Title	Effectiveness of the multidisciplinary Risk Assessment and Management Program for Patients with Diabetes Mellitus (RAMP-DM) for diabetic microvascular complications: A population-based cohort study
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Keywords: diabetes mellitus, risk stratification, multidisciplinary, microvascular complications

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Abstract: Aim: To evaluate the effectiveness of the multidisciplinary Risk Assessment and Management Program for Patients with Diabetes Mellitus (RAMP-DM) in reducing the risks of microvascular complications.

Methods: We conducted a prospective cohort study in 29,670 propensity score matched RAMP-DM participants and diabetic subjects under usual primary care (14,835 subjects in each group). The study endpoints were the first occurrence of any diabetic complications, nonproliferative diabetic retinopathy/pre-proliferative diabetic retinopathy (NPDR/pre-PDR), sight-threatening diabetic retinopathy (STDR) or blindness, nephropathy, end-stage renal disease (ESRD), neuropathy, and lower limb ulcer or amputation. Log rank-test and multivariable Cox proportional hazard regressions were employed to estimate the between-group differences in the incidences of study endpoints.

Results: After a median follow-up period of 36 months with >41,000 person-years, The RAMP-DM had lower incidence in any microvascular complications (760 versus 935, adjusted hazard ratio [HR],0.73; 95% confidence interval [CI] 0.66 - 0.81; P<0.001). The RAMP-DM group had lower incidences in all the specific microvascular complications except neuropathy (adjusted HR, 0.94; 95%CI, 0.61 - 1.45; P=0.778). The adjusted HR of the RAMP-DM to control group for ESRD, STDR or blindness, and lower limb ulcer or amputation were 0.40 (95%CI, 0.24 -0.69 ; P<0.001), 0.55 (95%CI, 0.39 - 0.78; P=0.001), and 0.49 (95%CI, 0.30 - 0.80; P=0.005), respectively.

Conclusion: The RAMP-DM intervention was associated with lower incidences of all microvascular complications except neuropathy over a three-year follow-up. The encouraging results provided evidence to support that

structured risk assessment and risk-stratified management provided by a multidisciplinary team is effective in reducing microvascular complications in diabetic patients.

Effectiveness of the multidisciplinary Risk Assessment and Management Program for patients with Diabetes Mellitus (RAMP-DM) on diabetic microvascular complications: a population-based cohort study

Short title: Effects of RAMP-DM on microvascular complications

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Conflict of interest

No conflicts of interest, financial or otherwise, are declared by the author(s).

Disclosure statement

There is nothing need to be disclosed.

Abstract

Aim: To evaluate the effectiveness of the multidisciplinary Risk Assessment and Management Program for Patients with Diabetes Mellitus (RAMP-DM) in reducing the risks of microvascular complications.

Methods: We conducted a prospective cohort study in 29,670 propensity score matched RAMP-DM participants and diabetic subjects under usual primary care (14,835 subjects in each group). The study endpoints were the first occurrence of any diabetic complications, **nonproliferative diabetic retinopathy/pre-proliferative diabetic retinopathy (NPDR/pre-PDR)**, sight-threatening diabetic retinopathy (STDR) or blindness, nephropathy, end-stage renal disease (ESRD), neuropathy, and lower limb ulcer or amputation. Log rank-test and multivariable Cox proportional hazard regressions were employed to estimate the between-group differences in the incidences of study endpoints.

Results: After a median follow-up period of 36 months with >41,000 person-years, The RAMP-DM had lower incidence in any microvascular complications (**760 versus 935, adjusted hazard ratio [HR],0.73; 95% confidence interval [CI] 0.66 – 0.81; *P*<0.001**). The RAMP-DM group had lower incidences in all the specific microvascular complications except neuropathy (adjusted **HR, 0.94; 95%CI, 0.61 - 1.45; *P*=0.778**). The adjusted HR of the RAMP-DM to control group for ESRD, STDR or blindness, and lower limb ulcer or amputation were **0.40 (95%CI, 0.24 - 0.69 ; *P*<0.001), 0.55 (95%CI, 0.39 - 0.78; *P*=0.001)**, and **0.49 (95%CI, 0.30 - 0.80; P=0.005)**, respectively.

