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第二型糖尿病女性患者的嚴重排尿障礙發生率較高：根據全國人口所進行的世代研究

Women with type 2 diabetes are associated with higher incidence of significant voiding dysfunction: A nationwide population-based cohort study

賴明志

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本論文係賴明志君（p01421017）在國立臺灣大學臨床醫學研究所完成之碩士學位論文，於民國 108 年 07 月 25 日承下列考試委員審查通過及口試及格，特此證明

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中文摘要

目標

本研究是在13年的期間內，評估第二型糖尿病女性患者的嚴重排尿障礙(VD)的發生率和風險。

研究材料和方法

這份世代群組研究使用了台灣全民健保研究資料庫(National Health Insurance Research Database, NHIRD)的資料，從2001年到2013年中，找出新診斷的第二型糖尿病患者（DM世代群組），以及符合年齡、共病現象和Charlson共病指標(CCI)分數的患者（非DM世代群組）。嚴重VD的定義為膀胱排尿有困難，需要bethanechol或tamsulosin的治療。對於嚴重VD的發生率，我們調查到2013年底為止。據此計算出嚴重VD的發生率（每年每一萬人），並使用Cox比例風險迴歸模型(Cox proportional hazards regression model)估算風險比例。使用Kaplan-Meier法(Kaplan-Meier)，在兩個世代群組中，繪製出嚴重VD的累積發生率圖形。

結果

在13年期間，第二型糖尿病女性患者的嚴重VD發生率為1.42%。DM世代群組和非DM世代群組共納入34,125位病患。嚴重VD發生率在DM世代群組和非DM世代群組中，分別約為有20.0位和11.4位（每年每一萬人）。針對混擾因子進行修正後，可以推算出，第二型糖尿病女性患者的嚴重VD發生率風險增加1.79倍。在10年的後續追蹤期間，DM世代群組的嚴重VD累積發生率顯著較高(2.01% vs. 1.07%, $p<0.0001$)。

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結論

對於女性，第二型糖尿病和嚴重 VD 的風險上升有關聯性。因此，臨床醫師應該教育女性病患，使其了解第二型糖尿病和嚴重 VD 之間的關聯性。

關鍵字：糖尿病;排尿障礙;發生率;女性;台灣

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英文摘要

Objective:

To evaluate the incidence and risk of significant voiding dysfunction (VD) in women with type 2 diabetes during a 13-year study period.

Materials and methods:

This cohort study utilized data from the National Health Insurance Research Database (NHIRD) of Taiwan to identify patients with type 2 diabetes (DM cohort) and age-, comorbidity-, and Charlson comorbidity index (CCI) score-matched cohort (non-DM cohort) from 2001 to 2013. Significant VD was defined as difficulty in bladder emptying requiring bethanechol or tamsulosin treatment. Significant VD occurrence was monitored until the end of 2013. Incidence rate of significant VD (per 10,000 person-years) was calculated, and hazards ratios were estimated using Cox proportional hazards regression models. Cumulative incidence of significant VD in both cohorts were plotted using the Kaplan-Meier method.

Results

Incidence of significant VD in women with type 2 diabetes is 1.42% during a 13-year period. A total of 34,125 patients were selected for the DM and non-DM cohorts, respectively. Incidence rates of significant VD were approximately 20.0 and 11.4 per 10,000 person-years for the DM and non-DM cohorts, respectively. After adjusting for potential confounders, a 1.79-fold increased risk of significant VD was observed in

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women with type 2 diabetes. Cumulative incidence of significant VD was significantly higher in the DM cohort at the 10-year follow-up (2.01% vs. 1.07%, $p<0.0001$).

Conclusion

Type 2 diabetes is independently associated with increased significant VD risk in women. Therefore, clinicians should be aware of and educate female patients about the association between type 2 diabetes and significant VD.

Key words: diabetes mellitus; voiding dysfunction; incidence; women; Taiwan

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1. Introduction

1.1 Background

The prevalence of diabetes mellitus has been increasing worldwide over the past few decades. In Taiwan, the prevalence of diabetes mellitus was 9.2 % in 1996 (Chang et al, 2000). Besides, more than 99% of people with diabetes had type 2 diabetes, with a higher incidence in patients aged 20-59 years (Jiang et al, 2012).

