보건학박사 학위논문

Drug Treatment Variation and Association with Health Outcome in Type 2 Diabetes Patients with Comorbidity and Demographic Difference

동반질환 및 인구학적 특성 차이에 따른 제 2 형 당뇨병 약물치료행태의 변이 및 건강결과와의 연관성 분석 연구

2018 년 8 월

서울대학교 보건대학원

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ABSTRACT

Abstract

Introduction

The prevalence of type 2 diabetes (T2D) has been increasing steadily with 422 million people being affected worldwide. While T2D care is delineated in numerous international clinical guidelines, significant variation in T2D management impacting morbidity and mortality has been reported. As it is known that uncontrolled variance affects quality of T2D care, the identification of factors that affect this variance is crucial. Of particular interest is the variability of drug treatment which is integral to T2D care. Difference in demographic factors and comorbid status might influence the treatment process and health outcome at the patient level, thereby causing an increased burden of providing optimal health care services to T2D patients. Considering that the proportion of T2D patients with other diseases further increases, the treatment variance related to the patient's comorbid status should be assessed. Moreover, identifying secondary treatment alternatives and its effect on health outcomes is important for future T2D care guidelines.

Therefore, this thesis aimed (1) to identify demographic factors that affect the variance of T2D drug treatment, (2) to explore treatment patterns and its relation to comorbid status of T2D patients and (3) to assess the association

between the variation of T2D drug treatment and health outcome while considering the patient's comorbid status.

Methods

For the first objective, a cross-sectional study was conducted including 24,628 T2D patients, among 183 practices from the GIANTT (Groningen Initiative to Analyze Type 2 Diabetes) database which included more than 80% of general practices in a province of the Netherlands. Multilevel logistic regression was used to examine the between practice variance in treatment and the effect of patient characteristics on this variance. Treatment variance was assessed for: glucose-lowering drugs/metformin, lipid-lowering drugs/statins, and blood pressure-lowering drugs/renin-angiotensin-aldosterone system (RAAS) blockers. Included patient characteristics were age, gender, diabetes duration, comorbidity, co-medication and practice characteristics were number of T2D patients, practice type, diabetes assistant availability.

For the second objective, a retrospective, observational exploratory study was conducted with 7,123 T2D patients aged 30 years and older without diabetes microvascular- or/and macrovascular complications. The South Korean 2009 and 2013 National Health Insurance Service-National Sample Cohort (NHIS-NSC) database was used. Number and type of comorbidity,

presence of diabetes complications were assessed on 14 chronic diseases and 6 diabetes complications. Also, number and type of glucose lowering drugs, presence of lipid lowering drug and/or blood pressure lowering drug treatment were assessed. The relationship of comorbid status, drug treatment and diabetes complications was explored using two-step cluster analysis and nonlinear canonical correlation analysis.

For the third objective, a retrospective cohort study was conducted using the South Korean National Health Insurance Service–National Sample Cohort (NHIS-NSC) database, enrolling 5,693 T2D patients with one or more diabetes-related comorbidities who switched from monotherapy to metformin combined sulfonylurea (MET+SU) or dipeptidyl peptidase-4 inhibitor (MET+DPP4i) between July 1, 2008 and December 31, 2013. The risk of hypoglycemia, cardiovascular disease (CVD) events and all-cause mortality was examined using Cox proportional hazard modeling and propensity score matching.

Results

First, treatment variance between practices and demographic factors that affect the variance of T2D drug treatment were identified. Through the analysis, existence of treatment variance between practices was observed and variation due to age, gender, multiple drug use, and comorbidity was identified. Variance

that was explained at practice level was 7.5% for glucose-lowering drugs, 3.6% for metformin, 3.1% for lipid-lowering drugs, 10.3% for statins, 8.6% for blood pressure-lowering drugs, and 3.9% for RAAS blockers. Within this variance, patient and practice characteristics explained 6.0% to 20.1% of the total variance in each drug treatment. The patient's age and the use of multiple chronic drugs were the most relevant patient characteristics, while number of T2D patients per practice was the most relevant practice characteristic.

Second, comorbidity and drug treatment patterns were identified and the associations between comorbid status, drug treatment pattern and occurrence of diabetes complications were analyzed. Through two step cluster analysis, 7 baseline and 12 follow-up comorbidity clusters, 20 treatment clusters exhibited significant similarities within group and dissimilarities between groups (average silhouettes 0.8). From these clusters, 5 groups were identified in terms of similarity among baseline comorbidity, drug treatment, and follow-up comorbidity clustering through nonlinear canonical correlation analysis. Combination treatment such as, metformin combined with sulfonylurea (MET+SU) was commonly observed among T2D patients with 2 or less comorbidities. Meanwhile, although metformin combined with dipeptidyl peptidase-4 inhibitors (MET+ DPP4i) or thiazolidinedione combined with sulfonylurea (SU+TZD) were observed in patients with 2 or more diabetes related comorbidities, common treatment patterns were less or not identified in

general as number of comorbidity increased and both type (diabetes unrelated- or related) of comorbidity were present. Especially, in group of T2D patients with 2 or more comorbidities of both type of comorbidity (diabetes unrelated-, related) present, patterns were not identified or identified treatment differed from other groups. Also occurrence of microvascular- or macrovascular complication and its relation to comorbidity and treatment pattern was not identified.

