Patient Empowerment Programme (PEP) in Primary Care Reduced All-cause Mortality and Cardiovascular Diseases in Patients with Type 2 Diabetes Mellitus: A Population-based Propensity Matched Cohort Study

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Abstract

Aims: To assess whether a structured diabetes education programme, Patient Empowerment Programme (PEP), was associated with a lower risk of first cardiovascular disease (CVD) event and all-cause mortality in a population-based cohort of type 2 diabetes mellitus (T2DM) patients in primary care.

Methods and Methods: A Chinese cohort of 27,278 T2DM patients without prior occurrence of CVD events on or before baseline study recruitment date was linked to the Hong Kong administrative database from 2008 to 2013. PEP was provided to T2DM patients treated at primary care outpatient clinics through community trained professional educators. 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 PEP with the occurrence of first CVD event, coronary heart disease, stroke, heart failure and death from any cause, controlling for baseline characteristics.

Results: During a median of 21.5 months follow-up, 795 (352 PEP participants and 443 non-PEP participants) patients suffered a first CVD event. After adjusting for confounding variables, PEP participants had a lower incidence of all-cause mortality (hazard ratio: 0.564; 95%CI:0.445-0.715; P<0.001), first CVD (hazard ratio: 0.807; 95%CI:0.696-0.935; P=0.004) and stroke (hazard ratio: 0.702; 95%CI:0.569-0.867; P=0.001) events than those without PEP.

Conclusions: Enrolment in PEP was associated with reduced all-cause mortality and first CVD events among T2DM patients. The CVD benefit of PEP might be attributable to improving metabolic control through empowerment of self-care and enhancement of quality of diabetes care in primary care.

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Manuscript Text

Introduction

Type 2 diabetes mellitus (T2DM) is a global epidemic that contributes to a significant burden of disease worldwide[1]. The rapid increase in T2DM prevalence over the past few decades[2] has led to the projection of 592 million patients by 2035[1]. Improvements in metabolic control, mediated by healthy lifestyle behaviors including physical and healthy diet activity, play an important role in managing T2DM by preventing and delaying disease progression of cardiovascular complications.

Besides conventional approaches such as pharmaceutical interventions and optimal medication, self-management education is an empowering process that teaches patients to initiate behavioral changes and strengthen management of their disease[3, 4]. With respect to diabetes, self-management education refers to "the ongoing process of facilitating the knowledge, skills, and ability necessary for diabetes self-care".[5] Despite considerable variations in the organization of structured diabetes self-management education, systematic reviews[6-8] and meta-analyses[9-11] have demonstrated improvements in glycemic and cardiovascular risk factor control in both individual and group-based patient education interventions.

Significant reduction in diabetes-related complications as a result of diabetes education in secondary care setting was found. In a systematic review of randomized controlled trials on educational interventions for T2DM[6], studies focused on the effect of diabetes education on metabolic control and intake of oral hypoglycaemic treatment. To date, only one study[12] investigated the effect of diabetes education on long-term cardiovascular disease outcomes. Thus, the study (structured intensive diabetes education programme, SIDEP) [12] on a sample of 547 Korean patients with T2DM under secondary care, reported that patients with intensive diabetes education programme, at a follow-up of beyond four years, had lower frequency of hospital admissions related to diabetic complications than those who did not take part in the programme. However, whether or not diabetes education in primary care settings has had a significant impact on reducing incidence of cardiovascular disease outcomes and mortality remains uncertain. There is paucity of large population-based studies on the long-term cardiovascular benefits associated with diabetes education

programme in a primary care setting. A recent study[13] on the impact of a Patient Empowerment Programme (PEP) intervention on metabolic control provides evidence supporting the value of structured diabetes education for T2DM patients in primary care settings. Given the significant improvements in metabolic control associated with PEP, we evaluated whether those benefits would translate into a reduction in cardiovascular disease events.

This population-based propensity matched cohort study was carried out to evaluate the influence of implementing PEP in a primary care versus the usual clinical practice. The risks of incidence of cardiovascular disease and all-cause mortality events between the PEP and usual clinical practice were compared. It was hypothesized that PEP participants would have significantly lower risks of cardiovascular disease and all-cause mortality events.