People with diabetes mellitus are at an increased risk for developing macrovascular and microvascular complications (Gross et al, 2005 ; Barr et al, 2007).. In the present study, the widely recognized microvascular and macrovascular complications from diabetes mellitus predispose patients to develop lower urinary tract dysfunction, including bladder dysfunction or urethropathy (Yu et al, 2004; Yang et al, 2007; Robinson et al, 2012). Studies showed that more than 50% of men and women with diabetes had bladder dysfunction (Goldman, 1999; Hill et al, 2008; Daneshgari et al, 2009). Diabetic bladder dysfunction or urethropathy can involve different degrees and combinations of voiding and storage symptoms. Voiding dysfunction (VD) is defined by ICS/IUGA as abnormally slow and/or incomplete micturition (Abrams et al, 2002). Currently, the two categories of drugs, cholinergic agents and alpha blockers, are being used for the treatment of VD in women (Chang et al, 2008; Gaitonde S, 2018). Although it is not life-threatening, diabetic VD substantially affects a patient's quality of life and may be associated with recurrent urinary tract infections and upper urinary tract damage.

1.2 Objectives

Data on lower urinary tract symptoms in women with diabetes mellitus have been widely reported (Brown et al, 1999; Hill et al, 2008; Dereli et al, 2016). However,

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studies on VD in women with diabetes mellitus are limited. In a hospital-based questionnaire study conducted in UK, 56 (38%) had VD in women with diabetes mellitus (Fayyad et al. 2009). Changxiao et al. estimated that the prevalence rate of VD by urodynamic diagnosis was 55.9% in Chinese women with DM (Changxiao H et al, 2014). The two reasons of this high prevalence of VD in women with DM may be as follows: the hospital-based study may involve patients with more comorbidities, and the questionnaire survey tends to identify patients with mild VD. In addition, these studies may be associated with very mild VD, which does not require treatment. Little is known about the impact of type 2 diabetes on seeking treatment for significant VD in women in a community. The aim of this study was to analyze the incidence and risk of seeking treatment for significant VD in women with type 2 diabetes during a 13-year period in Taiwan using data from a nationwide population-based healthcare database.

2. Materials and methods

2.1 Data source

The Longitudinal Health Insurance Database (LHID) contains 1 million randomly sampled beneficiaries (Bøje et al, 2014). The source population consisted of nearly the entire population of Taiwan (23 million inhabitants), and the LHID was derived from the National Health Insurance Research database (NHIRD) between 1999 and 2013. Clinical diagnoses of patients in the LHID were made by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study involved a secondary analysis of health-related databases and was approved by the Ethics Review Board of National Taiwan University Hospital (201903099W).

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2.2 Study design

A population-based retrospective cohort study was conducted using the LHID derived from the NHIRD in Taiwan from 1999 to 2013. This study was designed to evaluate the incidence and risk of significant VD in women with type 2 diabetes. Significant VD was defined as a feeling of difficulty in emptying the bladder which required bethanechol or tamsulosin treatment of more than 3 months in one year. The occurrence of significant VD was monitored until the end of 2013. The cohort group was matched with healthy volunteers stratified by age, Charlson comorbidity index (CCI) score, and comorbidities using the propensity score method at a 1:1 ratio (Alam et al, 2019).

2.3 Study participants

Patients older than 20 years old diagnosed with diabetes mellitus (ICD-9-CM code 250) between 2001 and 2012 were classified as the DM cohort. We excluded patients diagnosed with diabetes mellitus before 2001, with type 1 diabetes (ICD-9-CM code 250.X1), and with bladder cancer (ICD-9-CM code 188). The date of type 2 diabetes diagnosis was defined as the index date. Patients taking bethanechol or tamsulosin for 3 months before the index date were excluded (Fig. 1). The matched cohort without diabetes mellitus was also selected from the LHID.

The DM and non-DM groups were matched by stratifying age, CCI score, and comorbidities, including cerebrovascular diseases (CVA) (ICD-9-CM code 430-438), Parkinson's disease (PD) (ICD-9-CM code 332), spinal cord injury (SCI) (ICD-9-CM codes 952, 1, 806), and history of hysterectomy (the procedure codes of 65.5, 65.6, 68.3–5, 68.9). All patients included in the study were followed up between the index

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date and either the occurrence of significant VD, death, withdrawal from the National Health Insurance Program, or the end of the study period in 2013.

2.4 Statistical analysis

Basic demographic characteristics, CCI score, and comorbidities were compared between the two cohorts using t-test for age and chi-squared test for CCI score and comorbidities. The incidence rate of VD (per 10,000 person-years) was calculated for both cohorts. The number of new users of bethanechol or tamsulosin were calculated and reported annually from 2001 to 2013. The risk of developing significant VD was estimated for patients with and without type 2 diabetes, as well as those with associated risk factors. Hazards ratios (HRs) and 95% confidence intervals (CIs) were calculated by applying the univariate and multivariate Cox regression models. The cumulative incidence of significant VD in DM and non-DM cohorts were plotted using the Kaplan-Meier method, and their differences were examined using the log-rank test. Furthermore, the risk of developing significant VD was evaluated and stratified by age, CCI score, and comorbidities in each cohort. All data analyses were performed using SAS statistical software (Version 9.4, SAS Institute, Cary, NC, United States), and the two-sided significance level was set at $p < 0.05$.