Conclusion: The RAMP-DM intervention was associated with lower incidences of all microvascular complications except neuropathy over a three-year follow-up. The encouraging results provided evidence to support that structured risk assessment and risk-stratified management provided by a multidisciplinary team is effective in reducing microvascular complications in diabetic patients.

Clinical trial registry: NCT02034695, www.ClinicalTrials.gov

Keywords: diabetes mellitus, risk stratification, multidisciplinary, microvascular complications

List of Abbreviations

DBP	Diastolic Blood Pressure
DM	Diabetes Mellitus
DR	Diabetic Retinopathy
eGFR	Estimated Glomerular Filtration Rate
ESRD	End Stage Renal Disease
HR	Hazard Ratio
ICD-9-CM	International Classification of Diseases, Ninth Edition
ICPC-2	International Classification of Primary Care
NNT	Number Needed to Treat
NPDR	Non-Proliferative Diabetic Retinopathy
RAMP-DM	Multidisciplinary Risk Assessment and Management Program for Patients with diabetes mellitus
SBP	Systolic Blood Pressure
STDR	Sight-threatening Diabetic retinopathy

Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases all over the world. The prevalence of DM in the world is estimated to reach 592 million by 2035, with an increase of 54.2% in total case numbers compared to the year of 2013[1]. China has the largest number of diabetic patients. The number of diabetic patients in China is estimated to exceed 129 million in 2030, accounting for more than one quarter of the total diabetic cases in the world [2]. In Hong Kong, around 1 in 10 people has DM [3], and the prevalence of DM is increasing [4]. Diabetic patients have an increased risk of developing microvascular complications, including retinopathy, nephropathy and neuropathy. The prevalence of retinopathy and neuropathy is estimated to be 22% and 13% respectively in newly diagnosed DM patients [5]. The prevalence of proliferative retinopathy is 2% in diabetic patients with less than 5 years of duration of DM, and it increases 25% in patients with 25 or more years of DM [6]. Diabetic nephropathy develops in 25% Type 2 DM patients **after** 10 years after diagnosis [7] and end-stage renal disease (ESRD) develops in 14% Type 1 DM patients with 10 years duration of DM [8].

However, due to the insidious progress of microvascular complications, patients might be undetected or left untreated in early disease stage, which can lead to devastating impact on quality of life and life expectancy once the clinical significant complications are developed, such as ESRD, sight-threatening diabetic retinopathy (STDR), and amputation. Several modifiable risk factors, including HbA1c, blood pressure, eGFR are found to associate with development of microvascular complications [9-11]. Early screening and intervention of early stage of microvascular complications and modifiable risk factors are critical to prevent or delay the progress of disease severity. In recent years, guidelines have recommended risk factor screening and risk stratification management [12-14], setting personalized treatment goals based on patients' individual complication risks. Personalized management is advocated as a means of

translating the evidence from randomized control trials to real-world settings [15]. However, there is a lack of studies on the effectiveness of risk stratification-based personalized management [15].

Previous studies on short-term effectiveness of risk-stratification based intervention were conducted in the U.S. [16] and U.K. [17] . Both studies reported the increase in the percentages of subjects reaching target HbA1c, blood pressure in the intervention group. However, long-term effectiveness of the intervention was not reported. In Asia, attempt for the risk stratification management was made by the Joint Asia Diabetes Evaluation Program [18]. Clinicians can access a web-based comprehensive risk stratification model using an electronic portal. Between 2007-2009, 3687 people with diabetes across seven Asian countries, including Hong Kong, were enrolled [19]. The implementation of the structured care and effectiveness of this care model compared to usual care is not clear.

To enhance the management of diabetic subjects in primary care setting in Hong Kong, a multidisciplinary risk assessment and management program for patients with diabetes mellitus (RAMP-DM) has been operating in public general out-patient clinics since August 2009. The details of the intervention have been reported [20]. Compared to diabetic subjects under usual care, RAMP-DM group was found to have significant improvement in HbA1c, blood pressure control and reduction in cardiovascular events incidences at both 12-month [21] and 36–month [22] of follow-up.

