Macrovascular and Microvascular Disease in Obese Patients with Type 2 Diabetes Attending Structured Diabetes Education Program: A Population-based Propensity-matched Cohort Analysis of Patient Empowerment Programme (PEP)

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Running title: PEP was effective in Diabesity

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Abstract

Patient Empowerment Programme (PEP) in primary care was effective in preventing diabetes-related complications in patients with diabetes. Nevertheless, the effect of PEP on glycaemic control, weight control, and complications was unclear in obese type 2 diabetic patients. We aimed to assess whether PEP reduced all-cause mortality, first macrovascular and microvascular disease events. A cohort of 6,372 obese type 2 diabetic patients without prior occurrence of macrovascular or microvascular disease events on or before baseline study recruitment date was linked to the administrative database from 2008 to 2013. Non-PEP participants were matched one-to-one with the PEP participants using propensity score method with respect to their baseline covariates. Cox proportional hazard regressions were performed to estimate the associations of the PEP intervention with the occurrence of first macrovascular or microvascular disease events and death from any cause, controlling for demographic and clinical characteristics. During a median 31.5 months of follow-up, 350 (PEP/non-PEP: 151/199) patients suffered from a first macrovascular or microvascular disease event while 93 patients (PEP/non-PEP: 34/61) died from any cause. After adjusting for confounding variables, PEP participants had lower incidence rates of all-cause mortality (hazard ratio (HR): 0.589, 95% confidence interval (CI) 0.380-0.915, P=0.018) and first macrovascular or microvascular disease events (HR: 0.782, 95% CI 0.632-0.968, P=0.024) than those with PEP. Enrolment to PEP was an effective approach in reducing all-cause mortality and first macrovascular or microvascular disease events in obese patients with type 2 diabetes.

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Manuscript Text

Introduction

Type 2 diabetes mellitus (T2DM) and obesity are evolving pandemics that had increased risk of developing comorbidities and complications, and thus imposed major health and economic burden to health care system worldwide [1]. Since 1970s, the term 'diabesity' has coined to describe the individuals with co-occurrence of diabetes and obesity, in which they had pathogenic inter-relationship [2]. Obesity confers one of the major risk factors of T2DM [3] and diabetes-related complications including macro- and microvascular diseases [4]. Nowadays, the vast majority of T2DM patients reported to be obese in the US where obesity was highly prevalent [5].

There were much evidence for the benefits of modest weight loss, equivalent to 5-10% loss of total body weight, in obese patients with T2DM[6,7]. Despite well-established benefits of weight loss, controversies are being focused on the optimal approaches for achieving treatment goals of weight management. Towards the means of effective management of obese T2DM patients, narrative reviews [2,6] have consolidated a broad range of therapeutic approaches including surgical approach via bariatric surgery, pharmacologic approach via anti-obesity and incretin-based anti-diabetic medications, and non-surgical-pharmacologic approach via intensive lifestyle modification. Still, conventional approach of community-based education and support in promoting healthy lifestyle and behavioural changes is one of the key strategies for improving the standard of diabetes care in primary care setting [8].

Currently, structured self-management education provides one of the most reliable pathways to sustained empowerment and healthy behavioural changes in diabetic patients managing their own condition[9]. Clinical benefit of structured diabetes education program delivered in a group or individual basis has been confirmed in systematic reviews [10-13] and meta-analyses [14-16], and resulted in significant improvements in weight control, glycemic control and cardiovascular risk factor control. Although the explicit changes in body weight after structured diabetes education have been well recognized in clinical trials, whether structured education would be associated with modest weight loss and a lower risk of macrovascular and microvascular complications remains questionable in 'real-world' setting.

Notably, recent studies [17-21] examined the effects on glycemic control, quality of life and incidence of cardiovascular events and microvascular events of structured diabetes education program, Patient Empowerment Programme (PEP), versus the usual clinical practice in primary care setting. As yet, no randomised controlled trials, or population-based observational cohort studies have been conducted to investigate the effect of structured education on weight control, diabetes-related complications in diabesity patients. Furthermore, diabesity patients who enrolled to PEP have access to additional weight management program with exercise and nutrition empowerment sessions offered by trained dietitians and physiotherapists. Nevertheless, no prior studies explored the effect of dual program use on the diabesity patients, in which the effectiveness may be strengthened or hampered.

The main aim of this study was to test in a population-based propensity-matched cohort study on whether this structured diabetes education program in primary care promoted greater benefits on metabolic control and reduced macro- and microvascular diseases in patients with diabesity. The exploratory aim was to evaluate whether weight management program would improve macro- and microvascular diseases among diabesity patients who have attended PEP. We hypothesized that diabesity patients with PEP attendance were more effective than those without, and dual use of PEP and weight management program yielded additional benefits when compared to standalone participation of PEP.