Third, association between T2D drug treatment and health outcome were analyzed considering difference in type of treatment and patient's comorbid status. Results showed that MET+DPP4i treatment was associated with a lower risk of hypoglycemia, CVD events and all-cause mortality compared to MET+SU; adjusted HRs (95%CI), 0.39 (0.18–0.83), 0.72 (0.54–0.97), and 0.64 (0.39–1.05), respectively. Also type and number of comorbidities were identified as significant risk factors for CVD events and mortality.

Conclusion

This thesis identified factors that affect T2D treatment variation and analyzed treatment alternatives and its impact on health outcome. Considerable variance existed between clinic treatment rates. T2D patients' age was identified as characteristic that may account for justifiable variance in T2D

treatment. In addition, the presented study found that currently recommended diabetes drug treatment was adhered more in patients cluster with less comorbidity while combination therapy, such as, SU or DPP4i combined with MET or SU+TZD were more observed in complex comorbid status. Lastly, type, number of comorbidity were factors to increase risk of macrovascular complications and mortality. In T2D patients with comorbidities, MET+DPP4i treatment was associated with lower risks of hypoglycemia, CVD events and all-cause mortality compared with MET+SU.

Accordingly, T2D guideline adherence may improve if its more customized by patient's age and comorbidity status when developing treatment recommendations. Furthermore, T2D treatment guidelines could be extended for combination therapy in addition to the drug monotherapy with consideration of a patient's comorbidity status.

Keywords: type 2 diabetes, quality of care, drug treatment, variation(variance), epidemiology, risk factor, comorbidity, macrovascular complication, survival analysis, cluster analysis, non-linear canonical correlation analysis

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CHAPTER 1.

INTRODUCTION

Chapter 1.

Introduction

1.1 T2D and Its Complication: Emerging Public Health Burden

Type 2 diabetes (T2D) is the most commonly recognized form of diabetes globally, which its prevalence is in an increase with cultural and social transitions. In 2016, 11.3% Korean people aged 30 years or older was reported to have diabetes. The Mortality rate caused by diabetes was 19.2 per 100,000 people which was the 6th most common cause of death in Korea (Korean Diabetes Association & Korea National Health Insurance Service, 2015; Korean National Statistical Office, 2016; Korean National Health and Nutrition Examination Survey, 2017).

Complications of T2D, such as, cardiovascular disease, end-stage renal disease, visual loss, and limb amputation conduce morbidity and mortality in T2D patients (Stirban *et al.*, 2008). In Korea, 1.2% was reported to have end stage renal disease (ESRD) and 6.1% of T2D population had proliferative diabetic retinopathy (PDR) according to 2013 National Health Insurance Service data (Korean Diabetes Association, 2016).

In particular, T2D patients are at increased risk of CVD related events and mortality (International Diabetes Federation, 2017). The overall risk of CVD related death is two to four times higher in T2D patients than in the general population (Emerging Risk Factors Collaboration *et al.,* 2010). According to Korean diabetes fact sheet 2015, 248 ischemic heart disease occurred in T2D patients while 59 events were reported in non-diabetes population and events of ischemic stroke was 248 and 59 respectively.

T2D is a complicated metabolic disorder that social, behavioral, and surrounding risk factors play a complex role in addition to the disease itself. The interaction between these environmental factors, demographic factors, such as, age, physical activity, oral intake, genetic factors, and the disease itself leads to the development of insulin resistance (IR) and beta cell dysfunction, and this development of IR is known to forestall the onset of T2D (Facchini *et al*., 2001; Stumvoll *et al.,* 2005; Kahn *et al.,* 2006; Shanik *et al.,* 2008).

Due to the fact that the severity of T2D is affected by effective glycemic control, treatment of diabetes in the clinic is mainly aimed at effective blood glucose control. However, due to the progressive nature of T2D itself, blood glucose levels become increasingly difficult to control as the duration of treatment increases (Kahn *et al.* 2006; Del *et al.* 2007). According to a recent report, the cost of diabetes in the United States was known to be over $ 245 billion a year, including direct medical costs and productivity reductions. In

fact, for people with T2D, the cost of healthcare was reported as about 2.3 times that of the general population (ADA, 2015). In Korea, the medication cost has risen to 480.2 billion won in 2013 from 82.5 billion won in 2002 showing a rapid increase of T2D treatment cost (Korean Diabetes Association, 2016).

Because T2D and its complications increase the cost of care, lower quality of life, and takes a major part in causes of death, close and effective management of diabetes and its complicated conditions are important in individual level. Moreover, it affects social and economic burden in diabetes management at the national level.

1.2 T2D Management in Korea

Early detection and proper management of T2D can reduce the risk of complications such as cardiovascular disease, vision loss, and renal failure from 20% to 70% (Fox e*t al.*, 2015). The results of the study using the health insurance claim data of Korea showed that the coronary artery disease (CAD) and kidney disease was lowered about 20% when the medication was steadily received from the beginning of T2D. As the persistence level decreased, the risk of complications increased. In addition, the risk of complications increased with age, and it increased by more than 50% over 65 years of age.