The RAMP-DM intervention included systematically comprehensive screening of risk factors and early stage of diabetic microvascular complications at enrollment, including retinal photo examination, foot assessment, renal function test and urine albumin to creatinine ratio measurement. It was unclear yet, whether the RAMP-DM intervention was associated with reduction in microvascular complications. Therefore, this study aimed at investigating the effects of RAMP-DM intervention on the microvascular complications compared to usual primary care over 3-year follow-up. It was hypothesized that RAMP-DM participants would have significant lower incidences in microvascular complications, especially in the advanced stage diseases.

Methods

Study design

A prospective cohort study was conducted to compare the risks of developing different stages of three subtypes of diabetic microvascular complications over three years between diabetic subjects managed under RAMP-DM and those receiving usual primary care.

RAMP-DM intervention

The RAMP-DM was a territory-wide primary care service component for patients with DM in public primary care clinics in Hong Kong. It was launched since August 2009 by Hong Kong Hospital Authority, the sole public healthcare provider in Hong Kong. The details of the RAMP-DM program have been reported previously [20]. In brief, all the enrolled subjects would undergo a comprehensive risk assessment examinations including measurement of basic parameters, laboratory test, eye and foot assessment. The case manager, taken by an advanced practice nurse would review the examinations results, assessed the cardiovascular risks and

stratified patients into ‘very high’, ‘high’, ‘medium’ and ‘low’ risk groups according to the modified Joint Asia Diabetes Evaluation cardiovascular risk stratification flow chart [19]. The patients were then assigned to receive appropriate interventions and education provided by a team of multi-disciplinary healthcare professionals, including Associate Consultants in family medicine, Registered Nurses, Advanced Practice Nurses and allied health professionals (optometrist, dietitian, podiatrist, physiotherapist, etc) according to their stratified risk level and HbA1c level. According to patients’ risk levels, some RAMP-DM subjects have annual full risk factors screening and Nurse Intake Assessment, and others have the full assessment every 2-3 years with annual blood test and followed-up by their primary care doctors.

Diabetic patients under usual primary care continued to be managed by their primary care doctors without risk assessment and stratification. They were also eligible for referral to allied health professionals at their doctors’ discretion.

Subjects

The RAMP-DM aims at covering all diabetic patients in Hong Kong. All patients with DM who are followed up regularly at public primary care clinics are eligible to be enrolled in RAMP-DM. **Patients were invited to join RAMP-DM opportunistically when they saw their primary care doctors. The enrollment was on a voluntary basis.** Up to 31st December 2013, the end date of our study data collection period, there were 147,097 enrolled into RAMP-DM (out of a total of 206,238 patients receiving diabetic care under the primary care service of HA from August 2008 to July 2013). The remaining people with diabetes were continued to be enrolled into RAMP-DM after 31st July 2013, and they served as potential control subjects in this study.

We identified study subjects from the Clinical Management System database of the Hospital Authority. Inclusion criteria for this study are, 1) Age≥18; 2) Patients with documented International Classification of Primary Care (ICPC-2) codes T89/T90 before baseline; 3) Patients with at least one public primary clinics attendance before baseline. To evaluate the effectiveness of RAMP-DM in reducing primary microvascular complications, subjects with any pre-existing microvascular complications were excluded from the analysis. For the control group, patients who were enrolled in RAMP-DM on or before 31st July 2013 were also excluded in the analysis.

The baseline for each RAMP-DM participant was the first date of risk assessment of RAMP-DM between 1st August 2009 and 31st July 2010**. The subjects in control group were DM patients continuously managed in usual primary care. We set 31st January 2010, the middle date of the baseline among RAMP-DM subjects, as the baseline for the control group.** All subjects were observed until a study endpoint or three years since their baseline using the date of their last follow-up as a censor date.

Ethical approval of this study was granted by the Institutional Review Board of the University of Hong Kong/Hospital Authority： Hong Kong West Cluster (UW 10-369), New Territories East Cluster (CRE-2010.543), New Territories West Cluster (NTWC/CREC/1091/12), Kowloon East and Kowloon Central Cluster (KC/KE-10-0210/ER-3), Kowloon West Cluster (KW/EX/10-317 (34–04)), and Hong Kong East Cluster (HKEC-2010-093).