Methods

In 2010, the Hong Kong Hospital Authority has launched the Patient Empowerment Programme (PEP) which provided tertiary wide primary care service to the patients. PEP is a structured education programme which aims to enhance the quality of chronic disease management, to equip participants with the knowledge, skills and self-awareness of their own disease condition and to promote autonomous self-regulation to maximise their potential for health and well-being. Through structural health education including skill transfer, self-efficacy enhancement, mutual support groups, targeted treatment plan and weight management, participants' lifestyle modification and risk factor management could be enhanced effectively. Several medical experts in the non-government organisations organised 6-7 PEP sessions (2 disease-specific sessions and 4-5 generic sessions) on structural health education, disease-specific knowledge and lifestyle modification and post-

program follow-ups to enhance and maintain the participants' self-management. The total contact time of disease-specific and generic sessions is 8-10 hours (2 hours per session) and 5 hours (2.5 hours per session), respectively. Disease-specific components were delivered by experienced nurses through lecture-based learning sessions covering comprehensive information about diabetes, responsibility of self-care management, medications in diabetes control, and contingency management on hypo- and hyper-glycaemia. Each generic component session covers the importance of self-management and behaviour modification, healthy diet and regular exercise goal setting and problem-solving skills, sharing on self-monitoring experience, stress coping management, psychosocial support and networking, and communications with healthcare professionals. A detailed PEP setting and mode of education delivery has been described in the previous study[17-21]. This study included patients attended at least one session of PEP dated between 1 March, 2010 and 30 June, 2012.

Subjects

All patients with T2DM were sampled from a population-based cohort of patients attended the general outpatient clinics in Hong Kong Hospital Authority, the largest public health service provider in Hong Kong. The outcome evaluation included all obese patients (Body mass index $\geq$ 27.5 kg/m^2 [22] at baseline) with T2DM who had attended at least one PEP session. The T2DM subjects were identified with the International Classification of Primary Care-2 (ICPC-2) code of 'T90', through the clinical management system database of Hong Kong Hospital Authority. A total of 4,254 Diabesity subjects who had enrolled into PEP and attended at least one PEP session between 1 March, 2010 and 31 March, 2012 were included in the evaluation of the incidence in macro- and microvascular events. Out of 41,775 Diabesity subjects (PEP: 4,254, non-PEP: 37,221) within the database, 4,395 subjects (PEP: 326, non-PEP: 4,069) were excluded due to the prior diagnosis of macrovascular or microvascular diseases before baseline. Each patient was observed from baseline until the incidence of any macrovascular or microvascular disease events, death from any cause, or date of last follow-up as censoring, or 31 December, 2013, whichever came first. To evaluate the net effect of PEP on the post-intervention, 3,186 Diabesity patients who have not ever participated in PEP on or before 31 December, 2013 were matched to PEP subjects on propensity score matching (described below) as non-PEP group.

Patients having history of co-morbidities and diagnosis of macro- and microvascular disease events were defined according to the diagnosis coding system of *International Classification of Diseases, Ninth Edition, Clinical Modification* (ICD-9-CM) and *International Classification of Primary Care* (ICPC-2) in clinical management system database of the Hong Kong Hospital Authority. The complementary use of ICPC-2 and ICD-9-CM diagnosis coding systems were managed to identify the history of co-morbidities and diagnosis of macro- and microvascular disease events in both the primary and secondary care settings.

Ethics approval of this study was granted by institutional review board and clinical trial registry (NCT01935349, ClinicalTrials.gov).

Macrovascular and Microvascular Diseases

In the present study, four outcome events were our primary interests: 1) all-cause mortality, 2) first macrovascular event including coronary heart disease (CHD), stroke, or heart failure, 3) first microvascular event including retinopathy, nephropathy or neuropathy, and 4) first composite macro- and microvascular event. The incidence of CHD was defined as the earliest date of diagnosis with either ICPC-2 of K74-K76 or ICD-9-CM of 410.x-414.x or 798.x. The incidence of stroke was defined as the earliest date of diagnosis with either ICPC-2 of K89-K91 or ICD-9-CM of 430.x-438.x. The incidence of heart failure was defined as the earliest date of diagnosis with either ICPC-2 of K77 or ICD-9-CM of 428.x. The incidence of retinopathy was defined as the earliest date of diagnosis with either ICPC-2 of F83 or ICD-9-CM of 249.5x, 362.03-362.06 or 366.41. The incidence of nephropathy was defined as the earliest date of diagnosis with ICD-9-CM of 249.4x, 250.40-250.43, 581.x-585.x or 791.0. The incidence of neuropathy was defined as the earliest date of diagnosis with either ICPC-2 of N94 or ICD-9-CM of 249.6x, 250.6x, 337.1, 355.x or 357.2.

Baseline Covariates

Demographic, biometric data and disease characteristics, and treatment modalities and enrolment of co-intervention [23] for diabetes at baseline were treated as the covariates of

patients. Demographic characteristics of patients included sex, age, smoking status, alcohol status, and educational level. Biometric data included body mass index (BMI), hemoglobin A1c (HbA1c) level, blood pressure (BP), lipid profile, triglyceride and estimated glomerular filtration rate (eGFR) on the date within three-month period of baseline. Disease characteristics included the duration of T2DM, history of hypertension, family history of T2DM, insulin, oral anti-diabetic drugs, anti-hypertensive drugs and lipid-lowering agents used, Charlson Comorbidity Index[24] and the enrolment of co-intervention.