3. Results

3.1 Participants and descriptive data

During the follow-up period, there were 37,573 women with type 2 diabetes, including 536 patients (1.42%) with significant VD, but 3448 patients with type 2 diabetes (9.1%), including 96 patients with significant VD, could not be matched. After propensity score matching, there were 34,125 patients for each DM and non-DM cohorts. Moreover, the incidence of significant VD in the DM and non-DM cohorts was

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1.28% and 0.75%, respectively. The distributions of age, CCI score, and comorbidities were similar between the two cohorts (Table 1). The mean (± standard deviation; SD) ages of DM and non-DM cohorts were 57.8 (±13.7) and 57.9 (±13.6) years, respectively. The comorbidities in the DM and non-DM cohorts were CVA (7.24% vs. 7.24%), PD (0.97% vs. 0.97%), SCI (0.02% vs. 0.02%), and history of hysterectomy (0.47% vs. 0.47%). The mean follow-up periods were 6.4 and 6.6 years for the DM and non-DM cohorts, respectively. The mean interval between the diagnosis of type 2 diabetes and significant VD occurrence was approximately 4.3 years.

3.2 Main results

Table 2 shows the multivariate Cox hazard analysis with adjustment for age, CCI score, and comorbidities. The incidence rates of significant VD were approximately 20.0 and 11.4 per 10,000 person-years for the DM and non-DM cohorts, respectively, with a 1.79-fold (95% CI= 1.54-2.09, P<0.001) increased risk of significant VD after adjusting for age, CCI score, and comorbidities. The multivariate analysis showed that patients aged 70 years or older had an 8.48-fold (95% CI = 5.41-13.30, P<0.001) increased risk of significant VD than those aged 20-40 years. The multivariate risk of significant VD also increased with increasing CCI score, and patients with CCI score of ≥4 had a 2.68-fold (95% CI=1.68-4.30, P<0.001) increased risk of significant VD than those with CCI score of 0. After adjusting for age and CCI score, the risk of significant VD was higher in patients with CVA (HR =1.33, 95% CI = 1.06-1.66, P<0.05) and PD (HR = 1.71, 95% CI = 1.11-2.65, P<0.05) as comorbidities (Table 2). The cumulative incidence of significant VD estimated using the Kaplan-Meier analysis was significantly higher in the DM cohort than in the non-DM cohort by the end of the 13-year follow-up (log-rank test, p < 0.0001; Fig 2). Our population-based cohort study

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revealed that the cumulative incidence of significant VD was 0.94% and 2.01% at the 5th and 10th year after type 2 diabetes diagnosis.

3.3 The analysis of subgroups

To examine whether type 2 diabetes is an age-dependent risk factor for significant VD, we divided the patients into five groups by age. The DM cohort had significantly greater risk for the development of significant VD than the non-DM cohort in the subgroup with inverse association, whereas the 20-40-year subgroup had a 4.42-fold (95% CI= 1.49-13.15, P<0.01) increased risk of significant VD. We also divided the patients into five groups according to their CCI score. The DM cohort still had a significantly greater risks for the development of significant VD than the non-DM cohort in the subgroup with inverse association, whereas those with CCI score of 0 had a 2.52-fold (95% CI= 1.93-3.29, P<0.001) increased risk of significant VD (Table 3).

3.4 The analysis of new users of bethanechol, tamsulosin or combination therapy

Fig. 3 shows that the number of new users of bethanechol or tamsulosin calculated annually from 2001 to 2013. There were 356 and 180 new users of bethanechol and tamsulosin, respectively, between 2001 and 2013. The number of new users of bethanechol increased by 2.04 times during the13-year period, from 23 in 2005 to 47 in 2013. The number of new users of tamsulosin increased by 8.25 times during the 13-year period, from 4 in 2005 to 33 in 2013. A steady increase was found in the new users of bethanechol, but the rapid increase in the new users of tamsulosin flattened after 6 years. Especially, the combination therapy of bethanechol and tamsulosin has been used since 2007. The number of new users of the combined therapy increased by 3.0 times during the 7-year period, from 3 in 2009 to 9 in 2013 (Fig. 3).

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4. Discussion

4.1 The interpretation of our database

The NHIRD is nationwide anonymous eligibility, enrollment information, and claims for visits, procedures, and prescription medications of 99% of the entire estimated 23 million population of Taiwan (Hsiao et al, 2007). Our study used the LHID that contained all outpatient and inpatient medical claims of 1 million beneficiaries randomly sampled from the NHIRD during the period of January 1, 1999 to December 31, 2013. We identify a cohort based on health services, diagnoses, surgical procedures, and drug utilization from this database. As a result, we believe that our data are reliable, and the patients' characteristics are similar to those of the whole population.