Methods

PEP was launched in 2010 as a tertiary-wide primary care service component across the Hong Kong Hospital Authority with the purpose of providing quality chronic disease management to enhance primary care services. In the first evaluation cycle, from 1 March, 2010 to 30 September, 2010, two non-government organizations (NGOs) who were highly experienced in providing community medical education services, were invited to participate in the programme. From August 2011 onwards, four NGOs were invited to deliver PEP, offering full coverage of services across all district clusters in Hong Kong. A detailed description of the PEP setting, mode of education delivery and results from the first evaluation has been previously published[13]. The main function of PEP is to deliver sessions on disease-specific knowledge, self-management skills, self-efficacy and lifestyle modification to T2DM patients. This analysis summarized the second set of evaluation data derived from the quality of care evaluation of PEP provided by four NGOs with subsidies. This analysis included patients who attended at least one session of PEP from 1 March, 2010 to 30 June, 2012.

Subjects

Subjects with T2DM were selected from a population-based cohort of attendees of general outpatient clinics across Hong Kong Hospital Authority, the largest health service provider

in Hong Kong. All subjects with T2DM who attended at least one PEP session and had post-assessment conducted at 12 months from baseline were included in the outcome evaluation. The T2DM subjects were identified with the *International Classification of Primary Care-2* (ICPC-2) code 'T90', through the Hospital Authority's clinical management system database. A total of 17,839 T2DM subjects who had enrolled in PEP and attended at least one PEP session between 1 March, 2010 and 30 June, 2012 were included in the evaluation of incidence in CVD outcomes. Out of 193,765 T2DM subjects (PEP: 17,839, non-PEP: 175,926) within the database, 11,824 subjects (PEP: 756, non-PEP: 11,068) were excluded due to prior diagnosis of CVD before baseline. Each patient was observed from baseline until the incidence of a CVD event, death from any cause, or the date of last follow-up of general outpatient clinics as censoring, or 30 June, 2013, whichever came first. To evaluate the net effect of PEP post-intervention, 13,639 T2DM patients who had never participated in PEP on or before 30 June, 2013 were matched to PEP subjects on propensity score matching (described below) as non-PEP group.

We defined the subjects as having a history of co-morbidities and diagnosis of CVD 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 the clinical management system database of the Hong Kong Hospital Authority. The complementary use of ICPC-2 and ICD-9-CM diagnosis coding systems was able to capture the history of co-morbidities and diagnosis of CVD in both primary and secondary care settings.

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

Cardiovascular Disease

In this study, five outcome events were of interest: 1) first CVD event with one of the following diagnoses: coronary heart disease (CHD), stroke, or heart failure, 2) CHD, 3) stroke, 4) heart failure, and 5) all-cause mortality. Incidence of CHD was defined as the earliest date of diagnosis with ICD-9-CM of 410.x-414.x, 427.5, 798.1, 798.2 or 798.9. Incidence of stoke was defined as the earliest date of diagnosis with either ICPC-2 of K89-K91 or ICD-9-CM of 430, 431, 432.0, 432.1, 432.9, 433.00, 433.01, 433.10, 433.11,

433.20, 433.21, 433.30, 433.31, 433.80, 433.81, 433.90, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.9, 436 or 438. Incidence of heart failure was defined as the earliest date of diagnosis with either ICPC-2 of K77 or ICD-9-CM of 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43 or 428.9. Incidence of first CVD event was defined as the earliest date of diagnosis with any one of the CVD events.

Baseline Covariates

Covariates of patients included the collection of socio-demographic, biomedical data, disease characteristics, treatment modalities, and enrolment of co-intervention for diabetes [14, 15] at baseline. Socio-demographic characteristics of patients included sex, age, smoking status, alcohol status, and educational level. Biomedical data included body mass index (BMI), HbA1C level, blood pressure, lipid profile, triglyceride and estimated glomerular filtration rate (eGFR) taken within a six-month period from baseline. Disease characteristics included the duration of T2DM, family history of T2DM and the use of insulin.