Propensity Score Matching

A propensity score is the conditional probability of being intervention given the observed covariates [25]. The technique aims to form comparable PEP intervention and non-PEP groups by logistic regression with relevant baseline characteristics of each patient summarized into a single-index variable (the propensity score) and match patients in the non-PEP comparison pool to patients in the PEP intervention group based on the value of the propensity score [26-28]. Correspondingly, the propensity score was generated for each patient, modelling PEP intervention as a dependent variable and baseline covariates of patients (including sex, age, smoking status, alcohol status, educational level, HbA1c level, BMI, BP, triglyceride, total cholesterol-to-high density lipoprotein cholesterol ratio, low density lipoprotein cholesterol, eGFR, the level of duration of T2DM, history of hypertension, family history of diabetes mellitus, the use of insulin, oral anti-diabetic drugs, hypertensive drugs and lipid-lowering agent, Charlson Comorbidity Index and enrolment of co-intervention for diabetes) as independent variables. The propensity score mapping was made by using the "psmatch2" command [29] with the nearest neighbour without replacement approach in the STATA.

Data Analysis

Descriptive statistics were used to calculate the baseline characteristics of demographic and clinical data in PEP and non-PEP groups after propensity score matching. Differences in baseline characteristics between PEP and non-PEP groups were tested for matched-pairs [30] using independent t-test for continuous variables or chi-square test for categorical

variables. Independent t-test was used to assess the differences in HbA1c, systolic BP, diastolic BP, LDL-C and BMI between PEP and non-PEP groups at different time points. The cumulative incidence rate and incidence rate of all-cause mortality, macrovascular and microvascular disease events with the corresponding 95% confidence interval (CI) were reported in both groups based on the assumption that the observed incident cases followed a Poisson distribution.

Multivariable Cox proportional hazards regression was performed to estimate the effect of PEP on the dependent variable of macrovascular event, microvascular event, first composite event and all-cause mortality, accounting for all baseline characteristics of patients. For each model, survival curves were estimated by Kaplan-Meier method and their differences between PEP and non-PEP groups were compared using the log-rank test. Hazard ratio (HR) and the corresponding 95% CI were reported for each variable in the regression models. Predictive accuracy of Cox models was assessed and compared using Harrell's discrimination C-index, ranging from zero to one. A value of 0.5 indicates no predictive discrimination, and values of 0 or 1.0 indicate perfect separation of patients [31]. Goodness-of-fit of Cox regression model were assessed using Akaike information criterion and Bayesian information criterion. Similar analyses were pursued on the subgroup analysis of the effect of weight management on dependent variables among PEP participants.

All statistical analyses were performed using STATA Version 13.0. All significance tests were two-tailed and those with a p-value less than 0.05 were considered statistically significant.

Results

Table 1 shows cohort baseline characteristics after 1:1 propensity score matching. Out of 4,254 diabesity subjects, 3,186 (74.9%) were successfully matched with non-PEP participants using the demographic and clinical characteristics. As expected, the two groups had similar baseline demographic and clinical characteristics, as indicated in the insignificance of all the p-values (≥ 0.05).

Comparisons of PEP and non-PEP participants in five of the clinical parameters (HbA1c, systolic BP, diastolic BP, LDL-C and BMI) at different time points are displayed in Figure 1. Both groups did not show any significant difference in all of the parameters at baseline but PEP participants had smaller means in all clinical measurement after baseline by observation, when compared with non-PEP participants.

Table 2 and Figure 2 present Kaplan-Meier survival curves and the number of all-cause mortality, macro- and microvascular disease, and composite events at a median follow-up of 29.5 to 31.5 months (range, 0.5 to 46.5 months). PEP participants generally suffered from fewer death, macro- and microvascular disease events than the non-PEP participants. Specifically, 95 deaths (34 PEP participants and 61 non-PEP participants) were resulted during a total of 8,200 person-years for PEP groups and 8,164 person-years for non-PEP groups. In addition, 350 first macrovascular or microvascular disease events (151 PEP participants and 199 non-PEP participants) occurred during a total of 7,972 person-years for PEP participants and 7,926 person-years for non-PEP participants. This also coincides with the results obtained if macrovascular or microvascular disease events were considered individually.

Multivariable Cox Regression Analysis

Multivariable Cox regression analyses of all-cause mortality, macro- and microvascular disease events as dependent variables are shown in table 3. After adjusting for confounding variables, PEP participants had a lower incidence rate of all-cause mortality than the non-PEP participants (HR: 0.589, 95% CI 0.380-0.915; P=0.018). Log-rank test further suggested that there was a significant difference in the survival times between the two groups (chi-square statistic=8.47; P=0.004). Additionally, a lower risk of first macrovascular or microvascular disease event was observed among the PEP groups than the non-PEP groups (HR: 0.782, 95% CI 0.632-0.968; P=0.024) and the difference in survival time was significant (chi-square statistic=5.82; P=0.016). However, if the macrovascular or microvascular disease events were studied alone, those two groups were not significantly different in incidence rates (macrovascular diseases: HR: 0.828, 95% CI 0.619-1.108; P=0.205; microvascular diseases: HR: 0.761, 95% CI 0.567-1.021; P=0.069).