Propensity score matching

To reduce selection bias, the subjects in the RAMP-DM and control groups were matched using propensity score matching. Study subjects were paired based on observable characteristics which indicate a similar probability of receiving treatment (similar propensity score), but one of them received the intervention and the other did not. The propensity score is the conditional probability of receiving the intervention given the observed baseline covariates and it is independent of the outcomes. Propensity score matching is appropriate for studies with a large sample size and many covariates [23]. A propensity score was generated for each patient, and the RAMP-DM intervention was modelled as the dependent variable and the baseline covariates were the independent variables. The propensity score matching was conducted using the "psmatch2" STATA package by one-to-one matching without replacement and with a caliper of 0.001, which means the differences of propensity scores for each matched pair was within 0.001. The unmatched control subjects were discarded.

The baseline covariates for developing the propensity score were 1) demographic characteristics, including age, sex, whether on comprehensive social security assistance; 2) clinical parameters, including smoking status, duration of diabetes, HbA1c, low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglyceride systolic blood pressure (SBP), diastolic blood pressure (DBP) and estimated glomerular filtration rate (eGFR); 3) treatment modality, including oral glucose-lowering drugs, insulin, anti-hypertensive drugs and lipid-lowering drugs; and 4) comorbidities, measured by the Charlson comorbidity score[24].

Study endpoints

The endpoint for this study was the time to first occurrence of a diabetic microvascular complication, which was identified by the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) and ICPC-2 codes from the Clinical Management System of the Hospital Authority **(Supplementary Table)**.

Data analysis

The independent t-test or chi-squared test, as appropriate, was employed to compare the demographic and clinical parameters between the RAMP-DM and control groups at baseline and the end of follow-up. The cumulative incidence rates for each subtype of microvascular complications were reported. We constructed the 95% confidence intervals of the incidence rates based on the assumption that the observed incident events followed a Poisson distribution. **We calculated the number needed to treat (NNT) to reduce one diabetes-related complication by RAMP-DM. The NNT was calculated as the inverse of the absolute risk reduction [25]. The NNT is interpreted as the average number of patients needed to treat in order to reduce one unwanted outcomes. The lower the NTT, the more effective is the intervention.**

For each of the study endpoints, the Kaplan-Meier method was used to estimate the survival curves and the log-rank test was used to compare the between group differences. To estimate the magnitude of differences in endpoints, multivariable Cox proportional hazards regression models were employed to explore the effects of RAMP-DM on the dependent variables of each endpoint, adjusting for all the baseline covariates. The hazard ratio (HR) with 95% confidence interval of RAMP-DM were reported for each endpoint. The predictive accuracy

of each regression model was evaluated using Harrell's discrimination C-index, ranging from 0 to 1. A value of 0.5 indicates the model does not have predictive discrimination ability, and values of 1 indicate perfect ability to discriminate subjects [26]. Intention to treat analysis was adopted.

We performed all the statistical analyses using STATA Version 13.0 (StataCorp LP. College Station, Texus, US), and *P*-value less than 0.05 was considered as statistically significant.

Results

Baseline characteristics

From 1st Aug 2009 to 31st July 2010, a total of 18,459 diabetic subjects under primary care were enrolled in RAMP-DM. We identified 47,148 potential control subjects who met the inclusion criteria for the study. Subjects with any pre-existing microvascular complications were excluded in each group, giving 17,804 and 44,809 subjects in RAMP-DM and control groups, respectively. Limiting the eligibility to subjects with complete baseline data reduced the sample to 17,528 and 16,180 in RAMP-DM and control groups, respectively. To reduce selection bias, we further refined the study sample using propensity score matching. The final matched sample for this study comprised 14,835 RAMP-DM subjects and 14,835 control subjects.

The comparison of baseline characteristics between the two groups is shown in Table 1. At baseline, the RAMP-DM and control group had similar values in all the demographic, clinical parameters and treatment modality. The average age of the two cohorts was 65, and around 87% subjects were on oral glucose-lowering drugs. At the end of follow-up, the RAMP-DM subjects

showed significantly lower HbA1c (7.10% vs 7.21%, *P*<0.001) and SBP (130 mmHg vs 132 mmHg, *P*<0.001). The RAMP-DM group showed higher percentages of patients on all the four types of drugs (glucose-lowering drugs, anti-hypertensive drugs, lipid-lowering drugs and insulin) than the control group at the end of follow-up.