Since 2011, the Health Insurance Review & Assessment Service (HIRA) of Korea has been annually conducting evaluations for T2D care adequacy of all medical institutions nationwide for the purpose of improving the quality of T2D management and reducing the number of hospital admissions, hospitalization rates and deaths. Seven indicators are evaluated in four areas: periodic outpatient visits, regular prescription of medications, appropriateness of prescriptions, and tests to prevent and manage complications. The evaluation indexes include prevention of diabetes complications such as treatment persistence; the ratio of one or more outpatient visits per quarter and the yield rate of prescription day, appropriateness of prescription; duplicate prescription rate of the same medication group and performance rate of test enforcement for

prevention of diabetes complications and management; glycated hemoglobin test, lipid test, fundus examination, urine albumin test. Fortunately, the recent evaluation shows that regular medical outpatient visits through regular outpatient visits and proper prescriptions based on the guidelines are generally in good condition, and medical practice continues to improve after the initial evaluation. Of the 2.85 million outpatients with diabetes in 2016, 80% (2.26 million) of patients used only one medical institution steadily, and were continuously under the care of prescription drugs, and the rate of screening required for the prevention and management of diabetes complications is on the rise. However, the rate of lipid testing is 79% and the rate of fundus examination is 44%. The absolute number of test is still low, suggesting that aggressive testing is required.

As such, the T2D management in Korea has been continuously improving, but it has not yet reached the level of developed countries. While the number of patients admitted for T2D treatment was in average 137 per 100,000 populations on OECD countries, 281 per 100,000 populations were admitted for T2D care in Korea. This shows the need and necessity of more careful and effective management. In addition, the number of T2D patients and the cost of medical care services are continuously increasing. Based on all these facts, the importance of national T2D management is constantly emphasized.

1.3 Standard T2D Care

Previous studies have shown that T2D is associated with the manifestation of comorbidities such as atherosclerosis, nephropathy, retinopathy, cardiovascular disease and depression, leading to an increased risk of death from T2D and higher socioeconomic costs (Garcia *et al.,* 1974; Lee *et al.,* 2001; Wang *et al.,* 2013). Given the complexity of chronic diseases, guidelines are developed to standardize medical care, improve the quality of care and to reduce risks for negative health outcomes (Campbell *et al.,* 2002). Based on various scientific facts, including epidemiological studies, guidelines for T2D care have been developed in different countries to improve health care in T2D patients and to provide guidance for health care providers. Guidelines include; American Diabetes Association (ADA) standards, the European Association for the Study of Diabetes (EASD) guidelines, International Diabetes Federation (IDF) guidelines, the UK National Institute for Clinical Excellence (NICE), Dutch National Guidelines(NHG), and the Korean Diabetes Association (KDA).

Majority of the T2D guidelines recommend step-by-step therapies, suggests lifestyle modification (weight loss, diet control, and exercise) followed by metformin (MET) monotherapy, and if the blood glucose control is still inappropriate, treatment intensification is recommended (NICE, 2015;

ADA/EASD, 2017; IDF, 2017; AACE, 2018). The choice of second drug is tricky since it is less specified in guidelines. The choice at the second line may be according to individual need and acceptable from sulfonylurea (SU), α-glucosidase inhibitor (AGI), dipeptidyl peptidase-4 inhibitor (DPP4i), thiazolidinedione (TZD) etc. Finally, insulin can be initiated as a 3rd line with oral antidiabetic drugs (OAD). Maximum 3 OAD can be used of a different mechanism of action (Ashrafuzzaman *et al.*, 2016).

The Korean Diabetes Association (KDA) published 1st and 2nd guidelines since 1990. In 2007, the Diabetes Care Guideline TFT was issued and the 3rd edition guidelines were published. In 2010, three subcommittees (Diagnosis, Therapy, and Epidemiology Subcommittee) integrated which led the guideline related clinical research to diagnosis and treatment of diabetes better and published the 4th edition and the Diabetes Care Guidelines 2015 (5th edition) was published respectively.

According to KDA guideline, patients who have been diagnosed with diabetes for the first time are recommended to improve their lifestyle habits first, and if they cannot reach the glycated hemoglobin target, they are considered to start medication. As in the case of the ADA or EASD guideline, metformin is considered as the first-line treatment for oral medication alone in Korea, but the appropriate medication is selected according to the patient's condition. In Korea, metformin treatment against sulfonylurea began to be

favored in 2009, insurance for metformin monotherapy has been actively implemented since 2011, and 2015 Korea diabetes care guidelines directly presented metformin as the first line treatment. If it is unlikely to reach the goal of glycemic control with monotherapy, combination treatment is suggested. Guideline recommends to consider the mechanisms, interactions, costs, and compliance of combined drugs. However, a specific type of combination treatment is not presented and suggested to be practiced-dependent.

1.4 T2D Drug Treatment

About 90% of type 2 diabetes (T2D) patients are prescribed with medication (include insulin treatment). Therefore, proper management through proper medication can greatly prevent negative health outcomes such as, cardiovascular disease or/and cerebrovascular disease related morbidity and mortality.

Type of T2D drugs are classified according to their mechanism of action (Inzucchi, 2002; Krentz & Bailey, 2005; Levetan, 2007). The first is a sulfonylurea (SU) group that excites insulin secretion directly from beta cells, the second is a biguanide (metformin, MET) group that inhibits glucose synthesis in the liver, and the third is an alpha glucosidase inhibitor (AGi) group. Fourth is thiazolidinedione (TZD) group that works to improve peripheral insulin resistance, dipeptidyl peptidase-4 (DPP4) inhibitor for enhancing incretin effect and sodium-glucose co -transporter 2 (SGLT2) inhibitor that inhibits glucose uptake in renal proximal tubules. In addition, there are injection drugs, such as, GLP-1–receptor agonist (GLP-1RA), or basal insulin. GLP-1 receptor activated insulin secretion from pancreatic β-cells. Injection drugs should be considered as part of any combination regimen.