Subgroup Analysis

Among those 3,186 PEP participants, 94.0% (n=2994) had not participated in the weight management program. A higher risk of death, but not statistically significant, was observed among PEP participants who participated the weight management program than those who did not (HR: 1.824, 95% CI 0.516-6.442; P=0.351). This result was further confirmed by the corresponding log-rank test (chi-square statistic=0.13; P=0.716). Moreover, participation of weight management program was not associated with a lower incidence risk of macrovascular or microvascular disease events (HR: 0.861, 95% CI 0.420-1.765; P=0.682). Similar findings were obtained for the incidence of macrovascular and microvascular disease events individually.

Discussions

The major findings in this propensity matched cohort study revealed that lower composite macro- and microvascular complication and all-cause mortality were associated with PEP participation in a median of 31.5 months. Compared with non-participants, PEP participants had a reduction in composite macro- and microvascular complication by one-quarter (PEP/non-PEP: 151/199, HR=0.782) and all-cause mortality by half (PEP/non-PEP: 34/61, HR=0.589), after adjusting for demographic and clinical characteristics. Results of structured education program were promising, having reduced occurrence of death from any cause and diabetes-related complication events, mainly attributable to the sustainable improvement in glycemic control at various follow-up assessments. Moreover, the additional component of weight management program was not associated with a significant reduction in the mortality, macro- and microvascular events in diabesity patients who attended PEP. Once diabesity patients had participated weight management program in addition to PEP, effectiveness may be reduced due to potentially excessive intervention.

Macro- and microvascular complications have seldom been reported in the structured diabetes education literature. Besides evidence of prior observational studies from PEP [18,19], the role of structured diabetes education in the incidence of macro- and microvascular complication has only been investigated in the cost-effectiveness analysis of diabetes education and self-management for ongoing and newly diagnosed (DESMOND) [32], using the Sheffield Type 2 Diabetes Model for the long-term incidence of macro- and

microvascular complications. It was worthwhile noting that the Sheffield Type 2 Diabetes Model replicated the predicted risk of macro- and microvascular complications among T2DM patients, indicating that the effects of structured diabetes education on observed events of microvascular complication have not been shown in the literature. The results of current study investigated not only the effects of PEP on observed composite complication events, but also the effects of PEP on observed composite macro- and microvascular events. Interestingly, the decreased risk for composite events for PEP participants compared with non-PEP participants was mainly driven more by the occurrence of microvascular events and less by the occurrences of macrovascular events. Although there was no evidence of a significant reduction in macrovascular events or microvascular events separately among PEP group compared with non-PEP group, the incidence of microvascular event might play an slightly more important role on incidence of composite events in PEP patients.

Comparison with previous studies

It was noteworthy to compare findings of current study with previous studies which investigated the effects of lifestyle intervention for diabesity in the prevention and control of macro- and microvascular complications. The randomized controlled trial focusing on intensive lifestyle modification such as Look AHEAD (Action for Health in Diabetes) trial [33] demonstrated that the lifestyle intervention group had modest weight loss compared to usual care referring to diabetes education program but occurrence of cardiovascular events were not significantly less (HR=0.95, P=0.51) in lifestyle intervention group after a decade of follow-up. By contrast with lifestyle therapeutic approach, results from surgical approach significantly reduced the incidence of macro- and microvascular events. Evidence from long-term follow-up (at least 10 years) observational studies [34,35] consistently showed that bariatric surgery has considered as highly effective approach in reducing risk of macrovascular (HR=0.39-0.68) or microvascular diseases (HR=0.22-0.44) event, and composite event (HR=0.36) when compared to diabesity patients receiving usual care. Despite such effective therapeutic approach, adverse events following bariatric surgery were estimated to be 0.3%-1.0% [36] in a meta-analysis of 32 studies reporting results of bariatric surgery.

Strengths and Limitations of this study

There were several strengths in this study. First, as a result of the large patient load and clinical information fully available in the administrative database of Hong Kong Hospital Authority, the study was able to carry out propensity score matching using important baseline covariates. Secondly, owing to similar culture and natural course of T2DM patients with obese in Chinese population, the results would be presumably generalizable to other Chinese populations in primary care setting.

The study also had some limitations. Firstly, current study was performed as non-randomized study design but instead sourced from the clinical data of routine clinical practice in 'real-world' setting. For instance, those who joined PEP may have more health consciousness and motivation compared to those who did not join. We cannot rule out the possibility that PEP participants tended to have better skills and self-awareness, resulting in lower incidence of macro- and microvascular complications. These baseline characteristics were not measurable to isolate the effect of confounding variables on the outcomes. To adjust for confounding variables, the administrative database was lacking in the lifestyle and psycho-social factors such as quality of life and self-efficacy measures, which might result in less robust control for the unbalanced baseline covariates when selecting controls through propensity score matching.

Conclusion

Results of this propensity score matched cohort study provided evidence that structured diabetes education program was an effective approach in reducing not only HbA1C levels but also all-cause mortality and first microvascular or microvascular disease events in diabesity patients. However, dual use of structured education program and weight management program was not associated with reduction in event occurrences, partly due to potentially excessive program intervened on diabesity patients.