4.2 Summarize main results

To the best of our knowledge, this is the first study to report the incidence of significant VD (1.42%) in women with type 2 diabetes over a 13-year period. Our study involving only women with type 2 diabetes decreases the confounding effect of concurrent benign prostate enlargement, which shares the same VD. However, information regarding the incidence of VD in women with DM is extremely limited. In hospital-based studies, only the prevalence of VD in women with DM reported in UK and China are 38 % and 55.9%, individually (Fayyad et al, 2009; Changxiao H et al, 2014).. In our community-based study, the incidence of significant VD in women with type 2 diabetes is 1.42%. Although the higher prevalence of VD in women with DM was reported in previous studies, our results showed the lower incidence of significant VD in women with type 2 diabetes. This difference may be present because our patients may only have visited the hospitals when their conditions were already serious. In this

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study, we found that increased risks of significant VD in women were associated with age of more than 50 years, CCI score of more than 0, and comorbidities of CVA and PD, but comorbidities of SCI and history of hysterectomy were not associated with increased risk of significant VD. No event of significant VD in SCI patients may be a reflection of more serious VD with intermittent catheterization program or Foley catheter insertion. Only three events of significant VD were observed in patients with history of hysterectomy, which may reflect advances in surgical techniques and management options (Kietpeerakool et al, 2019) After adjusting the effects of age, CCI score, CVA, and PD, the risk of significant VD remained higher in the DM cohort than in the non-DM cohort. Our finding showed a 1.79-fold increased risk of significant VD in women with type 2 diabetes after adjusting for these confounding factors. The incidence rates of significant VD in women was 20.0 and 10.5 per 10,000 person-years in the DM and non-DM cohorts, respectively. Although after matching, the incidence of significant VD in women with type 2 diabetes was underestimated and decreased to 1.28%, the relationship between type 2 diabetes and significant VD in women is still established suggesting that it is highly probable that type 2 diabetes is an independent medical condition that causes significant VD in women.

Initial studies suggested that long standing diabetes mellitus causes paralysis of the detrusor muscle leading to VD (Hill et al, 2008). Our cohort study first indicated that the cumulative incidence of significant VD, which could be considered as long-term probability, was 0.93% and 2.01% at the 5th and 10th year, respectively, after the diagnosis of diabetes mellitus. These patients with type 2 diabetes in our cohort were newly diagnosed, and the mean interval between the diagnosis of type 2 diabetes and significant VD occurrence was 4.3 years. However, in a urodynamic study, time to

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diabetic cystopathy with VD in women was reported in at least 8-9 years after the diagnosis of diabetes mellitus (Kebapci et al, 2007).. This difference may be due to detrusor underactivity, diabetic urethropathy, or poor health-habit counseling among women in Taiwan, as the time to occurrence of significant VD in women with type 2 diabetes is lower in our study than in the urodynamic study (Yang et al, 2007; Lee et al,2009).

4.3 The interpretation of results of subgroup analysis

Studies have shown that elderly women with CVA, PD, SCI, or history of hysterectomy complained of voiding difficulty, such as small caliber or urinary retention (Sveinbjornsdottir S, 2016 ; Quadri et al, 2018; Akkoç et al, 2019; Kietpeerakool et al, 2019).In the earlier study, detrusor-impaired contractility with VD is common in elderly women older than 70 years old (Abarbanel et al, 2007). Our subgroup analyses showed that women with type 2 diabetes have an age-dependent increasing incidence rate of significant VD, but the risk of significant VD was higher in the patients aged 20-40 years, which may reflect the influence of childbirth, detrusor underactivity, or diabetic urethropathy (Yang et al, 2007; Lee et al,2009; Beaumont T, 2019).. In addition, a possible misclassification bias cannot be avoided because patients with type 1 diabetes cannot totally be excluded by ICD-9-CM codes 250.X1, especially patients aged 20-40 years. The small sample size of women with type 2 diabetes aged 20-40 years with significant VD is another bias with the effects of inflated false discovery rate. Therefore, it is more believable that the occurrence of significant VD in women with type 2 diabetes aged 41-50 years was 2.66-fold higher. The CCI-dependent increasing incidence rate of significant VD in women with type 2 diabetes was also found, but lower CCI score had a greater magnitude of the risk of significant VD and

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the occurrence of significant VD in women with type 2 diabetes with a CCI score of 0 was 2.52-fold higher. This suggests that the urological and medical care of women with type 2 diabetes in Taiwan should be more aggressive. It is highly probable that type 2 diabetes is an independent medical condition that causes significant VD in women, which could impact the comprehensive care of urinary symptoms of patients with type 2 diabetes through effective diabetes mellitus therapy (Tai et al, 2016). However, because the severity of type 2 diabetes cannot be determined through our national databases, this hypothesis could not be validated. We recommend that additional prospective studies are conducted to verify the age- and CCI-related elevated risk of significant VD in women with type 2 diabetes. Owing to the effect of type 2 diabetes, the risk of significant VD in patients with CVA was 1.80-fold higher, which was similar to that in patients without CVA. On the contrary, the risk of significant VD in women with type 2 diabetes who have PD was not significantly different. In short, women with PD are highly associated with significant VD compared to those with CVA.