These medications have different blood glucose lowering effects by different mechanism of action and the advantages of each drug are different. These medications may show unwanted adverse effects, such as hypoglycemia, weight gain, GI-tract problems (Del *et al.* 2007; Black *et al.*, 2007, Alhadid *et al.*, 2012). Thus, difference in type of side effects, contraindications, and cost should also be considered for treatment.

Recent reports show an increase in the use of combination therapy in early stage of treatment. Especially, a combination therapy with high baseline blood glucose level (HbA1c, 9.5%) has been reported effective for long-term blood glucose control and reduction of complications (Van Gaal *et al.*, 2003; Dailey, 2004; Giorgino *et al.*, 2005; Phung *et al.*, 2014).

According to Korea diabetes fact sheet 2015, prescriptions for metformin increased up to 80% in 2013 (Korean Diabetes Association, 2016). The prescription of dipeptidyl peptidase-4 (DPP-4) inhibitors was noticed as the 3rd popular treatment (38.4%) which its use increased dramatically since 2008. Also, it was reported that 60% of T2D patients were being treated with two or more classes of antidiabetic medication.

To help health care providers apply efficient combination therapy, several guidelines have been produced (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2008; Guzmán *et al.*, 2010; Inzucchi *et al.*, 2012; Sinclair *et al.*, 2012; Garber *et al.*, 2013).

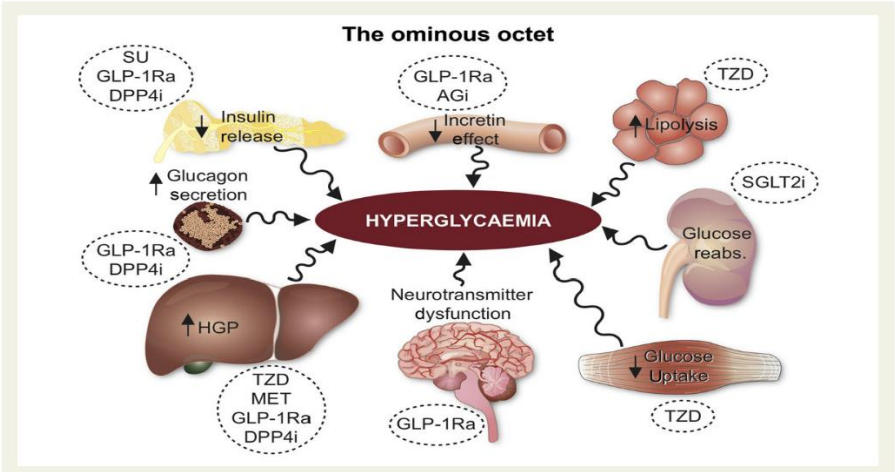

Figure 1-1. Type of T2D drugs and their mechanism of action (From Ferrannini, 2015)

However, unlike commonly recommending metformin as first-line treatment, guidance for ulterior pharmacological drugs and their purpose in combination is presented ambiguously and extensively. Even though prior studies have induced some guidelines practice-friendly, lack of evidence to standardize specific treatment approach remains (Bailey, 2013).

Although metformin can cause gastrointestinal (GI) problems, it is well recommended as first-line treatment, due to, good glucose lowering effect, and low risk of hypoglycemia (Saenz *et al.,* 2005). In case of sulfonylurea, it remains as a common choice despite the high risk of hypoglycemia and weight gain is well known, SUs remain a common choice due to good glucose lowering effort and low cost. In recent, DPP4- inhibitors are gaining prominence due to

their effect on glucose level while being at low risk of hypoglycemia or weight benefits.

Throughout the years, several antidiabetic agents have introduced range of treatment options for early intensification of treatment of T2D. Considering these diverse treatment methods, it is likely to improve glycemic control and harness extra glycemic benefits of an additional agent while accommodating patient preferences.

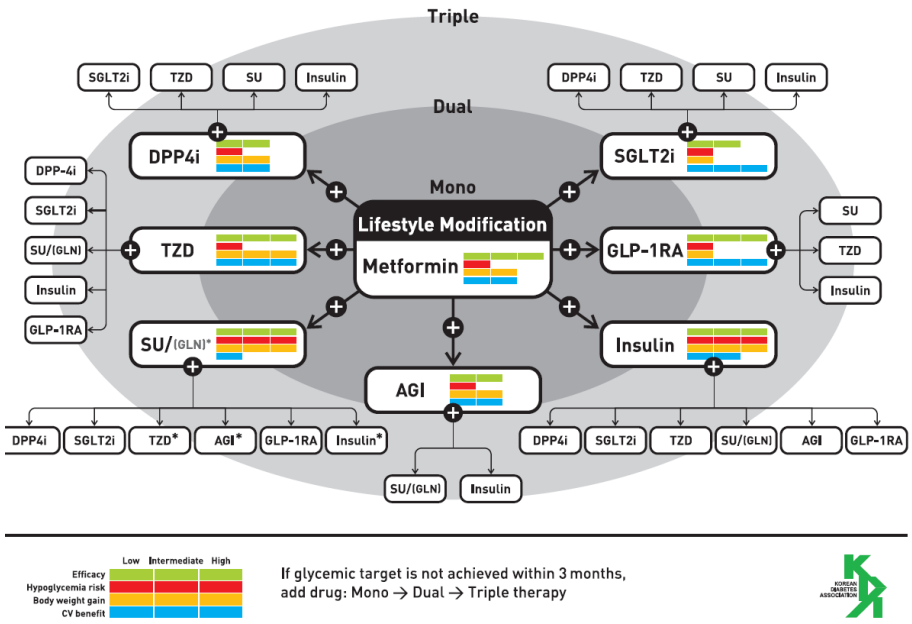

Figure 1-2. Algorithm for medication treatment of T2D (From Diabetes Care Guidelines, Korean Diabetes Association, 2017)