Propensity Score Matching

A propensity score is the conditional probability of being selected for the intervention group given the observed covariates[16]. The technique aims to form equivalent PEP intervention and non-PEP comparison groups by summarizing relevant baseline characteristics of each patient into a single-index variable (the propensity score) and then matching patients in the non-PEP comparison pool to patients in the PEP intervention group based on the value of the propensity score [17-19]. Correspondingly, the propensity score for each patient was generated by logistic regression, modelling the PEP intervention as dependent variable and baseline covariates of patients as independent variables. Variables used for propensity score matching included sex, age, smoking status, alcohol status, educational level, HbA1c level, blood pressure, triglyceride, total cholesterol-to-high density lipoprotein cholesterol ratio, low density lipoprotein cholesterol, eGFR, duration of T2DM (≤5 years/ >5-10 years/ >10 years), history of hypertension, family history of T2DM, use of insulin and enrolment of co-intervention. The propensity score mapping was made by using the “psmatch2” command[20]

by one-to-one matching with the nearest neighbour and without replacement approach in STATA.

Data Analysis

Descriptive statistics were used to calculate the baseline characteristics of socio-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 using independent t-test for continuous variables or Chi-square test for categorical variables. The incidence rate of all-cause mortality and CVD events in PEP and non-PEP groups were reported. The 95% confidence interval (CI) of incidence rate was constructed based on the assumption that the observed incident cases followed a Poisson distribution.

Cox proportional hazards regression was performed to estimate the effect of PEP on the dependent variable of first CVD events. Multivariable cox proportional hazards regression models in propensity score matching were performed, accounting for all baseline characteristics of patients. Sensitivity analysis was performed using the PEP participants who completed the programme and propensity matched non-PEP participants. 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 its 95% confidence intervals 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[21]. Goodness-of-fit for Cox regression model were assessed using Akaike information criterion (AIC) and Bayesian information criterion (BIC).

All statistical analyses were performed using STATA Version 13.0 (StataCorp LP. College Station, Texas, U.S.). 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 characteristics after 1:1 propensity score matching. Among 17,083 T2DM subjects, 13,639 (79.8%) of them were successfully matched with non-PEP participants with regard to demographic and clinical characteristics. PEP participants (mean=7.3, SD=6.4) had a significantly shorter duration of T2DM than non-PEP participants (mean=7.6, SD=6.4) (t=-3.798, P<0.001). More PEP participants enrolled into co-intervention on or before baseline date (91% versus 20%, χ^2=14055.994, P<0.001) whereas more non-PEP participants used insulin during treatment (3% versus 2%, χ^2=79.191, P<0.001). For sensitivity analysis, 6,153 PEP participants who completed the programme were also matched with the non-PEP participants on one-to-one basis. Similarly, PEP participants who had completed the programme were more likely to enrol in the co-intervention on or before baseline date (91% versus 23%, χ^2=5860.232, P<0.001) and less likely to use insulin (1.6% versus 3.3%, χ^2=35.904, P<0.001) than the non-PEP participants.

Table 2 and Figure 1 present Kaplan-Meier survival curves and the number and incidence rates of all-cause mortality and CVD events at a median follow-up of 21.5 months (range, 0.5 to 40.5 months). Among 13,639 PEP participants and non-PEP participants, the former generally suffered from fewer cases of all-cause mortality and CVD events. During a total of 25,240 person-years for PEP participants and 25,102 person-years for non-PEP participants, 335 deaths (113 PEP participants and 222 non-PEP participants) occurred. Also, 795 incidences of first CVD event (352 PEP participants and 443 non-PEP participants) occurred during a total of 25,035 person-years for PEP participants and 24,876 person-years for non-PEP participants. Similar findings were obtained for the incidence of some cardiovascular diseases such as CHD, stroke and heart failure.

Multivariable cox Regression Model

Multivariable cox regression analyses on the dependent variable of all-cause mortality and cardiovascular disease events are shown in Table 3. After adjusting for confounding variables, PEP participants were associated with a lower risk of all-cause mortality (HR=0.564, 95%CI: 0.445-0.715, P<0.001) than non-PEP participants. Log-rank test suggested that there was a significant difference in the survival time between the two groups (χ^2=35.65, P<0.001). Moreover, PEP participants were also associated with a lower

incidence of first CVD event (HR=0.807, 95%CI: 0.696-0.935, P=0.004) than the non-PEP participants and the difference in survival time was significant (χ^2=10.61, P=0.001).