4.4 Summarize the trend of new users of bethanechol, tamsulosin or combination therapy

Current drugs, such as bethanechol or tamsulosin, have been used for the treatment of VD in women since 2000. Bethanechol, a cholinergic agent produces the effects of the parasympathetic nervous system stimulation. Bethanechol is usually prescribed in elderly women for detrusor atony, urinary retention, or incomplete bladder emptying (Gaitonde S, 2018). Tamsulosin, an alpha-1-adrenergic receptor (a1-AR) blocker is effectively used to improve voiding symptoms in those with benign prostatic hyperplasia (BPH) (Roehrborn et al, 2004).Tamsulosin is also used for the treatment of VD in women (Chang et al, 2008).. In Taiwan, bethanechol has been prescribed to treat

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VD in women for a long time, and tamsulosin for treating VD in women has been the most commonly used alpha blocker. Other alpha blockers such as doxazosin or terazosin may be used for treating VD in women or hypertension. To eliminate the confounding effects, we only used the prescription of bethanechol or tamsulosin as the occurrence of significant VD. Owing to the occurrence of significant VD with seeking treatment, we believe that the incidence of significant VD among women with type 2 diabetes in our study is more reliable than those reported in a previous study by questionnaire or urodynamic studies (Fayyad et al, 2009; Changxiao H et al, 2014). Given that doctors may use bethanechol to treat constipation (Poetter et al, 2013) or tamsulosin to shorten the passage time of smaller ureteral stones (Abdel-Meguid et al, 2010), we exclude patients receiving bethanechol or tamsulosin therapy within 3 months before the index date. In this study, we found that the number of new users of bethanechol and tamsulosin increased by 2.04 and 8.25 times, respectively, between 2005 and 2013. The number of new users of combination therapy of bethanechol and tamsulosin increased by 3.0 times between 2009 and 2013. We believe that many doctors know that tamsulosin can be used to treat women VD. We also find a gradually increasing trend of the use of combination therapy of bethanechol and tamsulosin since 2007.

4.5 Limitations

This study had limitations inherited from the NHIRD. First, ICD-9-CM codes were used to identify cohorts in the NHIRD. All insurance claims in the NHIRD were made by medical doctors according to the standard criteria, but this study may not have the same quality as that of a prospective well-designed study. Second, the NHIRD did not contain personal information regarding laboratory data, record of alcohol and cigarette

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use, and exercise that may be confounding variables influencing voiding function. Therefore, we used a propensity score to match age, CCI score, and comorbidities to minimize this potential influence. Third, the diagnoses of diabetes mellitus and comorbidities were completely dependent on the ICD-9-CM codes, especially diabetes mellitus. We adopted the diabetes mellitus diagnosis as at least two outpatient visits or one hospitalization that was already validated (Lin et al,2017). Fourth, type 1 diabetes was present in less than 1% of the diabetic population in Taiwan (Jiang et al, 2012). We excluded the patients diagnosed with type 1 diabetes (ICD-9-CM codes 250.X1), but a possible misclassification bias cannot totally be avoided. Fifth, we only analyzed tamsulosin use for significant VD in women with type 2 diabetes, rather than including all alpha blockers. Therefore, the incidence of significant VD in women with T2DM might be mildly underestimated.

5. Conclusion

To our knowledge, this is the first study to report that the incidence of significant VD in women with type 2 diabetes was 1.42% during a 13-year period. Type 2 diabetes is independently associated with an increased risk of significant VD in women, especially women type 2 diabetes aged 41-50 years or with a lower CCI score. Therefore, clinicians should be aware of and educate patients about the association between type 2 diabetes and significant VD in women. Further large-scale prospective clinical studies are needed before definite conclusions can be drawn.

6. Future perspectives

This is the first study to report that the incidence and risk of significant VD in women with type 2 diabetes in a community. The data will be used to educate patients about the

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association between type 2 diabetes and significant VD in women despite some inherited limitations from our database. Because the due date of our database is March 2019, we cannot modify our data. To solve this problem, we plan to perform further large-scale retrospective studies from the National Health Insurance Research database of the entire population in Taiwan.