1.5 Variation in T2D Drug Treatment and Patients' Characteristics

Many countries, including Korea, continue to develop guidelines and quality assessment for T2D management, which ultimately upgrades the level of T2D treatment overall, leading to prevention of complications and reduction of mortality for the entire T2D population (Woolf *et al.,* 2010; Sidorenkov *et al.,* 2013). However, reports showed that these established guidelines are not properly followed (McGlynn *et al.,* 2003; Koro *et al.,* 2004; Harris *et al.,* 2005; Bennett *et al.,* 2011; Bennett *et al.,* 2011; Rettig, 2011; Desai *et al.,* 2012; Desai *et al.,* 2012; Satman *et al.,* 2012; Diab *et al.,* 2013).

In spite of significant progress made in improving the quality of T2D care, difference between guidelines recommend optimal treatment and observed treatment in practice still remains. The United States and Europe show that even though these standardized guidelines are applied to medical institutions, differences in drug treatment rates between medical institutions are still found. In the Netherlands, despite active efforts to improve the quality of drug treatment for T2D, the recent quality assessment shows that the proportion of medical institutions that follow the guidelines for drug treatment had variance of 35% to 95% or 60% to 95% depending on the type of drugs (van den Berg *et al.,* 2014). In Korea, the problems of physicians' responsibilities being unclear and lack of patient-centered self-management support system has been

raised through the 'Chronic Illness Management System for Clinical Diseases'. It is pointed out that a patient-oriented interactive service should be provided and the need of protocol development of items that needs to be clarified under doctor's management for efficient patient treatment. However, current prescription-related indicators in Korea do not directly manage prescribing behaviors and prescription rates for medical institutions, regions, and diabetes-related drugs, so it is difficult to directly grasp the current situation.

Variation of treatment quality may be caused by multiple factors on the level of organization, practice, or patient (Srinivasan M *et al.*, 2001; Arday *et al.*, 2002; Yarzebski *et al.*, 2002; Parnes *et al.*, 2004; Hickling *et al.*, 2005; Boyd *et al.*, 2005; Grant *et al.*, 2005; Foley *et al.*, 2006; Hicks *et al.*, 2006; Holland, 2008).

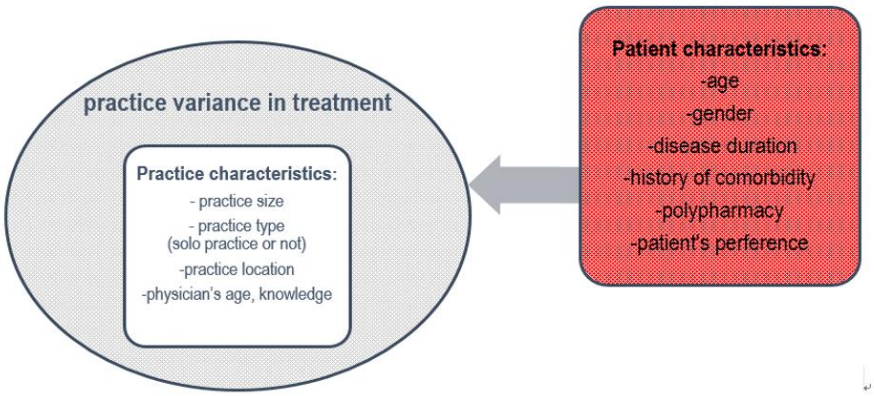

Figure 1-3. Patient characteristics and practice variance in treatment

Several studies have shown that in actual practice, unexpected factors, such as, treatment complexity and competing demands influence the adherence of the guidelines. Due to the fact, patients' characteristics have become important factors for a good quality of treatment.

In practice, certain level of between provider variations in adherence to clinical practice guidelines is justified by differences in individual patients' characteristics. Such as, age, gender, socio-economic status and clinics, diabetes duration, baseline risk factor level (HbA1c, BP level, LDL-cholesterol), baseline treatment status (polypharmacy), history of malignancies, and history of psychological disorders (Fig. 1-2, Table 1-1) can justify non adherence to guidelines and providers are responsible for adjusting their clinical decisions (Cabana *et al.*, 1999; Trudy van der Weijden *et al.*, 2010). Table 1-1 lists patient's characteristics with probable influence on treatment variance in clinical setting. Justified characteristics presents evidence that the treatment variance could be reasonable if variance is observed in practice due to the characteristic. In case of characteristics presented as Mixed or unjustified characteristics, more evidence is needed or treatment variance cause by characteristics should be mediated to prevent uncontrolled treatment variance in clinical setting that could affect the quality of T2D care.

Treatment variance due to clinical characteristics are mostly controlled since several treatments are already considered for T2D patients with the

indicated conditions and recommended in several guidelines. Meanwhile variance, due to demographic factors need further studies. Most T2D patients have multiple conditions and risk factors which may require prioritization in treatment plans (Schulman-Green *et al.,* 2006). For these reasons, healthcare providers' treatment decisions could be influenced by differences in individual patients' characteristics and this would be lead to variance of treatment rates among various clinical practices and eventually will cause negative influence on the quality of treatment in diabetes care. However, limited studies have taken place to focus on the variation of diabetes care related to treatment decisions of health care providers.