Sensitivity Analysis

PEP participants who completed the programme were associated with a lower risk of death (HR=0.593, 95%CI: 0.406-0.868, P=0.007) than those without PEP. The result of log-rank test also evidenced a significant difference in survival time between the two groups (χ^2=14.02, P<0.001). In addition, participants who completed the PEP were also associated with a lower incidence of first CVD event (HR= 0.716, 95%CI: 0.571-0.897, P=0.004) than non-PEP participants. The difference in survival time was also significant (χ^2=10.15, P=0.001).

Discussion

This is the first study investigating the association of a structured diabetes education programme with the risk of CVD events and all-cause mortality. The major findings in this propensity matched cohort study suggests that lower all-cause mortality was associated with the PEP enrolment, in spite of low cumulative (0.0123) and incidence rate (0.665 cases/ 100 person-years) of all-cause mortality in this population-based cohort. Compared with non-PEP participants, PEP participants had only half of mortality events (PEP/non-PEP: 113/222) and 43.6% lower risk of all-cause mortality (HR=0.564, 95%CI: 0.445-0.715; P<0.001) after adjusting for socio-demographic and clinical characteristics. Moreover, PEP was associated with a reduction in CVD events including stroke and heart failure in T2DM patients predominantly managed in primary care setting. Once the T2DM patients participated in PEP, all-cause mortality and CVD events occurred less frequently within a time span of less than 2 years, regardless of whether the PEP was completed or not. The impact of PEP on CVD benefit might be attributable to improvement in intermediate outcomes such as metabolic controls through empowerment of self-care and enhancement of quality of diabetes care in primary care.

Nonetheless, given the paucity of longitudinal data on observed events among subjects with or without diabetes education program, only the association of a diabetes education programme with occurrence of diabetes-related hospitalization has been investigated so far

[22]. Recent study showed that subjects enrolling in education programme generally had a significant HR of 0.10 (95%CI: 0.023-0.438; P=0.002) of being hospitalized due to diabetes-related acute events when compared to subjects in control group. The SIDEP[12], which was based on T2DM patients on secondary care, reported significantly lower diabetes-related hospitalization in those with diabetes education group than those without. Diabetes-related acute events may be in part attributed to CVD events but those previous studies did not display the breakdown information about the reduction in occurrence of CVD events.

Over a period of approximately two-years, our analyzed data investigated not only the effect of PEP on observed CVD events, but also the effect of PEP on observed CVD subtypes. Interestingly, the effect of PEP differed according to CVD subtypes. The PEP interventions did not significantly affect the occurrence of CHD event, but PEP participants had significantly lower risk of stroke event (HR=0.702, 95%CI: 0.569-0.867; P=0.001) compared with non-PEP participants. The PEP had no significant impact on risk association (HR=0.773, 95%CI: 0.558-1.070; P=0.121) in the sensitivity analysis. Conversely, the incidence of heart failure was not significantly lower (HR=0.809, 95%CI: 0.574-1.139; P=0.224) in PEP participants than in non-PEP participants while the risk association became borderline significant (HR=0.573, 95%CI: 0.341-0.961; P=0.035) upon further selection of participants who completed PEP in the sensitivity analysis. Therefore, the increased risk for CVD events for PEP participants compared with non-PEP participants was mainly driven by the occurrence of stroke and heart failure, and less by the occurrence of CHD. There was no evidence of a significant reduction in CHD events among the PEP group compared with the non-PEP group, suggesting that the incidence of stroke and heart failure played an important role in the significant effect of PEP on incidence of composite first CVD events. Consequently, the current study underlined the need for comprehensive outcome evaluation which further breakdown composite CVD outcome into subtypes, rather than examination of single composite CVD outcome.

Structured diabetes education curriculum delivered in the PEP group resulted in a remarkable reduction by 19.3% and 43.6% in the incidence of CVD events and incidence of all-cause mortality, respectively. It is noteworthy that the effect of PEP on the event occurrence was comparable with the effect of international randomized controlled trials focusing on intensive glucose control. Empirical evidence from population-based

randomized controlled trials that had intervened with intensified glucose control therapy over a prolonged follow-up period, for instance, UKPDS[23] and Steno-2[24] trial, were undoubtedly effective in decreased risk of CVD events and all-cause mortality. However, results from ADVANCE trial[25] showed that there was no significant difference in the incidence of all-cause mortality between the intervention and control groups although intervention was significantly associated with decreased risk of CVD events. Moreover, the intensive lifestyle intervention in Look AHEAD trial[26] focusing on overweight or obese T2DM were not associated with any reduction in CVD events, though weight loss was significant, after a median of 10-year period. Therefore, this population-based propensity matched study demonstrated the beneficial effects of PEP in reducing CVD and all-cause mortality events, supporting the public-private partnership and integration of the health sector with NGOs for service delivery in diabetes care.