Observed incidence of microvascular complications

Table 2 shows the observed number of the first diagnoses of each subtype of diabetic microvascular complication and the incidence rates over a median follow-up period of 36 months among 14,835 subjects in each group. More than 43,000 and 41,000 person-years of observation were available for each of the study endpoints in the RAMP-DM and control group, respectively. The RAMP-DM group showed lower incidence rates for all the endpoints. **NPDR/non-PDR** was the most prevalent microvascular complication in both groups **(535** and **594** retinopathy events in RAMP-DM and control group, respectively). Over the observation period, **51** cases of STDR or blind occurred in the RAMP-DM group, which was around half that in the control group (**90** cases). The number needed to treat by RAMP-DM to reduce one microvascular complication was **85**.

Multivariable Cox Regression Models

The Kaplan-Meier survival curves for each study end point are shown in Figure 1. For all severer microvascular complications, including STDR or blindness (*P*<0.001), ESRD (*P*<0.001), ulcer or amputation (*P*=0.009), significant lower incidence rates were observed in RAMP-DM group, and the differences became larger over the follow-up period. The incidences of neuropathy were almost identical between the two groups (*P*=0.778).

The HR between RAMP-DM and control groups for each study endpoint was estimated by multivariable Cox regression models, adjusting for all the baseline covariates. As shown in Table 3, compared to the control group, the RAMP-DM group significantly reduced the incidence of both **NPDR/pre-PDR (HR: 0.85, 95% CI: 0.76-0.96,** *P*=0.007) and nephropathy **(HR: 0.54, 95% CI: 0.45-0.66,** *P*<0.001). The reduction was more evident in severer stages of disease. The HR for STDR or blind and ESRD were **0.55 (95%CI: 0.39-0.78, *P*=0.001) and 0.40(95%CI: 0.24-0.69, *P*<0.001)**, respectively. The two groups did not show difference in the incidence of neuropathy (**HR: 0.94, 95% CI: 0.61-1.45, *P*=0.78**), but the RAMP-DM group had substantial lower incidence in ulcer or amputation **(HR: 0.49, 95% CI: 0.30-0.80, *P*=0.005).**

Discussion

To the best of our knowledge, this was the first study investigating the long-term effects of a multidisciplinary risk-stratification based DM management on microvascular complications in Chinese population. With more than 41,000 person-years follow-up, this population-based cohort study found that RAMP-DM intervention was associated with reduction in the incidences of all the studied diabetic microvascular complications, except neuropathy. The RAMP-DM **was more effective in reducing the incidences of severe microvascular complications,** prompting that the HR for developing STDR or blindness, ESRD and ulcer or amputation were **0.55, 0.40 and 0.49**, respectively. These findings provided evidence of the effectiveness of multidisciplinary risk-stratification based management in **a** real world primary setting.

Significant lower incidences of retinopathy, nephropathy and amputation were observed in the RAMP-DM group, which might be partly attributed to the significant decreases in HbA1c and blood pressure observed in the RAMP-DM group. Also, the RAMP-DM group had higher percentage of subjects on glucose-lowering drugs, insulin, anti-hypertensive drugs and lipid-lowering drugs, indicating the RAMP-DM participants were under more intensive treatment. HbA1c and blood pressure were found to be associated with the risks of developing diabetic retinopathy [9], nephropathy [10] and neuropathy [27] . Previous studies found that intensive glucose control were associated with lower incidences of microvascular complications. The United Kingdom Prospective Diabetes Study found that, over 10 years follow-up, the intensive glucose control reduced the risk of aggregated microvascular complications (RR: 0.75, *P*=0.0099) and retina photocoagulation (RR: 0.71, *P*=0.0031), but no effects were found in reducing renal failure (RR: 0.73, *P*=0.45) and amputation (RR: 0.61, *P*=0.099) **[28]**. The Preterax and Diamicron Modified Release Controlled Evaluation trial showed that over 5 years of follow-up, the intensive control group showed decrease in the incidence of nephropathy (HR 0.79, *P*=0.006), but not significant effect on retinopathy (HR 0.95, *P*=0.50) [29]. Compared to interventions that only emphasized on medical intervention, multidisciplinary interventions were found to be more effective to reduce renal and ophthalmological complications. The Steno-2 study implemented a multifactorial intervention including a combination of medications and focused behavior modification **[30].** It was reported that the intervention group had lower risks for nephropathy (relative risk 0.44, *P*=0.004), retinopathy (relative risk 0.57, *P*=0.01) and autonomic neuropathy (relative risk 0.53, *P*=0.004) over 13.3 years follow-up compared to the conventional care group . A physician-led structured diabetes management program in Germany also showed lower incidence of chronic renal insufficiency (relative risk 0.49) and amputation (relative risk 0.63)

among the intervention group over 4 years' follow-up. This program involved education and structured evidence-based care by physicians [31].

