (0.62–1.53)	0.918
1 target achieved	1.08 (0.83–1.40)	0.586	0.90 (0.64–1.26)	0.533
Hemoglobin (g/dl)	0.87 (0.79–0.94)	0.001	0.97 (0.87–1.08)	0.579
Log10 (ACR) (mg/mmol)	1.77 (1.51–2.08)	<0.001	1.46 (1.20–1.77)	0.001
GFR (per 10 ml/min per 1.73 m ²)	0.92 (0.87–0.98)	0.010	1.00 (0.98–1.02)	0.981
Individual target, model 1†				
LDL cholesterol target achieved	0.87 (0.67–1.12)	0.273	1.08 (0.80–1.45)	0.628
A1C achieved	0.74 (0.60–0.92)	0.006	0.76 (0.58–0.99)	0.040
Blood pressure target achieved	0.65 (0.50–0.84)	0.001	0.90 (0.67–1.21)	0.495
Individual target, model 2‡				
LDL cholesterol target achieved	0.84 (0.64–1.09)	0.178	1.05 (0.77–1.42)	0.760
A1C achieved	0.70 (0.69–1.11)	0.284	0.83 (0.63–1.10)	0.194
Blood pressure target achieved	0.75 (0.58–0.98)	0.034	1.00 (0.74–1.37)	0.977
Individual target, model 3§				
LDL cholesterol target achieved	0.95 (0.71–1.28)	0.754	1.05 (0.72–1.53)	0.798
A1C achieved	0.83 (0.64–1.08)	0.173	0.77 (0.56–1.08)	0.133
Blood pressure target achieved	0.98 (0.73–1.32)	0.891	1.12 (0.78–1.61)	0.548

*Those with follow-up time <1.0 year were respectively excluded. †Model 1, adjusted for age and sex. ‡Model 2, adjusted for age, sex, disease duration, BMI, waist circumference, log₁₀ (triglyceride), log₁₀ (HDL cholesterol), current smoker, ex-smoker, peripheral arterial diseases, neuropathy, retinopathy, diet, oral antidiabetes drugs, antihypertensive drugs, ACEIs/ARBs, and lipid-lowering drugs and use of insulin at baseline. §Model 3, adjusted for above variables plus hemoglobin, log₁₀ (ACR), and GFR.

abetic patients. However, the impact of failure to attain these treatment targets has not been addressed in a “nontrial” real-life situation. Our study shows that achieving treatment targets at baseline was associated with subsequent reduced risk of CHD in a dose-dependent manner. As for individual treatment goals, both blood pressure and A1C targets and albuminuria had prognostic values. These findings corroborate with the beneficial effects of multifaceted management on clinical outcomes in patients with diabetes (30–32).

In contrast to Caucasians in whom 80% of deaths were claimed to be due to cardiovascular diseases (World Health Organization Multinational Study of Vascular Disease in Diabetes) (33), in this analysis, end-stage renal disease, stroke, and cancers take on similar proportions as causes of death. In this respect, it is now accepted that Asian diabetic patients have higher risk for renal complications than Caucasians (34,35), while with increased survival due to better management of

acute cardiovascular complications being reported worldwide, other causes such as malignancy may then take on more important roles as causes of death in these patients with multiple comorbidities.

Several limitations in this study need to be acknowledged. First, interventions and changes in glycemic, blood pressure, and lipid control after enrollment were not assessed. Many of these patients were prescribed medications after enrollment to improve their metabolic control and risk factors (e.g., ACEIs, ARBs, or lipid-lowering drugs). This might explain the attenuated effect of treatment targets in predicting CHD after adjustments of confounders. However, albuminuria, GFR, and hemoglobin remain predictive of future CHD. In addition, albuminuria also predicts subsequent development of stroke. These findings highlight the importance of early prevention of occurrence of albuminuria, decline of GFR, and subclinical fall in hemoglobin. Second, this study was hospital based. However, the lack of a comprehensive health insur-

ance policy and integrated primary health care system in Hong Kong leads to the majority of patients, especially those with chronic illnesses, being managed in public hospitals. This is supported by the observation of similar mortality rates in this cohort compared with other studies. The annualized mortality rate of 16.43 per 1,000 person-years and 14.08 per 1,000 person-years incident CHD event rate in our study are similar to figures reported in several community- or hospital-based databases (33,34). Third, some patients might have died or been hospitalized outside Hong Kong. However, such numbers are likely to be few due to the heavily subsidized health care system in Hong Kong and the reduced emigration flux from the mid-1990s.

In conclusion, in a nonclinical trial setting, the number of recommended treatment goals carried prognostic significance in a stepwise manner in predicting CHD. This was in part explained by their effects on renal function. Taken together, type 2 diabetic patients with albuminuria,

reduced renal function, and low blood hemoglobin, even in the subclinical stage, were at risk for developing CHD. Our findings highlight the importance of achieving treatment goals and periodic monitoring of renal parameters for prevention and intensified therapy.

Acknowledgments—This work was partially funded by the Li Ka Shing Institute of Health Sciences and the Hong Kong Foundation for Research and Development in Diabetes established under the auspices of The Chinese University of Hong Kong.

We thank all medical and nursing staff at the Diabetes Mellitus and Endocrine Centre, the Prince of Wales Hospital, for their commitment and dedication in implementing the structured diabetes care protocol and its continuous quality improvement.

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