Competing interest

None declared

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Author Contributions

C.K.H.W. wrote the manuscript and researched data. F.W.K.C. and A.C. contributed to acquisition of data and reviewed/edited the manuscript. W.C.W.W. and C.L.K.L. contributed to study design. Y.F.W. and A.K.C.C reviewed/edited the manuscript, contributed to statistical analysis and interpretation of results. W.C.W.W. and C.L.K.L. reviewed/edited the manuscript.

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554 **Figure Legend:**

555

556 Figure 1 Comparisons of PEP and non-PEP participants in HbA1c, SBP, DBP, LDL-C and
557 BMI at baseline, 12-month, 24-month and 36-month follow-up

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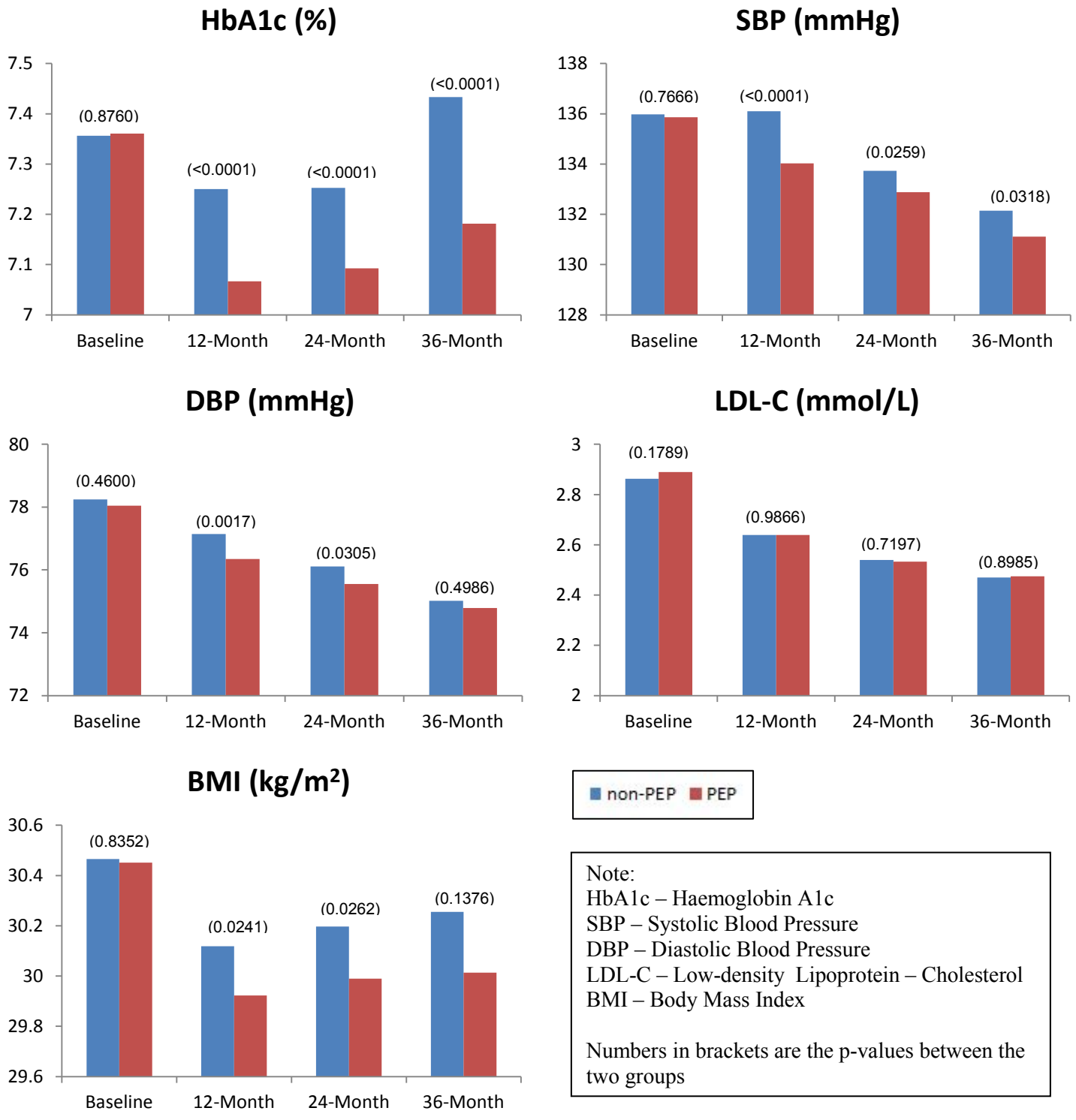
559 Figure 2 Kaplan-Meier Survival Curves for All-cause Mortality, Macrovascular and
560 Microvascular Disease Events

Figure 1 Comparisons of PEP and non-PEP participants in HbA1c, SBP, DBP, LDL-C and BMI at baseline, 12-month, 24-month and 36-month follow-up



Note:
HbA1c – Haemoglobin A1c
SBP – Systolic Blood Pressure
DBP – Diastolic Blood Pressure
LDL-C – Low-density Lipoprotein – Cholesterol
BMI – Body Mass Index

Numbers in brackets are the p-values between the two groups

Figure 2 Kaplan-Meier Survival Curves for All-cause Mortality, Macrovascular and Microvascular Disease Events