Strengths and Limitations of this study

The strengths of this study included the use of a population-based cohort of patients with T2DM in Hong Kong Hospital Authority administrative database that was highly representative of the Hong Kong general population. Since the clinical characteristics were well captured by the administrative database through routine clinical practice, this allowed for the consideration of important baseline covariates such as physical assessment, laboratory results, diabetes-related medical history, and drugs dispensed for propensity score matching. Given the control of baseline covariates achieving balance in the PEP and non-PEP groups, propensity score matching was applied to offset the selection bias in this sample.

There were several limitations in this study. First, the current study was not a randomized controlled trial so it could not eliminate bias in the PEP group on outcomes. The clinical data coming from the 'real-world' setting were extracted from routinely collected medical records in an administrative database that was not specially designed for this cohort study. Both the PEP and non-PEP participants with available baseline covariates were presumably included in the analysis. Therefore, the unobserved baseline covariates were not taken into account for analysis. Many subjects in the PEP group had also participated in a concurrent multi-disciplinary risk assessment and management program[14, 15] that might have added benefit to CVD outcomes. To confirm the benefit of PEP, a multi-

center cluster randomized controlled trial, the strongest study design implemented in DESMOND[27], would be required. However, it may not be possible to conduct such a high-evidence trial in the 'real-world' primary care setting. Second, the long-term benefits of PEP on outcomes still remains uncertain after the second year. A longer follow-up period of beyond 21.5 months on the sustained benefits of outcomes in the intervention group compared to control group will be studied. Third, not all PEP participants were included in the analysis due to missing values. Therefore the propensity score could not be calculated. However, about 80% of eligible PEP participants were included in the analysis. Finally, data from this study was not entirely representative of Chinese populations in other parts of the world, or those under secondary care or in the private sector. However, findings were generated from a large population-based database of the public service that manage over 50% of diabetic patients in Hong Kong.

Conclusion

In conclusion, the findings of this study showed that enrolment in the Patient Empowerment Programme (PEP) was associated with decreased all-cause mortality and CVD events, especially with stroke and heart failure, in patients with T2DM. Programme completion was related to the reductions in CVD events. Results of this study provided evidence that a structured diabetes education programme led to at least a short-term reduction of CVD and deaths from any cause, in addition to the benefits on metabolic control and quality of primary care among T2DM patients . Future studies about the long-term benefits of PEP on mortality and CVD outcomes are warranted.

Competing interest

None declared

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Author Contributions

C.K.H.W. wrote the manuscript and researched data. K.L.C. and F.W.K.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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References