For each subtype of microvascular complication, we investigated both early stage and advanced stage of disease. Interestingly, we found RAMP-DM was more effective in reducing more severe stage of disease. RAMP-DM group showed substantial decrease in the incidence of STDR or blindness (HR: 0.55, P=0.001), while for the incidence of mild diabetic retinopathy (NPDR/pre-PDR), the difference between two groups was not evident until 24 months (Figure 1). A possible explanation might be that diabetic subjects under RAMP-DM had systematic diabetic retinopathy screening, leading to a higher detection rate of diabetic retinopathy. Early detection allows more timely management for subjects diagnosed with mild, non-clinical significant diabetic retinopathy which might result in a lower incidence of STDR. As diabetic retinopathy can be totally asymptomatic until it develops into STDR, early screening for diabetic retinopathy is critical in preventing further deterioration by giving timely intensive treatment. A previous study showed that a systematic screening program could effectively reduce the prevalence of blindness [32]. **We should note that even the RAMP-DM group might have higher detect rate for NPDR/non-PDR due to the systemic screening, the RAMP-DM management was still associated with significant lower incidences of NPDR/non-PDR, which might due to better control of blood glucose and blood pressure.**

The similar findings were observed for neuropathy. The incidence of mild neuropathy (lower limb ulcer or amputation not included) was similar between RAMP-DM and control groups (HR: 0.940, P=0.778), and the survival curves were almost overlapped (Figure 1). However, RAMP-

DM group had **significantly lower** incidence of lower limb ulcer or amputation (HR: 0.493, P=0.005), and the difference became more evident after 12 months. Patients enrolled in RAMP-DM undertook comprehensive foot examination, including physical examination for callosity, corn, ulcer, skin infection, deformities, nail pathology, temperature, ischaemic changes and peripheral pulses, monofilament test and vibration perception threshold by biothesiometer. Early screening was **likely** to detect more cases asymptomatic neuropathy, leading to relatively "higher" incidence of early stage neuropathy in the RAMP-DM group. While the incidence of lower limb ulcer or amputation was remarkably lower in the RAMP-DM group. Tight glycemic control [27, 33], structured education program [34] and multidisciplinary management [30, 31] **have been found in other studies to decrease the incidence of neuropathy effectively**. As a multidisciplinary intervention, RAMP-DM included disease education on knowledge, self-care and lifestyle during nurse intervention. The risk-stratification management might also raise the doctors' awareness to offer more intensive management of high risk patients. All these efforts might contribute to the lower incidences of severer neuropathy in the RAMP-DM group.

We found RAMP-DM was associated with lower incidences of both nephropathy (ESRD not included) and ESRD. The presence of asymptomatic nephropathy was mainly through albuminuria and eGFR. Diabetic patients under usual primary care also undertook annual blood test in Hong Kong. However, patients enrolled in RAMP-DM might receive more intensive management in preventing future deterioration of disease, resulting in lower incidences of nephropathy and ESRD.

RAMP-DM is the program to stratify diabetic patients with different risk levels so that they can receive regular assessment and screening and can be provided early with additional interventions or management. RAMP-DM is a way of increasing the focus on patients that need a more intensive treatment. The RAMP-DM is organizational investment from the Hospital Authority and Food & Health Bureau, that administrative support, central information technology system and screening facilities were well provided. In addition, the Food & Health Bureau of government commissioned **annual audit and evaluation of quality of care in three consecutive years**, which facilitate quality improvement of diabetes care and adherence to the structured risk-stratification based protocol among RAMP-DM patients. Therefore, this program could effectively translate the systematic management protocol into the real-world setting.