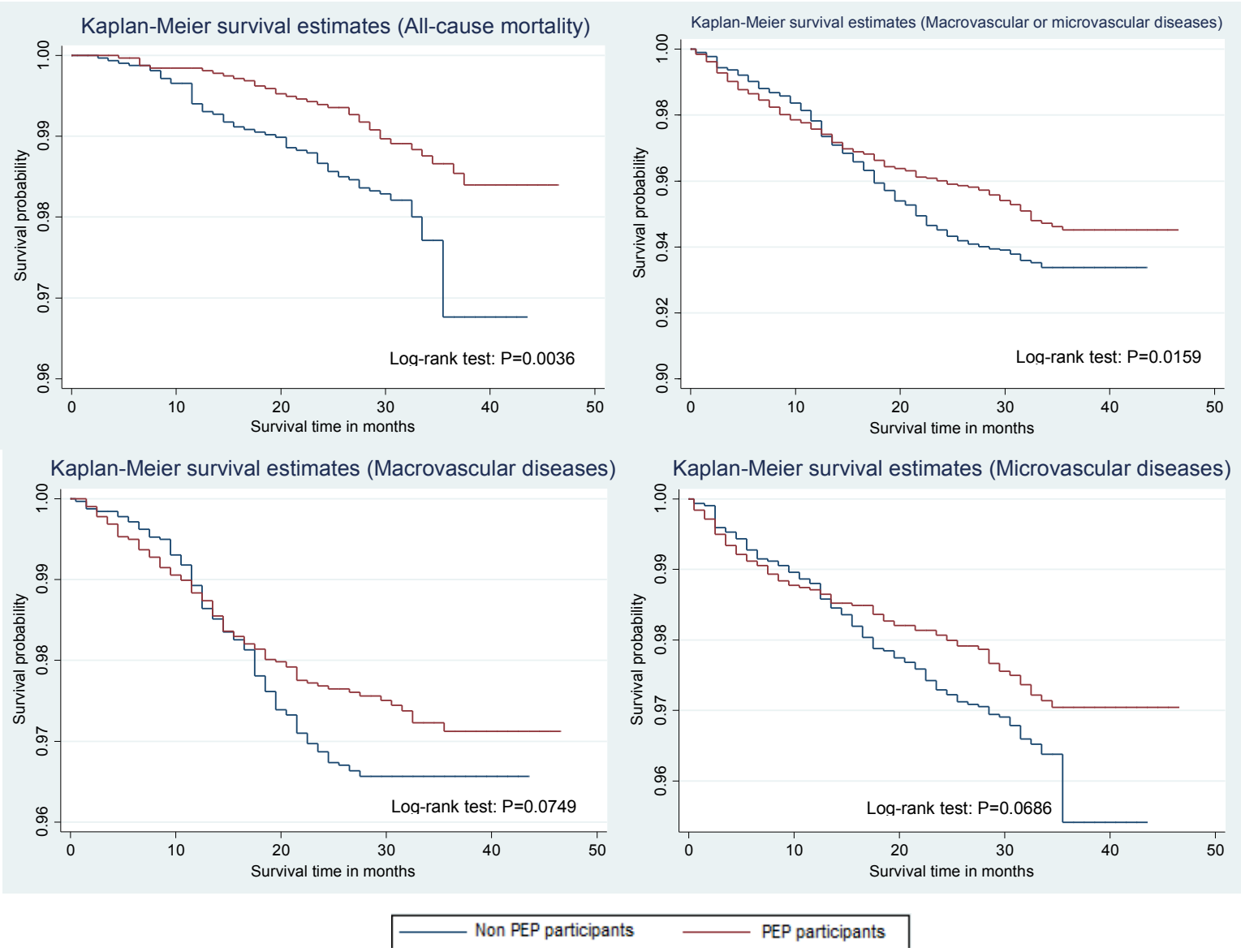


Table 1. Socio-demographic and Clinical Characteristics

Factor	PEP Participants vs non-PEP Participants				PEP Participants			
	Total (N=6,372) % (N)	PEP (N=3,186) % (N)	Non-PEP (N=3,186) % (N)	P-value	Total (N=3,186) % (N)	WM attended (N=2,994) % (N)	WM not attended (N=192) % (N)	P-value
Socio-demographic								
Sex				0.410				0.403
Female	61.7 (3,932)	61.2 (1,950)	62.2 (1,982)		62.2 (1,982)	62.4 (1,868)	59.4 (114)	
Male	38.3 (2,440)	38.8 (1,236)	37.8 (1,204)		37.8 (1,204)	37.6 (1,126)	40.6 (78)	
Age (mean±SD), year	61.60±10.64 (6,372)	61.64±9.75 (3,186)	61.57±11.47 (3,186)	0.785	61.64±9.75 (3,186)	60.49±8.93 (192)	61.71±9.79 (2,994)	0.092
Smoking status				0.755				0.645
Non-smoker	95.8 (6,103)	95.9 (3,054)	95.7 (3,049)		95.7 (3,049)	95.7 (2,864)	96.4 (185)	
Smoker	4.2 (269)	4.1 (132)	4.3 (137)		4.3 (137)	4.3 (130)	3.6 (7)	
Alcohol status				0.803				0.585
Non-drinker	79.8 (5,084)	79.9 (2,546)	79.7 (2,538)		79.7 (2,538)	79.8 (2,388)	78.1 (150)	
Drinker	20.2 (1,288)	20.1 (640)	20.3 (648)		20.3 (648)	20.2 (606)	21.9 (42)	
Educational level				0.379				0.024*
No formal education/ Primary	53.7 (3,421)	53.1 (1,693)	54.2 (1,728)		54.2 (1,728)	54.7 (1,639)	46.4 (89)	
Secondary/ Tertiary	46.3 (2,951)	46.9 (1,493)	45.8 (1,458)		16.3 (519)	16.4 (490)	15.1 (29)	
Laboratory results at baseline (mean±SD)								
BMI, kg/m^2	30.46±2.90 (6,372)	30.45±2.91 (3,186)	30.47±2.88 (3,186)	0.835	30.45±2.91 (3,186)	31.06±3.07 (192)	30.41±2.89 (2,994)	0.003*
HbA1c, %	7.36±1.13 (6,372)	7.36±1.09 (3,186)	7.36±1.17 (3,186)	0.876	7.36±1.09 (3,186)	7.19±0.93 (192)	7.37±1.10 (2,994)	0.023*
Systolic blood pressure, mmHg	135.92±16.04 (6,372)	135.86±16.62 (3,186)	135.98±15.43 (3,186)	0.767	135.86±16.62 (3,186)	134.35±17.07 (192)	135.96±16.59 (2,994)	0.194
Diastolic blood	78.14±10.51 (6,372)	78.05±10.87 (3,186)	78.24±10.15 (3,186)	0.460	78.05±10.87 (3,186)	78.34±11.22 (192)	78.03±10.85 (2,994)	0.701

