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.

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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 attainment 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 orginal 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 enrolment: A1C <7.0%, blood pressure <130/80 mmHg, and LDL cholesterol <2.6 mmol/l (13). Linked by the Hong

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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.

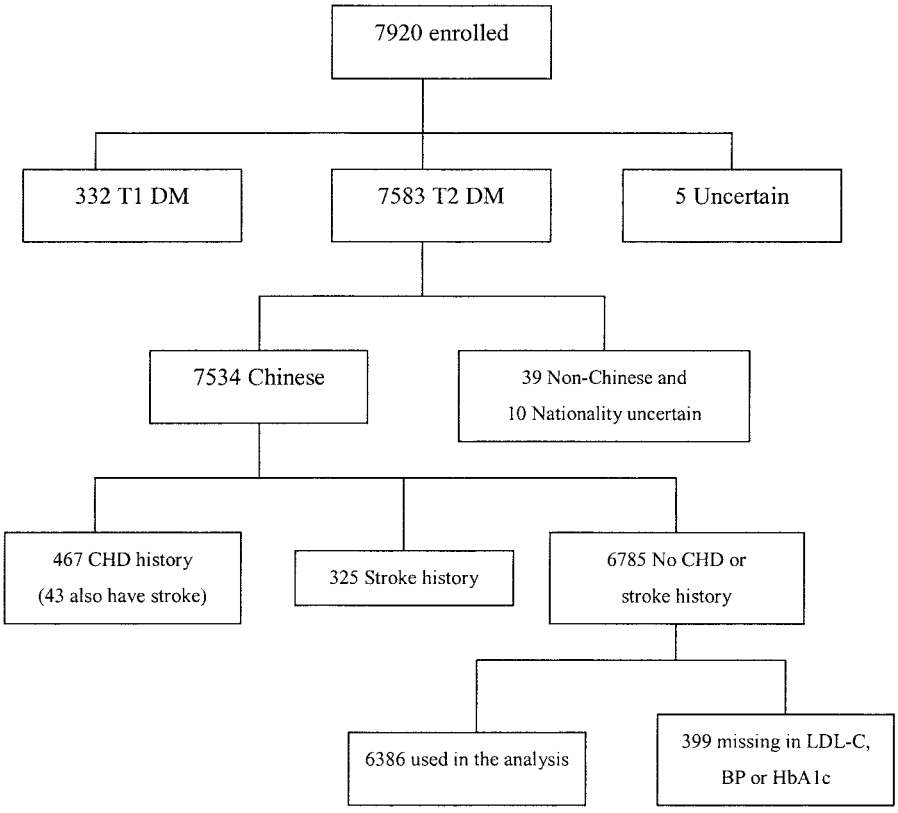

Figure 1—*Study profile. Between 1995 and 2005, 7,920 diabetic patients were recruited consecutively for comprehensive assessment. Among them, 7,585 had type 2 diabetes (T2DM), 332 had type 1 diabetes (T1DM), and 5 had uncertain disease classification; 49 had non-Chinese or uncertain ethnicity, 467 had 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 monofilament 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. Microalbminuria 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 μmol/l (original mg/dl converted to μmol/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; Boerhringer 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			
	2–3	1	0	*P*
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 logarithmically 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 individual 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