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8. Figures and tables

Figure 1. Flowchart showing the study participant selection

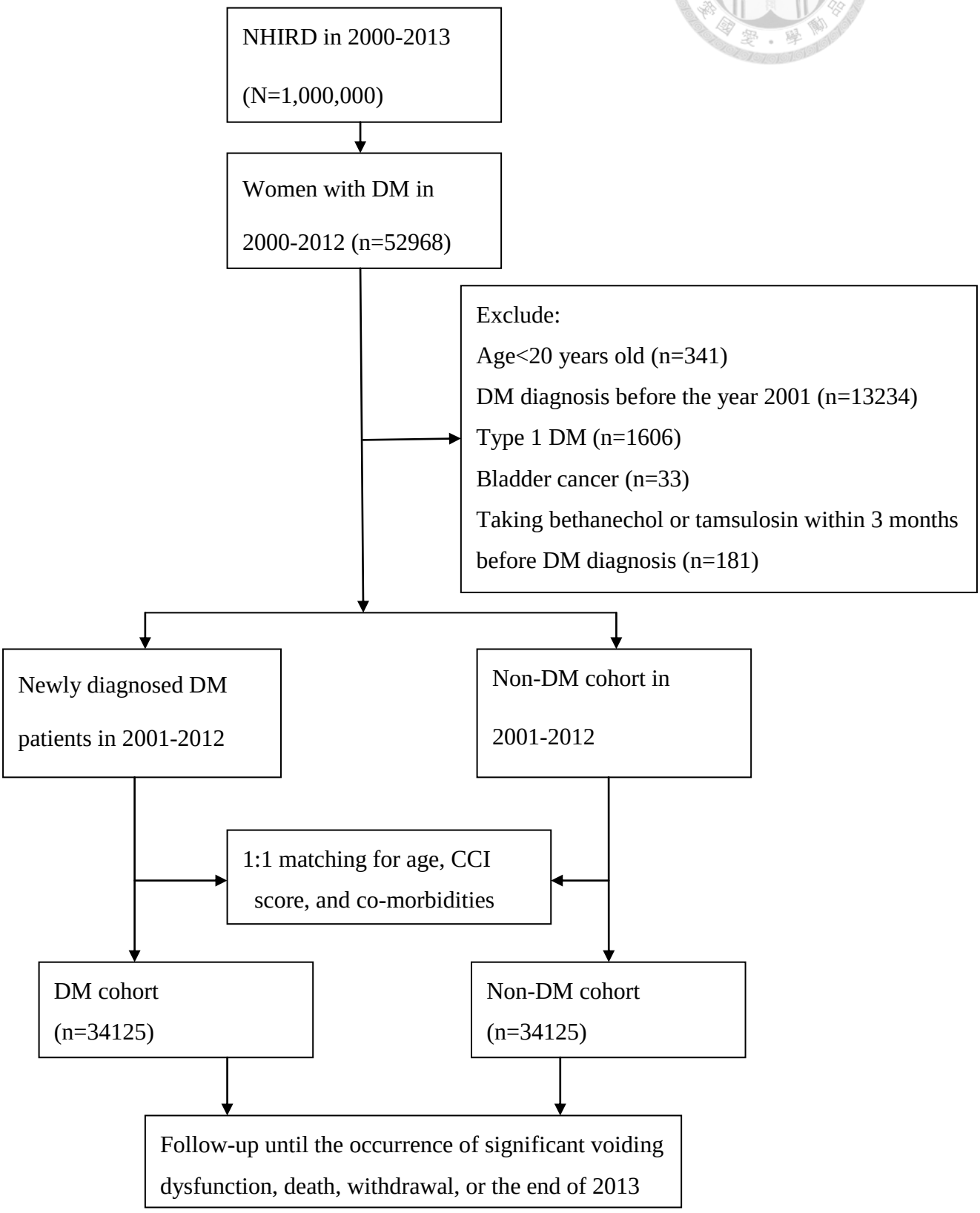

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Table 1. Characteristics between patients with and without DM

	DM	non-DM	P-value
Female, no, (%)	34125 (100.00)	34125 (100.00)	
age, year, no, (%)			0.99
20-40	3600 (10.55)	3600 (10.55)	
41-50	6106 (17.89)	6106 (17.89)	
51-60	10341 (30.30)	10341 (30.30)	
61-70	7796 (22.85)	7796 (22.85)	
≧71	6282 (18.41)	6282 (18.41)	
CCI, no. (%)			0.99
0	18838 (55.20)	18838 (55.20)	
1	10097 (29.59)	10097 (29.59)	
2	3806 (11.15)	3806 (11.15)	
3	1032 (3.02)	1032 (3.02)	
≧4	352 (1.03)	352 (1.03)	
comorbidity, no. (%)			
CVA			1.00
No	31654 (92.76)	31654 (92.76)	