Accounting for these patient characteristics would therefore be an essential feature of fair and accurate comparisons of quality of care among healthcare providers. To overcome increase in treatment variance that could influence in negative health outcome and improve the quality of treatment in T2D patients, variance of treatment among clinical practices must be identified. Role of individual patients' characteristics in this variance should be justified and unjustifiable factors should be assessed and mediated.

Table 1-1. Potentially justified and unjustified patient characteristics related to T2D drug treatment variation

Characteristics	Justification[1)]	Evidence or study results of treatment variation[2)]	Reference
Age	Justified	- Older adults (>65–70 years) often have a higher atherosclerotic disease burden, reduced renal function, and more comorbidities. - Studies suggested that glycemic targets for treatment initiation or intensification in elderly should be less ambitious than in younger people	Booth et al.(2006), Ismail-Beigi et al.(2011), Brown et al.(2003), Gregg et al.(2000), van Hateren et al.(2011)
Gender	Unjustified	- Women with T2D were consistently less likely to receive the recommended medications, such as antihypertensive and cholesterol-lowering medication. - Men with T2D were significantly more likely to receive oral combination drugs, ACE inhibitors and calcium channel blockers for Coronary Heart Disease(CHD)	Manteuffel et al. (2014), Krämer et al.(2012)
Comorbidity	Justified/ Unjustified	- Diabetes-related comorbidity enhanced cardiovascular risk factor management. - Conditions associated with a significantly shortened life expectancy (e.g., stage IV lung cancer or class IV heart failure) may preclude attention of clinicians to patients' diabetes-related risk factors of longer-term events. - Diabetes unrelated comorbidity(ex: mental disorder) had no impact or negative or possive effect on risk factor management.	Riddell et al. (2011), Piette et al. (2006), Woodard et al. (2011), Lagu et al. (2008), Psarakis. (2006), Whyte et al. (2007), Morriss et al.(2005) , Desai et al.(2002), Dixon et al.(2004)
-cardiovascular /microvascular	Mixed		
-malignancies	Mixed		
-psychological disorders	Unjustified		
Polypharmacy	Justified	- Previous studies conducted in the USA showed that a higher number of concurrently used drugs was either negatively associated or not associated with treatment modifications.	Stack et al. (2010), de Vries et al. (2014), Rodondi et al. (2006), Voorham et al. (2010)

1) Justified: prior studies show evidence based treatment difference, unjustified: prior studies show treatment difference but more evidence is needed, mixed: prior studies show either evidence based treatment variance or no existing treatment variance.
2) Evidence was described for justified characteristics and study results were presented for unjustified or mixed characteristics.

Table 1-1. Potentially justified and unjustified patient characteristics related to T2D drug treatment variation *(continued)*

Characteristics	Justification[1)]	Evidence or study results of treatment variation[2)]	Reference
HbA1c level	Justified	- In relation to prevention of microvascular complications in type 2 diabetes patients, maintenance of tight blood glucose control was identified to have a beneficial effect on diabetes-related microvascular complications, both in randomized clinical trials and in observational studies.	Beulens et al. (2009), Stratton et al. (2000)
Blood pressure level	Justified	- Several studies show that hypertension increases the already high risk for cardiovascular disease in T2D patients.	Turner et al. (1998), Cushman et al. (2016), Arguedas (2009),
LDL level	Justified	- Several studies show that control of LDL level is one of the crucial factors for the reduction of cardiovascular comorbidity and all-cause mortality in T2D patients.	Gaede et al. (2008), Baigent et al.(2005)
BMI	Justified	- Body mass index(BMI) has been shown to be associated with decreased glucose tolerance, alterations in glucose insulin homeostasis, reduced metabolic clearance of insulin, and decreased insulin-stimulated glucose disposal in prior studies.	Vazquez et al. (2007), Haupt et al. (1999)
Diabetes duration	Justified	- It is known that the beneficial effects of improved glycaemic control decrease with longer diabetes duration and prevalence of T2D patients with complications increase. Facts also relate to the progressive characteristics of the disease.	Emanuele (2010), Turnbull et al.(2009), Holman (2008), Duckworth et al. (2009)
ACR (Albumin-Creatinine ratio)	Justified	- Since Micro-albuminuria is one of the earliest signs of diabetic nephropathy, treatments for T2D patients with symptoms were reported to receive more medication, and in those receiving additional care by a diabetes support facility.	Rutten et al. (2006), Hellemons et al. (2013)

1) Justified: prior studies show evidence based treatment difference, unjustified: prior studies show treatment difference but more evidence is needed, mixed: prior studies show either evidence based treatment variance or no existing treatment variance.
2) Evidence was presented for justified characteristics and study results were presented for unjustified or mixed characteristics.

1.6 Control Variation in T2D Treatment, Improve Quality of Care

Throughout the years, numerous treatments for T2D care have evolved targeting different pathophysiological defects of which strengthen the idea of individualized treatment in consideration of improvement in quality of care. Related to this matter, several clinical practice experience have shown that individualized approach of T2D patients is essential with phenotype, such as, patient and disease individual characteristics (Scheen, 2016; Aghaei Meybodi *et al.*, 2017).