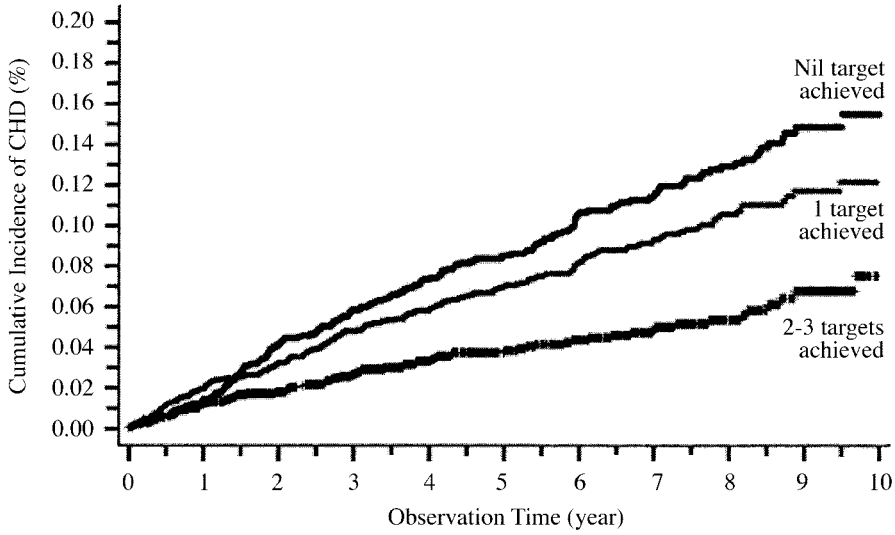

Figure 2—*Cumulative incidence of CHD or stroke stratified by the number of targets achieved at baseline in Chinese type 2 diabetic patients. The curves from top to bottom: nil target achieved, one target achieved, two targets achieved, and three targets achieved.* P *value for log-rank test <0.0001.*

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 m^2 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 hemoglobin, 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 benefical 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, $\log_{10}$ (triglyceride), $\log_{10}$ (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, $\log_{10}$ (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 Cacuasians 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 insurance 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.