Strength and limitations of this study

This propensity score matched prospective comparative effectiveness study had several strengths. First, the study sample was extracted from the Clinical Management Systemof the Hospital Authority, which recorded data on all the people with diabetes managed in the public healthcare sector. This population-based sample was highly representative of the Hong Kong population with diabetes. Second, large sample size and three-year follow-up presented sufficient subjects to examine different stage of diabetic microvascular complications. Third, comprehensive covariates were included to develop propensity score matching for the two groups. The observed risk factors that might affect the incidence of diabetic complications were included. We further adjusted all the covariates during multivariable Cox regression to minimize any possible bias. Fourth, this comparative effectiveness study was based on data obtained from real patients under

primary care, and thus applicable to a real-world setting. Fifth, we used an intention-to-treat analysis, giving a more conservative estimate of the effectiveness of RAMP-DM.

Several limitations should be aware when interpreting the results. The important limitation of this study was that we could not carry out a randomized study therefore unobserved potential confounders might affect the results, although we have minimised this by including as many possible covariates as we can in propensity score matching. Second, not all the RAMP-DM subjects were included in the analysis due to missing data at baseline and some subjects were further excluded due to unavailable matched control pairs. **Third, the RAMP-DM patients and usual care patients might come from the same or different public primary care clinics. Unfortunately, we did not have the clinic information since all the patients were free to choose different public primary care clinics for their follow-up.** Fourth, three years are not long enough to project the long term benefits of RAMP-DM. **We need longer follow-up to evaluate the longer term effects of RAMP-DM. It would be interesting to see whether the effects of RAMP-DM would maintain over a longer term.**

Conclusions

This prospective comparative effectiveness study in a pragmatic primary care setting found that RAMP-DM was associated with decreased risks of first occurrence of retinopathy, STDR, nephropathy, ESRD, and lower limb ulcer or amputation over a three-year follow-up. These findings supplemented the effectiveness of RAMP-DM and provided imperative translational evidence of the effectiveness of multidisciplinary risk-stratification based management for people with diabetes.

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Figure legends

Figure 1. Kaplan-Meier survival curves

ESRD, End stage renal disease; STDR, Sight-threatening diabetic retinopathy.

All the P values were from Log-rank test.

Table 1

Table 1. Basic Characteristics at Baseline and the end of follow-up

	At baseline			At the end of follow-up* (RAMP-DM 35.5 months, Control 34.0 months)		
	RAMP (N=14,835)	Control (N=14,835)	*P* value[a]	RAMP (N=14,381)	Control (N=13,778)	*P* value[a]
	Mean ± SD or %	Mean ± SD or %		Mean ± SD or %	Mean ± SD or %	
Socio-demographic						
Age (year)	65.0±11.2	65.1±11.9	0.85			
Female	53.29%	53.43%	0.82			
On CSSA	9.86%	9.88%	0.95			
Clinical measures						
T2DM	**99.73%**	**99.76%**	**0.56**			
Duration of DM (year)	8.1±6.7	8.1±6.2	0.63			
Current smoker	9.86%	9.88%	0.61	8.29%	8.58%	0.60
SBP (mmHg)	136±17	136±17	0.89	130±15	132±16	<0.001
DBP (mmHg)	75±10	75±10	0.98	71±10	73±10	<0.001
HbA1c (%)	7.16±1.17	7.16±1.25	0.83	7.10±1.07	7.21±1.21	<0.001
TC (mmol/L)	5.03±0.94	5.04±0.96	0.40	4.41±0.81	4.46±0.87	<0.001
HDL-C (mmol/L)	1.22±0.32	1.21±0.33	0.16	1.27±0.33	1.30±0.35	<0.001
LDL-C (mmol/L)	3.09±0.82	3.10±0.84	0.26	2.49±0.69	2.52±0.72	<0.001
Triglyceride (mmol/L)	1.62±1.04	1.64±1.05	0.69	1.45±0.89	1.43±0.96	0.20
eGFR (ml/min/1.73m^2)	81.27±20.89	81.38±20.36	0.15	82.37±25.17	81.38±24.78	0.002
Charlson comorbidity score[b]	0.14±0.49	0.14±0.49	0.88	0.10±0.40	0.10±0.42	0.12
Treatment modality						
On glucose-lowering drugs	86.98%	86.89%	0.82	89.28%	84.60%	<0.001
On insulin	1.48%	1.64%	0.24	5.89%	4.75%	<0.001
On anti-hypertensive drugs	75.82%	75.86%	0.94	81.93%	78.85%	<0.001
On ACEI or ARB drugs	**42.43%**	**43.70%**	**0.03**	**52.65%**	**47.14%**	**<0.001**
On lipid-lowering drugs	16.73%	16.91%	0.69	52.26%	49.17%	<0.001

[a] Significant differences (P <0.05) between groups by independent t-test or by Chi-square test, as appropriate

[b] Add up the comorbidity component score in Charlson comorbidity index

* The number of subjects decreases with time due to death.