T2D is a dysenteric disease which its characteristics significantly changed depending on each patient's genetic factors, the underlying pathogenic mechanisms and individuals' clinical characteristics. (Cantrell *et al.*, 2010; Leslie *et al.*, 2016; Kaul *et al.*, 2016). For these reasons, type of T2D treatment should be based on individualization that predicates evident to patients and the drug treatment. In fact, current clinical practices gradually tend to take into account personalized approach considering evidence-based patient and disease individual characteristics Moreover, availability of several glucose-lowering agents with different acting mechanism increases the potential of a patient-oriented treatment approach in clinical settings.

However, the ideal way to use these resources and to perform effective personalized treatment in the daily clinical care of T2D patients is still questionable and more evidence is needful (Raz *et al.*, 2013).

Related to the fact, the concept of individual treatment approach is being noticed by several guidelines. In fact, the statement on personalized T2D management by the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) has raised strong influence on the patient-centered medical approach concept in current T2D care setting (Inzucchi *et al.*, 2015; Garber *et al.*, 2016).

Apparently, patient-centered care and guideline based standardized recommendations may be considered as rather conflicting approaches. However, current T2D care includes various treatment choice in clinical setting and personalized approach may increase uncontrolled variance in treatment that could influence the quality of T2D care. Due to the fact, it should be strongly recognized that providing particle guidance to enhance the ability of healthcare providers in customizing T2D therapy to improve patient outcomes should be recognized.

The existence of variance treatment in practice is inevitable, since substantially different clinical characteristics of the patient are taken into account in clinical practice. Therefore, the goal of quality control of diabetes treatment is to control the variance that could negatively affect the patient's

treatment and health outcome eventually. Increase of variance could be prevented by analyzing the factors affecting the variance and developing secondary treatment alternatives (Streja *et al.*, 1999; Khunti *et al.*, 2001; Srinivasan *et al.*, 2001; James *et al.*, 2002; Arday *et al.*, 2002).

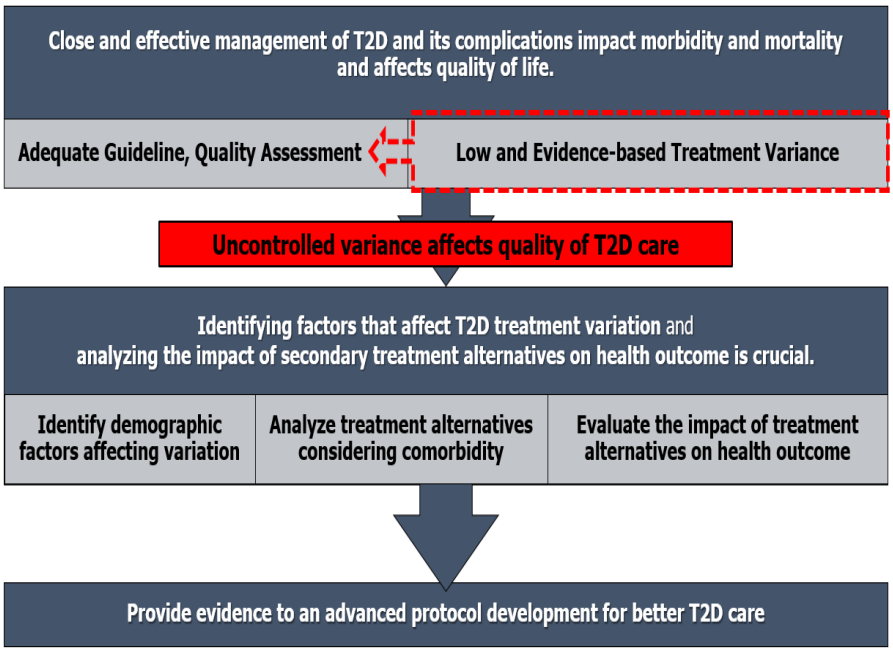

Figure 1-4. Treatment variance and quality of T2D care

Effective diabetes management affects the morbidity of related complications, which can lead to reduced mortality from diabetes and ultimately, improved quality of life (Figure 1-4). In order for this effective

diabetes management to actually work well, three core elements, evidence-based clinical guideline, accurate quality assessment, and minimal variance of evidence-based treatment in clinical setting are needed. Of these three factors, management of treatment variance in clinical setting is the most fundamental factor because uncontrolled treatment variations can ultimately affect the quality of diabetes management by affecting accurate quality assessment and adequate guideline development.

As more than one factor can determine T2D treatment method, some variation of the guideline naturally exists. However, the variation must be less as possible, and it must be a variance based on evidence-based factors. In order to find an adequate T2D treatment, it is necessary to identify the factors of treatment variability, to confirm its legitimacy, and to find an alternative treatment variant management. It is also necessary to check the relevance of health alternatives.

1.7 Study Objectives

The quality improvement of diabetes treatment is based on the adequate quality measurement of the treatment and the variation in treatment provided to the patient. Due to the fact that variations of treatment affects mortality and morbidity of T2D population, it is important to identify the factors that affect the variance. In particular, the presence or absence of comorbidity in T2D patients affects the treatment process and outcome at the patient level, leading to a burden of providing health care services. Accordingly, it is necessary to assess common comorbid clusters and its relation to treatment patterns. In addition, the variability of drug treatment, which is the main act of diabetes care, is an indicator of the difference in the quality of treatment for the patient, so it is necessary to identify the characteristics of the patient that affects treatment variation and to identify the relationship with the health outcome.

The thesis aims to provide evidence for developing better T2D treatment protocols that would effectively control variation in T2D treatment and eventually improve the quality of T2D care. Thesis include studies that focuse on 1) identifying demographic factors that affect treatment variance and 2) analyzing the effect of comorbidity on variation while exploring treatment alternatives and 3) assessing association between treatment alternatives with health outcomes.