[1] Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes research and clinical practice. 2014; **103**: 137-149
[2] Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus--present and future perspectives. Nature Reviews Endocrinology. 2012; **8**: 228-236
[3] Anderson RM, Funnell MM. Using the empowerment approach to help patients change behavior: American Diabetes Association, 2002.
[4] Tang TS, Funnell MM, Brown MB, Kurlander JE. Self-management support in "real-world" settings: an empowerment-based intervention. Patient education and counseling. 2010; **79**: 178-184
[5] Funnell MM, Brown TL, Childs BP*, et al.* National Standards for Diabetes Self-Management Education. Diabetes care. 2009; **32**: S87-S94
[6] Loveman E, Frampton GK, Clegg AJ. The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review. Health technology assessment. 2008; **12**: 1-116, iii
[7] Jarvis J, Skinner TC, Carey ME, Davies MJ. How can structured self-management patient education improve outcomes in people with type 2 diabetes? Diabetes, Obesity and Metabolism. 2010; **12**: 12-19
[8] Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N. The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation. Health technology assessment. 2003; **7**: iii, 1-190
[9] Steinsbekk A, Rygg LO, Lisulo M, Rise MB, Fretheim A. Group based diabetes self-management education compared to routine treatment for people with type 2 diabetes mellitus. A systematic review with meta-analysis. BMC Health Serv Res. 2012; **12**: 213
[10] Norris SL, Lau J, Smith SJ, Schmid CH, Engelgau MM. Self-management education for adults with type 2 diabetes: a meta-analysis of the effect on glycemic control. Diabetes care. 2002; **25**: 1159-1171
[11] Minet L, Moller S, Vach W, Wagner L, Henriksen JE. Mediating the effect of self-care management intervention in type 2 diabetes: a meta-analysis of 47 randomised controlled trials. Patient education and counseling. 2010; **80**: 29-41
[12] Ko SH, Song KH, Kim SR*, et al.* Long-term effects of a structured intensive diabetes education programme (SIDEP) in patients with Type 2 diabetes mellitus—a 4-year follow-up study. Diabetic Medicine. 2007; **24**: 55-62
[13] Wong CKH, Wong WCW, Lam CLK*, et al.* Effects of Patient Empowerment Programme (PEP) on Clinical Outcomes and Health service Utilization in Type 2 Diabetes Mellitus in Primary Care: An Observational Matched Cohort Study. PLOS One. 2014; **9**: e95328
[14] Fung CSC, Chin WY, Dai D*, et al.* Evaluation of the quality of care of a multi-disciplinary risk factor assessment and management programme (RAMP) for diabetic patients. BMC Family Practice. 2012; **13**: 116
[15] Jiao FF, Fung CSC, Wong CKH*, et al.* Effects of the Multidisciplinary Risk Assessment and Management Program for Patients with Diabetes Mellitus (RAMP-DM) on biomedical outcomes, observed cardiovascular events and cardiovascular risks in primary care: a longitudinal comparative study. Cardiovascular Diabetology. 2014; **13**: 127

[16] D'Agostino RBJ. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med. 1998; **17**: 2265-2281
[17] Rosenbaum PR. Observational studies: Springer, 2002.
[18] Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983; **70**: 41-55
[19] Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized studies. Journal of educational Psychology. 1974; **66**: 688
[20] Leuven E, Sianesi B. PSMATCH2: Stata module to perform full Mahalanobis and propensity score matching, common support graphing, and covariate imbalance testing. Statistical Software Components. 2012:
[21] Harrell F, Lee KL, Mark DB. Tutorial in biostatistics multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Statistics in medicine. 1996; **15**: 361-387
[22] Adepoju OE, Bolin JN, Phillips CD*, et al.* Effects of diabetes self-management programs on time-to-hospitalization among patients with type 2 diabetes: A survival analysis model. Patient education and counseling. 2014; **95**: 111-117
[23] Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HAW. 10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. New England Journal of Medicine. 2008; **359**: 1577-1589
[24] Gæde P, Lund-Andersen H, Parving H-H, Pedersen O. Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes. New England Journal of Medicine. 2008; **358**: 580-591
[25] The ADVANCE Collaborative Group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. New England Journal of Medicine. 2008; **358**: 2560-2572
[26] The Look AHEAD Research Group. Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes. New England Journal of Medicine. 2013; **369**: 145-154
[27] Khunti K, Gray LJ, Skinner T*, et al.* Effectiveness of a diabetes education and self management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. Bmj. 2012; **344**: e2333