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Yes	2471 (7.24)	2471 (7.24)	
PD			1.00
No	33794 (99.03)	33794 (99.03)	
Yes	331 (0.97)	331 (0.97)	
SCI			1.00
No	34119 (99.98)	34119 (99.98)	
Yes	6 (0.02)	6 (0.02)	
Hysterectomy			1.00
No	33966 (99.53)	33966 (99.53)	
Yes	159 (0.47)	159 (0.47)	

Abbreviations: DM, diabetes mellitus; CCI, Charlson comorbidity index; CVA, cerebrovascular diseases; PD, Parkinson's disease; SCI, spinal cord injury

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Table 2. Incidence rates and hazard ratios (HR) of significant VD for DM and potential risk factors in multivariate cox regression model analysis

				HR (95% CI)	
variables	Event	Person-years	Rate	Univariate	Multivariate
DM					
No	258	226195	11.4	1.00	1.00
Yes	440	219063	20.0	1.76 (1.51, 2.06)***	1.79 (1.54, 2.09)***
age, year					
20-40	21	51401	4.0	1.00	1.00
41-50	54	87521	6.1	1.51 (0.91, 2.50)	1.44 (0.87, 2.38)
51-60	130	135764	9.5	2.38 (1.50, 3.77)***	2.15 (1.35, 3.41)**
61-70	187	101752	18.3	4.56 (2.91, 7.16)***	3.85 (2.45, 6.07)***
≧71	306	68819	44.4	11.23 (7.22, 17.49)***	8.48 (5.41, 13.30)***
CCI					
0	256	252464	10.1	1.00	1.00
1	258	131636	19.6	1.94 (1.63, 2.30)***	1.49 (1.24, 1.78)***
2	125	46436	26.9	2.67 (2.15, 3.30)***	1.55 (1.23, 1.95)***
3	38	11645	32.6	3.24 (2.30, 4.55)***	1.52 (1.06, 2.17)*

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≧4	21	3076	68.2	6.82 (4.37, 10.65)***	2.68 (1.68, 4.30)***
comorbidity$^{\omega}$					
CVA					
No	580	417150	13.9	1.00	1.00
Yes	118	28107	41.9	3.04 (2.50, 3.71)***	1.33 (1.06, 1.66)*
PD					
No	676	442117	15.2	1.00	1.00
Yes	22	3141	70.0	4.68 (3.06, 7.16)***	1.71 (1.11, 2.65)*
SCI					
No	698	445209	15.6	1.00	1.00
Yes	0	49	0	-	-
Hysterectomy					
No	695	442991	15.6	1.00	1.00
Yes	3	2267	13.2	0.83 (0.27, 2.59)	-

CI: confidence interval.

Rate: incidence rate, per 10,000 person-years.

*p<0.05.

**p<0.01.

***p<0.001.

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Table 3. Subgroup analysis for incidence and hazard ratio (HR) of significant VD between patients with and without DM, stratified by age and CCI

	DM			non-DM			HR (95%CI)
	Event	Person-years	Rate	Event	Person-years	Rate	Multivariate
age, year							
20-40	17	25605	6.6	4	25795	1.5	4.42 (1.49, 13.15)**
41-50	39	43350	9.0	15	44170	3.4	2.66 (1.46, 4.82)**
51-60	90	66858	13.4	40	68905	5.8	2.34 (1.61, 3.39)***
61-70	119	50218	23.7	68	51533	13.2	1.78 (1.32, 2.40)***
≧71	175	33029	52.9	131	35790	36.6	1.45 (1.16, 1.82)**
CCI							
0	180	124142	14.5	76	128321	5.9	2.52 (1.93, 3.29)***
1	155	64832	23.9	103	66803	15.4	1.57 (1.22, 2.01)***
2	69	22799	30.2	56	23636	23.6	1.28 (0.90, 1.83)
3	22	5767	38.1	16	5877	27.2	1.50 (0.78, 2.85)

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≧4	14	1520	92.0	7	1555	44.9	2.28 (0.92, 5.65)
comorbidity							
CVA							
No	367	205592	17.8	213	211558	10.0	1.79 (1.52, 2.12)***
Yes	73	13470	54.1	45	14637	30.7	1.80 (1.24, 2.60)***
PD							
No	428	217573	19.6	248	224543	11.0	1.82 (1.55, 2.12)***
Yes	12	1490	80.5	10	1651	60.5	1.28 (0.55, 2.96)

ω: comorbidities of SCI and hysterectomy not listed due to small sample sizes about both of significant VD events

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Figure 2. Kaplan-Meier probability for DM and non-DM patients with significant VD