Table 2

Table 2. Number of diabetic complication and all-cause death at a median follow-up of 36 months

	RAMP-DM group (N=14,835)					Control group (N=14,835)					NNT
	Cumulative incidence		Incidence rate (Cases/ 100 person-years)			Cumulative incidence		Incidence rate (Cases/ 100 person-years)			
	No. of events	Rate (%)	Estimate	95% CI*	Person-years	No. of events	Rate (%)	Estimate	95% CI*	Person-years	
Any microvascular complication	**760**	**5.13%**	**1.77**	**(1.65,1.91)**	**42,818**	**935**	**6.31%**	**2.29**	**(2.15,2.45)**	**40,755**	**85**
NPDR/pre-PDR	535	3.61%	1.24	(1.14,1.35)	43,029	594	4.01%	1.45	(1.33,1.57)	41,087	250
STDR or blindness	51	0.34%	0.12	(0.09,0.15)	43,972	90	0.61%	0.21	(0.17,0.26)	41,912	370
Nephropathy	**163**	**1.10%**	**0.37**	**(0.32,0.43)**	**43,899**	**266**	**1.79%**	**0.64**	**(0.56,0.72)**	**41,777**	**145**
ESRD	**20**	**0.13%**	**0.05**	**(0.03,0.07)**	**44,026**	**47**	**0.32%**	**0.11**	**(0.08,0.15)**	**42,007**	**526**
Neuropathy	49	0.33%	0.11	(0.08,0.15)	43,986	52	0.35%	0.12	(0.09,0.16)	41,966	5,000
Lower limb ulcer or amputation	28	0.19%	0.06	(0.04,0.09)	44,019	49	0.33%	0.12	(0.09,0.15)	41,976	714

ESRD, End stage renal disease;HR,Hazard Ratio;NNT, number needed to treat; NPDR, non-proliferative diabetic retinopathy; SE,standard error;STDR, Sight-threatening diabetic retinopathy.

* The 95%CI was constructed based on Poisson Distribution

Table 3

Table 3. Multivariable Cox proportional hazard regression all endpoints

	RAMP-DM vs Control			
	HR†	SE	95%CI	P-value
RAMP-DM subjects vs Control subjects (All subjects, N=29,670)				
Any microvascular complications	**0.73**	**0.04**	**(0.66,0.81)**	**<0.001**
NPDR/pre-PDR	0.85	0.05	(0.76,0.96)	0.01
STDR or blindness	0.55	0.10	(0.39,0.78)	0.001
Nephropathy	**0.54**	**0.05**	**(0.45,0.66)**	**<0.001**
ESRD	**0.40**	**0.11**	**(0.24,0.69)**	**<0.001**
Neuropathy	0.94	0.21	(0.61,1.45)	0.78
Ulcer or amputation	0.49	0.12	(0.30,0.80)	0.01

ESRD, End stage renal disease;HR=Hazard Ratio;NPDR, non-proliferative diabetic reti
SE=standard error;STDR, Sight-threatening diabetic retinopathy.
† HR>1 indicates greater risk for endpoints

Adjusted for age, sex, whether on CSSA, duration of DM, smoking status, SBP, DBP, HbA1c, TC, I triglyceride, eGFR, Charlson comorbidity score, glubose-lowering drugs, insulin, anti-hypertensive drugs and lipid-lowering drugs.

Supplementary Table

Supplementary Table. ICD-9CM, ICPC-2 codes for diabetic macrovas

Disease	ICPC-2 Codes
Nonproliferative diabetic retinopathy /pre-proliferative diabetic retinopathy	F83
Sight threatening diabetic retinopathy (STDR) or blindness	F94
Diabetic nephropathy	NA
End-stage renal disease (ESRD)	NA
Neuropathy	N94
Ulcer of lower limb or amputation	L81

Figure

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