Factor	PEP Participants vs non-PEP Participants				PEP Participants			
	Total (N=6,372) % (N)	PEP (N=3,186) % (N)	Non-PEP (N=3,186) % (N)	P-value	Total (N=3,186) % (N)	WM attended (N=2,994) % (N)	WM not attended (N=192) % (N)	P-value
pressure, mmHg								
Triglyceride, mmol/L	1.76±1.06 (6,372)	1.75±0.98 (3,186)	1.77±1.12 (3,186)	0.425	1.75±0.98 (3,186)	1.83±0.94 (192)	1.74±0.99 (2,994)	0.246
TC/HDL-C ratio	4.15±1.10 (6,372)	4.16±1.11 (3,186)	4.14±1.10 (3,186)	0.626	4.16±1.11 (3,186)	4.26±1.14 (192)	4.15±1.11 (2,994)	0.187
LDL-C, mmol/L	2.88±0.80 (6,372)	2.89±0.81 (3,186)	2.86±0.78 (3,186)	0.179	2.89±0.81 (3,186)	2.92±0.75 (192)	2.89±0.81 (2,994)	0.583
eGFR, ml/min/1.73m^2	85.02±20.98 (6,372)	84.94±19.98 (3,186)	85.09±21.93 (3,186)	0.782	84.94±19.98 (3,186)	84.15±17.89 (192)	85.00±20.11 (2,994)	0.568
clinical								
Duration of T2DM, year	5.82±5.40 (6,372)	5.72±5.57 (3,186)	5.91±5.21 (3,186)	0.155	5.72±5.57 (3,186)	5.30±4.61 (192)	5.75±5.63 (2,994)	0.277
Duration of T2DM, year				0.583				0.707
≤5 years	60.3 (3,840)	60.4 (1,923)	60.2 (1,917)		60.2 (1,917)	60.0 (1,796)	63.0 (121)	
5-10 years	23.1 (1,471)	22.6 (721)	23.5 (750)		23.5 (750)	23.6 (708)	21.9 (42)	
>10 years	16.7 (1,061)	17.0 (542)	16.3 (519)		16.3 (519)	16.4 (490)	15.1 (29)	
History of hypertension	82.9 (5,282)	82.6 (2,633)	83.1 (2,649)	0.595	83.1 (2,649)	83.5 (2,499)	78.1 (150)	0.055
Family history of diabetes mellitus				0.927				0.076
Yes	42.3 (2,697)	42.6 (1,356)	42.1 (1,341)		42.1 (1,341)	42.4 (1,270)	37.0 (71)	
No	8.7 (554)	8.6 (275)	8.8 (279)		8.8 (279)	8.9 (267)	6.3 (12)	
Unknown	49.0 (3,121)	48.8 (1,555)	49.2 (1,566)		49.2 (1,566)	48.7 (1,457)	56.8 (109)	
Insulin used	1.5 (97)	1.4 (46)	1.6 (51)	0.609	1.6 (51)	1.6 (49)	1.0 (2)	0.524
Oral anti-diabetic drugs used	85.2 (5,429)	85.1 (2,712)	85.3 (2,717)	0.860	85.3 (2,717)	85.4 (2,556)	83.9 (161)	0.565
Anti-hypertensive drugs	87.7 (5,589)	87.6 (2,792)	87.8 (2,797)	0.849	87.8 (2,797)	87.9 (2,633)	85.4 (164)	0.300