Table 1. Socio-demographic and Clinical Characteristics of Subjects at Baseline

Factor	PEP Participants vs non-PEP			PEP Completers vs non-PEP		
	PEP (N=13,639)	Non-PEP (N=13,639)	P-value	PEP (N=6,153)	Non-PEP (N=6,153)	P-value
Socio-demographic						
sex, %			0.45			0.83
female	58	59		59	59	
male	42	41		41	41	
age (mean±SD), year	65±9.8	65±11	0.26	65±9.4	65±11	0.99
smoking status, %			0.09			0.35
non-smoker	95	95		96	96	
smoker	5	5		4	4	
alcohol status, %			0.61			0.70
non-drinker	81	81		81	80	
drinker	19	19		19	20	
educational level, %			0.91			0.67
no formal education/ primary	53	53		51	51	
secondary/ tertiary	47	47		49	49	
Biomedical data at baseline (mean±SD)						
BMI, kg/m^2	25.6±3.9	26.0±4.0	0.17	25.5±3.9	25.6±3.9	0.24
HbA1c, %	7.4±1.3	7.4±1.5	0.22	7.4±1.2	7.3±1.3	0.34
systolic blood pressure, mmHg	134±17	134±16	0.33	135±18	135±17	0.65
diastolic blood pressure, mmHg	75±10	75±10	0.88	75±10	75±10	0.64
triglyceride, mmol/L	1.6±0.96	1.6±1.1	0.96	1.6±1.0	1.6±1.1	0.56
TC/HDL-C ratio	4.0±1.2	4.0±1.1	0.78	4.0±1.2	4.0±1.1	0.88
LDL-C, mmol/L	2.9±0.81	2.9±1.0	0.63	2.9±0.82	2.9±1.1	0.40
eGFR, $ml/min/1.73m^2$	85±20	84±25	0.51	85±20	85±24	0.42
Clinical						
duration of T2DM, year	7.3±6.4	7.6±6.4	<0.01*	7.3±6.5	7.5±6.3	0.17
duration of T2DM, %			0.90			0.98
≤5 years	49	50		50	50	
5-10 years	25	25		24	24	
>10 years	26	25		26	26	
history of hypertension, %	15	15	0.85	15	15	0.49
family history of T2DM, %			0.77			0.76
yes	43	44		43	43	
no	9	9		8	8	
unknown	48	47		49	49	
insulin used, %	1.6	3.3	<0.01*	1.5	3.2	<0.01*
enrolment of co-intervention on/before baseline, %	91	20	<0.01*	91	23	<0.01*

Note:

PEP=Patient Empowerment Programme; BMI=Body mass index; HDL=High-density lipoprotein; TC=Total cholesterol; LDL=Low-density lipoprotein; eGFR=Epidermal growth factor receptor; T2DM=Type 2 Diabetes Mellitus;

* p-value<0.05

Table 2. Number and incidence rates of all-cause mortality and cardiovascular disease events at a median follow-up of 21.5 months

Event	Cases with event	Incidence rate (Cases/ 100 person-years)		
		Estimate	95% CI*	Person-years
PEP Participants (N=13,639)				
All-cause mortality	113	0.448	(0.369,0.538)	25240
CVD	352	1.406	(1.263,1.561)	25036
CHD	155	0.616	(0.523,0.721)	25174
Stroke	161	0.641	(0.546,0.748)	25128
Heart failure	59	0.234	(0.178,0.302)	25207
Non-PEP Participants (N=13,639)				
All-cause mortality	222	0.884	(0.772,1.009)	25102
CVD	443	1.781	(1.619,1.955)	24876
CHD	178	0.711	(0.610,0.823)	25048
Stroke	230	0.921	(0.806,1.049)	24961
Heart failure	98	0.391	(0.317,0.476)	25064

Note:
PEP=Patient Empowerment Programme; CVD=Cardiovascular Disease; CHD=Coronary Heart Disease; CI=Confidence Interval
* The 95%CI was constructed based on Poisson Distribution

Table 3. Multivariate Cox proportional hazard regression on the dependent variable of all-cause mortality and cardiovascular disease events

	PEP factor			Harrell's C-statistic
	HR†	95%CI	P-value	
PEP Participants vs non-PEP Participants (N=27,278)				
All-cause mortality	0.564	(0.445,0.715)	<0.001*	0.799 (0.772,0.825)
CVD	0.807	(0.696,0.935	0.004*	0.730 (0.712,0.749)
CHD	0.840	(0.670,1.054	0.132	0.741 (0.714,0.769)
Stroke	0.702	(0.569,0.867	0.001*	0.721 (0.694,0.747)
Heart failure	0.809	(0.574,1.139	0.224	0.874 (0.846,0.901)
Sensitivity Analysis, PEP Completers vs non-PEP Participants (N=12,306)				
All-cause mortality	0.593	(0.406,0.868	0.007*	0.818 (0.783,0.852)
CVD	0.716	(0.571,0.897	0.004*	0.749 (0.724,0.774)
CHD	0.716	(0.503,1.019	0.063	0.769 (0.731,0.807)
Stroke	0.773	(0.558,1.070	0.121	0.747 (0.712,0.783)
Heart failure	0.573	(0.341,0.961	0.035*	0.885 (0.847,0.923)