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References

1. Roglic G, Unwin N, Bennett PH, Mathers C, Tuomilehto J, Nag S, Connolly V, King H: The burden of mortality attributable to diabetes: realistic estimates for the year 2000. *Diabetes Care* 28:2130–2135, 2005
2. Yach D, Leeder SR, Bell J, Kistnasamy B: Global chronic diseases. *Science* 307:317, 2005
3. UKPDS: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS38). *BMJ* 317:703–713, 1998
4. Collins R, Armitage J, Parish S, Sleigh P, Peto R: MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *Lancet* 361: 2005–2016, 2003
5. Brenner BM, Cooper ME, De Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G, Snapinn SM, Zhang Z, Shahinfar S, the RENAAL Study Investigators: Effects of Losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
6. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 348:383–393, 2003
7. UKPDS: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
8. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, Thomason MJ, Mackness MI, Charlton-Menys V, Fuller JH, the CARDS Investigators: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 364:685–696, 2004
9. Parris ES, Lawrence DB, Mohn LA, Long LB: Adherence to statin therapy and LDL cholesterol goal attainment by patients with diabetes and dyslipidemia. *Diabetes Care* 28:595–599, 2004
10. Saaddine JB, Engelgau MM, Beckes GL, Gregg ED, Thompson TJ, Narayan KMV: A diabetes report card for the United States: quality of care in the 1990s. *Ann Intern Med* 136:565–574, 2002
11. Piwernetz K, Home PD, Snorgaard O, Antsiferov M, Staehr-Johansen K, Krans M: Monitoring the targets of the St Vincent Declaration and the implementation of quality management in diabetes care: the DIABCARE initiative: the DIABCARE Monitoring Group of the St Vincent Declaration Steering Committee. *Diabet Med* 10:371–377, 1993
12. Laakso M, Pyorala K: Age of onset and type of diabetes. *Diabetes Care* 8:114–117, 1985
13. American Diabetes Association: Clinical practice recommendation. *Diabetes Care* 28 (Suppl. 1):S1–S79, 2005
14. Kong AP, So WY, Szeto CC, Chan NN, Luk A, Ma RC, Ozaki R, Ng VW, Ho CS, Lam CW, Chow CC, Cockram CS, Chan JC, Tong PC: Assessment of glomerular filtration rate in addition to albuminuria is important in managing type II diabetes. *Kidney Int* 69:383–387, 2006
15. So WY, Ozaki R, Chan NN, Tong PC, Ho CS, Lam CW, Ko GT, Chow CC, Chan WB, Ma RC, Chan JC: Effect of angiotensin-converting enzyme inhibition on survival in 3773 Chinese type 2 diabetic patients. *Hypertension* 44:294–299, 2004
16. Levey AS, Greene T, Kusek JW, Beck GJ: A simplified equation to predict glomerular filtration rate from serum creatinine (Abstract). *J Am Soc Nephrol* 11:A0828, 2000
17. Kidney Disease Outcomes Quality Initiative (KDOQI): KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcomes Quality Initiative. *Am J Kidney Dis* 39:S1–S246, 2002
18. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 18:499–502, 1972
19. Gooley TA, Leisenring W, Crowley J, Storer BE: Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 18:695–706, 1999
20. Wu AY, Kong NC, de Leon FA, Pan CY, Tai TY, Yeung VT, Yoo SJ, Rouillon A, Weir MR: An alarmingly high prevalence of diabetic nephropathy in Asian type 2 diabetic patients: the MicroAlbuminuria Prevalence (MAP) study. *Diabetologia* 48: 17–26, 2005
21. Dinneen SF, Gerstein HC: The association of microalbuminuria and mortality in NIDDM. *Arch Intern Med* 257:1413–1418, 1997
22. Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, Schroll M, Jensen JS: Urinary albumin excretion: an independent predictor of ishemic heart disease. *Arterioscler Thromb Vasc Biol* 19:1992–1997, 1999
23. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A: Albuminuria reflects widespread vascular damage: the Steno hypothesis. *Diabetologia* 32:219–226, 1989
24. Vlagopoulos PT, Tighiouart H, Weiner DE, Griffith J, Pettitt D, Salem DN, Levey AS, Sarnak MJ: Anemia as a risk factor for cardiovascular disease and all-cause mortality in diabetes: the impact of chronic kidney disease. *J Am Soc Nephrol* 16: 3403–3410, 2005
25. Foley R: Anaemia and the heart: what's new in 2003? *Nephrol Dial Transplant* 18 (Suppl. 8):viii13–viii16, 2003
26. Anand IS, Chandrashekhar Y, Ferrari R, Poole-Wilson PA, Harris PC: Pathogenesis of oedema in chronic severe anaemia: studies of body water and sodium, renal function, haemodynamic variables, and plasma hormones. *Br Heart J* 70:357–362, 1993
27. Wang AY, Wang M, Woo J, Lam CW, Lui SF, Li PK, Sanderson JE: Inflammation, residual kidney function, and cardiac hypertrophy are interrelated and combine adversely to enhance mortality and cardiovascular death risk of peritoneal dialysis patients. *J Am Soc Nephrol* 15:2186–2194, 2004
28. Tong PC, Kong AP, So WY, Ng MH, Yang X, Ng MC, Ma RC, Ho CS, Lam CW, Chow CC, Cockram CS, Chan JC: Hematocrit, independent of chronic kidney disease, predicts adverse cardiovascular outcomes in chinese patients with type 2 diabetes. *Diabetes Care* 29:2439–2444, 2006
29. Thomas MC, Cooper ME, Rossing K, Parving HH: Anaemia in diabetes: is there a rationale to TREAT? *Diabetologia* 49: 1151–1157, 2006
30. Gaede P, Vedel P, Parving H-H, Pedersen O: Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* 353:617–622, 1999
31. Leung WY, So WY, Tong PC, Chan NN, Chan JC: Effects of structured care by a pharmacist-diabetes specialist team in patients with type 2 diabetic nephropathy. *Am J Med* 118:1414, 2005

32. So WY, Tong PC, Ko GT, Leung WY, Chow CC, Yeung VT, Chan WB, Critchley JA, Cockram CS, Chan JC: Effects of protocol-driven care versus usual outpatient clinic care on survival rates in patients with type 2 diabetes. *Am J Manag Care* 9:606–615, 2003
33. Morrish NJ, Wang SL, Stevens LK, Fuller JH, Keen H: Mortality and causes of death in the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 44 (Suppl. 2):S14–S21, 2001
34. Fuller JH, Stevens LK, Wang SL: Risk factors for cardiovascular mortality and morbidity: the WHO Multinational Study of Vascular Disease in Diabetes. *Diabetologia* 44 (Suppl. 2):S54–S64, 2001
35. Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV: Ethnic disparities in diabetic complications in an insured population. *JAMA* 287:2519–2527, 2002