Factor	PEP Participants vs non-PEP Participants				PEP Participants			
	Total (N=6,372) % (N)	PEP (N=3,186) % (N)	Non-PEP (N=3,186) % (N)	P-value	Total (N=3,186) % (N)	WM attended (N=2,994) % (N)	WM not attended (N=192) % (N)	P-value
used								
Lipid lowering agents used	43.1 (2,745)	43.9 (1,400)	42.2 (1,345)	0.164	42.2 (1,345)	42.0 (1,257)	45.8 (88)	0.295
Charlson Comorbidity Index	3.79±1.25 (6,372)	3.79±1.18 (3,186)	3.79±1.32 (3,186)	0.952	3.79±1.18 (3,186)	3.73±1.19 (192)	3.80±1.18 (2,994)	0.429
Enrolment of co-intervention on/before baseline	17.5 (1,113)	17.6 (560)	17.4 (553)	0.817	17.4 (553)	17.5 (525)	14.6 (28)	0.295

Note:

PEP = Patient Empowerment Programme; WM = Weight Management; BMI = Body mass index; HDL = High-density lipoprotein; TC = Total cholesterol; LDL = Low-density lipoprotein; eGFR = estimated glomerular filtration rate; T2DM = Type 2 Diabetes Mellitus

* Significant differences ($P < 0.05$) by independent t-test or by chi-square test, as appropriate

Table 2. Number and incidence rate of all-cause mortality, macrovascular and microvascular disease events at a median follow-up of 31.5 months

Event	Cumulative incidence		Incidence rate (Cases/ 100 person-years)			Median follow-up periods (Months)
	Cases with event	Rate	Estimate	95% CI*	Person-years	
Total (N= 6,372)						
All-cause mortality	95	0.0149	0.581	(0.470,0.710)	16,364	31.5
Composite Macrovascular or Microvascular Diseases	350	0.0549	2.202	(1.977,2.445)	15,898	31.5
Macrovascular Diseases	189	0.0297	1.172	(1.011,1.352)	16,123	31.5
Microvascular Diseases	185	0.0290	1.147	(0.988,1.325)	16,125	31.5
PEP Participants (N=3,186)						
All-cause mortality	34	0.0107	0.415	(0.287,0.579)	8,200	30.5
Composite Macrovascular or Microvascular Diseases	151	0.0474	1.894	(1.604,2.221)	7,972	29.5
Macrovascular Diseases	82	0.0257	1.015	(0.807,1.260)	8,080	30.5
Microvascular Diseases	79	0.0248	0.977	(0.773,1.218)	8,087	30.5
Non-PEP Participants (N=3,186)						
All-cause mortality	61	0.0191	0.747	(0.572,0.960)	8,164	31.5
Composite Macrovascular or Microvascular Diseases	199	0.0625	2.511	(2.174,2.885)	7,926	31.5
Macrovascular Diseases	107	0.0336	1.330	(1.090,1.607)	8,044	31.5
Microvascular Diseases	106	0.0333	1.319	(1.080,1.595)	8,038	31.5

Note:

PEP = Patient Empowerment Programme; CI = Confidence Interval

* The 95%CI was constructed based on Poisson Distribution

Table 3. Multivariable Cox proportional hazard regression on the dependent variable of all-cause mortality, macrovascular and microvascular disease events, adjusted for the socio-demographic and clinical characteristics

	PEP factor				AIC	BIC	Harrell's C-statistic
	HR†	s.e.	95%CI	P-value			
PEP Participants vs non-PEP Participants (N= 6,372)							
All-cause mortality	0.589	0.132	(0.380,0.915)	0.018*	1,420	1,589	0.896 (0.866,0.927)
Composite Macrovascular or Microvascular Diseases	0.782	0.085	(0.632,0.968)	0.024*	5,889	6,058	0.700 (0.670,0.729)
Macrovascular Diseases	0.828	0.123	(0.619,1.108)	0.205	3,139	3,308	0.751 (0.714,0.789)
Microvascular Diseases	0.761	0.114	(0.567,1.021)	0.069	3,101	3,270	0.706 (0.665,0.747)
	WM factor				AIC	BIC	Harrell's C-statistic
	HR†	s.e.	95%CI	P-value			
PEP with WM session attended vs PEP without WM session attended (N= 3,186)							
All-cause mortality	1.824	1.174	(0.516,6.442)	0.351	453	604	0.916 (0.870,0.962)
Composite Macrovascular or Microvascular Diseases	0.861	0.315	(0.420,1.765)	0.682	2,348	2,499	0.697 (0.654,0.741)
Macrovascular Diseases	1.198	0.515	(0.516,2.783)	0.675	1,266	1,417	0.759 (0.703,0.815)
Microvascular Diseases	0.402	0.290	(0.098,1.650)	0.206	1,230	1,381	0.716 (0.659,0.773)

Note:

WM = Weight Management; PEP = Patient Empowerment Programme; HR = Hazard Ratio;

CI = Confidence Interval; AIC = Akaike information criterion; BIC = Bayesian information criterion

† HR > 1 indicates greater risk for event

* Significant difference (P < 0.05)