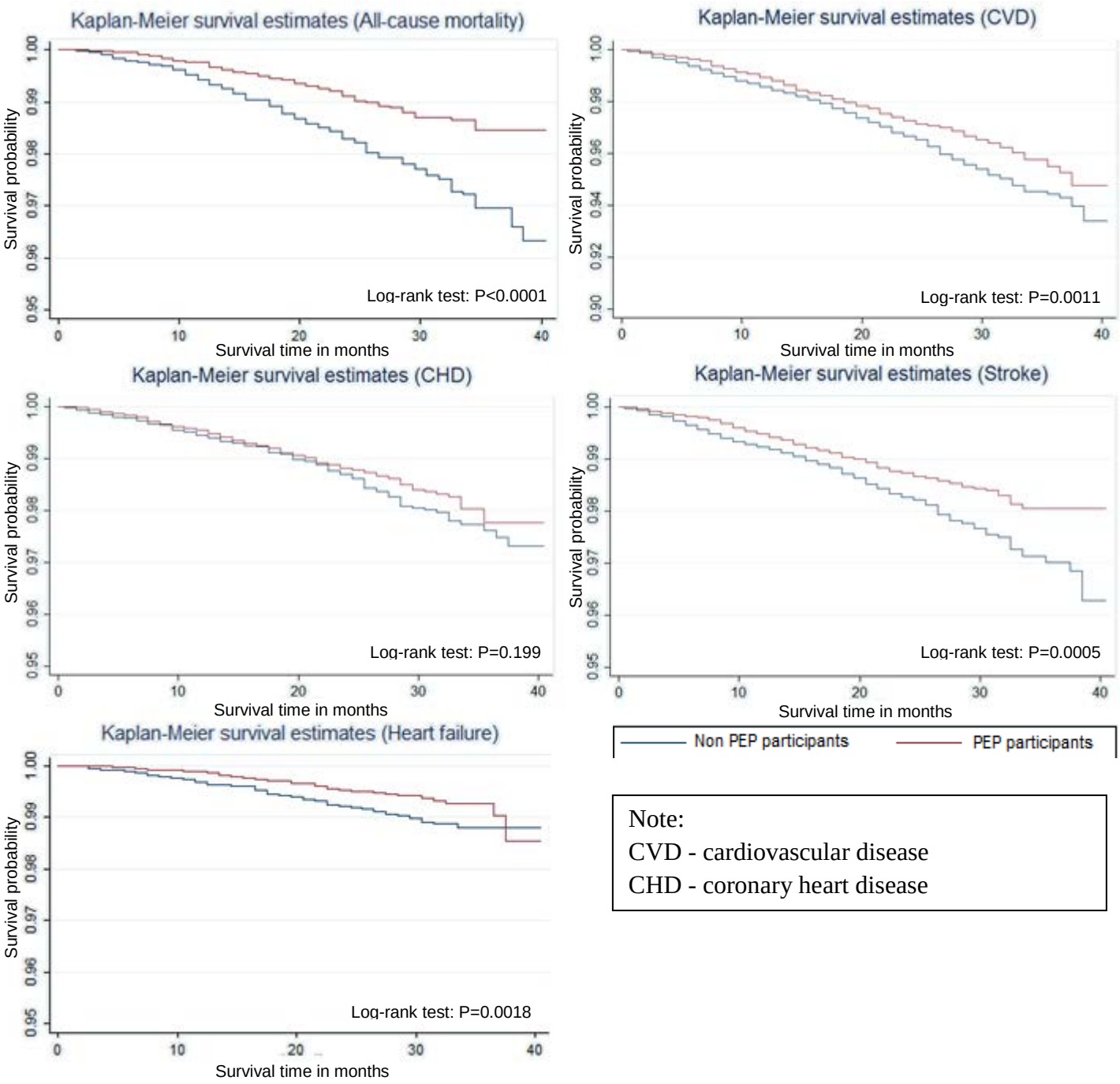
Note:

HR=Hazard Ratio; CVD=Cardiovascular Disease; CHD=Coronary Heart Disease

† HR>1 indicates greater risk for death of PEP patients compared with non-PEP patients

* p-value<0.05

Figure 1 Kaplan-Meier Survival Curves for All-cause Mortality and Cardiovascular Disease Events



Note:
CVD - cardiovascular disease
CHD - coronary heart disease