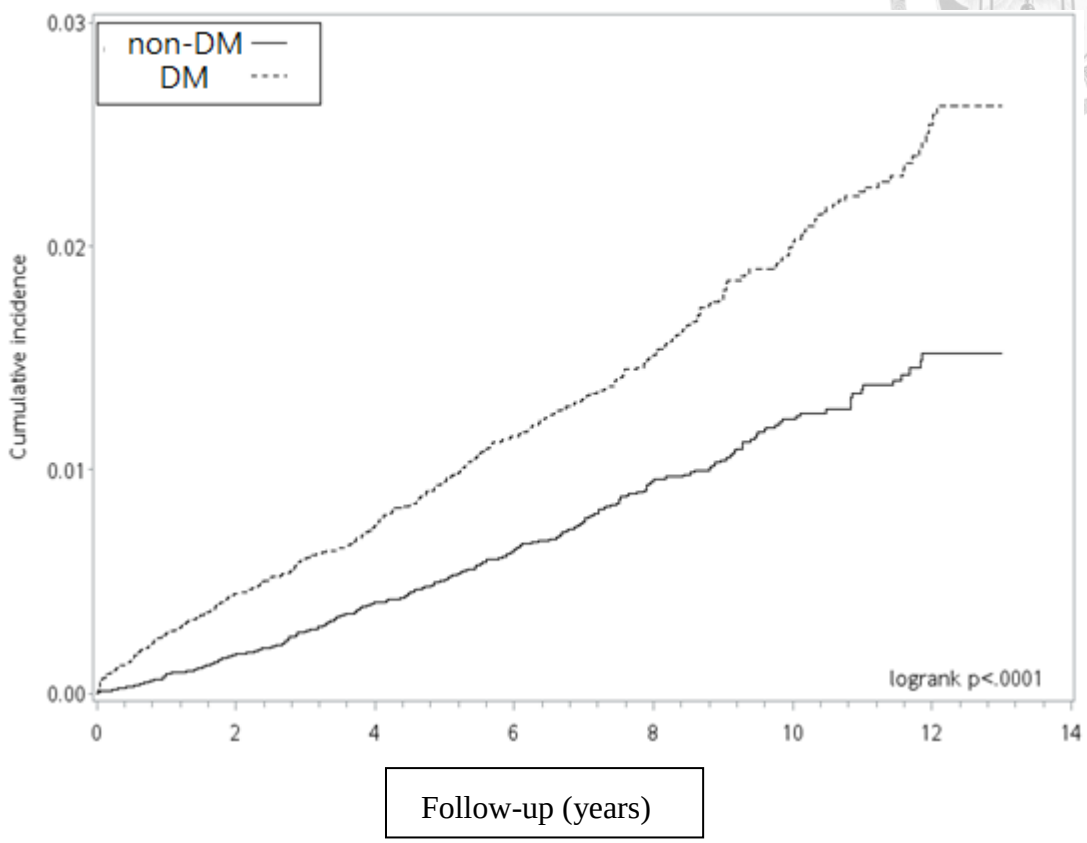

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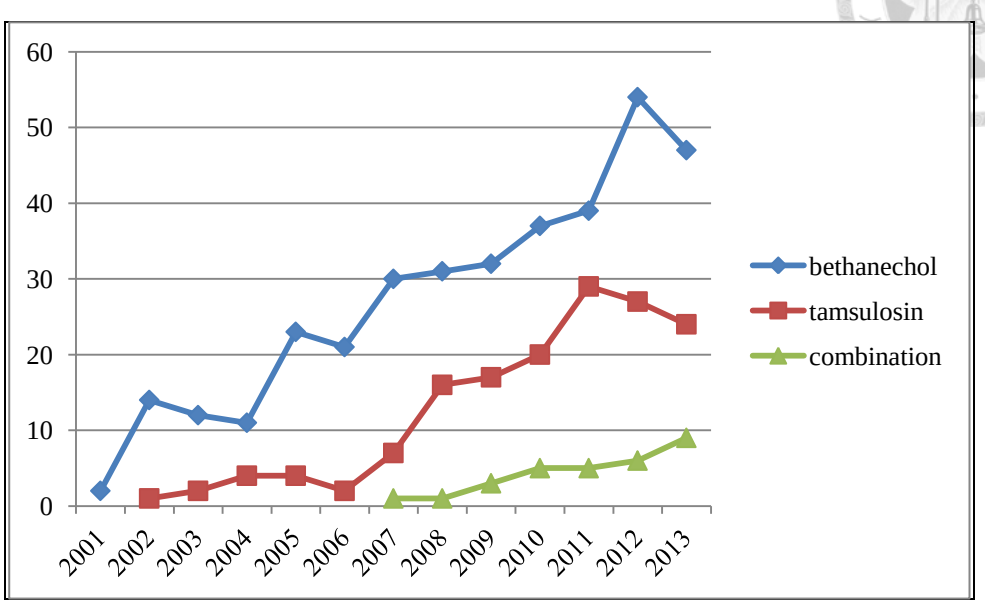
Figure 3. The number of new users of bethanechol, tamsulosin, or combination therapy by year



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Appendix

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