Therefore, this study has the following research purposes;

(1) Identify demographic factors that affect the variance of T2D drug treatment.

(2) Identify treatment patterns and its relation to comorbid status of T2D patients.

(3) Assess the association between the variation of T2D drug treatment and the cardiovascular morbidity considering comorbid status.

1.8 Conceptual Framework

Donabedian model is recognized in many studies related to quality and health outcomes (Donabedian, 1988). Since 1966, this model continues to perform as the basis to assess the quality and performance of health services.

Donabedian model includes quality measures, such as, structure, process, and outcome measures and contends that these three type of measures are related to each other in a subjacent framework. Well-formed structure should comply with sufficient process, and such process should yield admirable outcomes (Donabedian, 1966; Donabedian. 1988). This Donabedian's conceptual framework underlines the significance of apprehending the process, structure and quality of health care as important characteristics when health outcomes is considered to be analyzed (Canadian institute for health information, 2008).

Numerous quality indicators were exploited under Donabedian's conceptual framework. These indicators are basically utilized to identify health care providers that preformed standards of quality of care, and to assess the quality of internal health care and improvement initiatives provided to the patients. Indicators are normally grouped into measures of structure, process, and outcome. Outcome indicators measure the results of care, including

surrogate and hard clinical outcomes. Unlike structure and process indicators, outcome indicators can possibly be affected by other factors that are not controllable by organization or clinician (Mant, 2001). Thus, structure and peculiarly process indicators are frequently used to measure the quality of care (Saaddine *et al.,* 2006; De Vos *et al.,* 2009; Chassin *et al.,* 2010).

Donabedian model is also used in T2D care on individual level and national level (The TRIAD Study Group, 2002; Canadian institute for health information, 2008; López-López *et al.,* 2012; Nocella *et al.,* 2016). TRIAD, the Translating Research into Action for Diabetes Study(TRIAD) group, also addressed several studies using Donabedian's conceptual framework on the effects of system or patient-level characteristics on processes or outcomes for T2D patients (The TRIAD Study Group, 2002).

Numerous indicators for the quality measurement of T2D care have been exploited, which aims on the structure or the process of care. (Nicolucci *et al.*, 2006; Wens *et al.*, 2007; American Diabetes Association, 2009; Martirosyan *et al.,* 2008; AHRQ, 2009; NHS, 2009; Calvert *et al.,* 2009; NCQA, 2010).

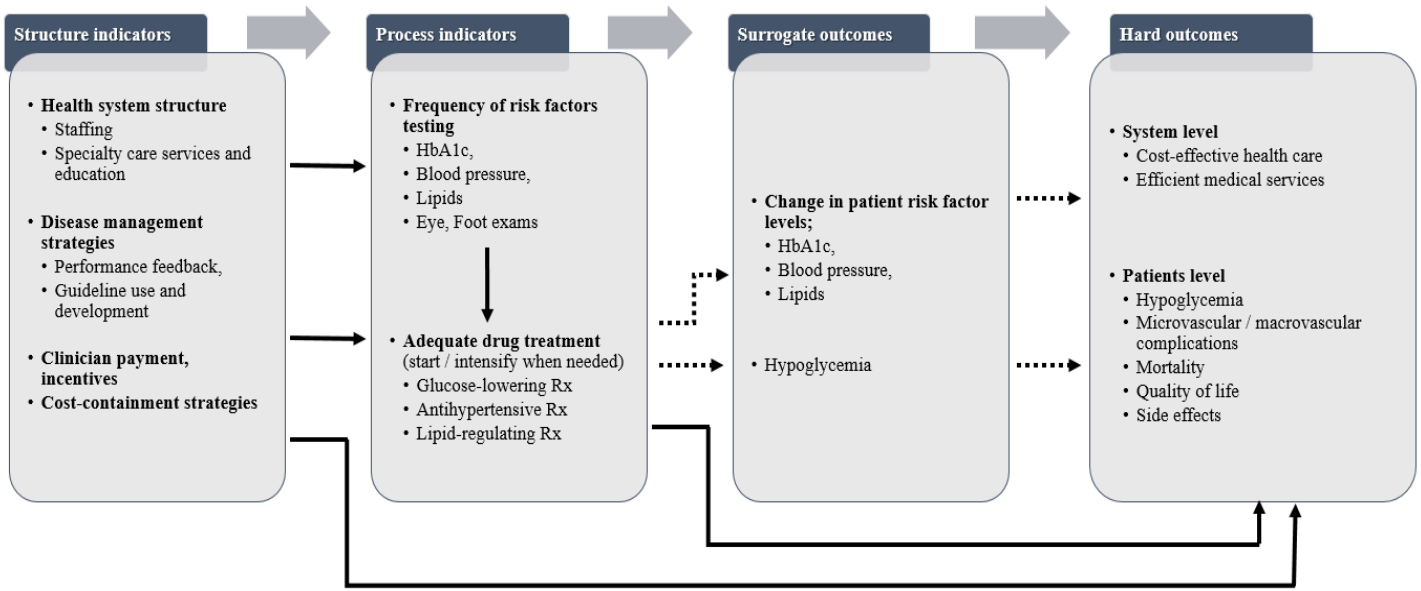

Figure 1-5. Relationships between T2D quality indicators and health outcomes

Figure 1-5 describes relevant quality indicators that have been developed as elements of T2D care based on underlined evidence or expert agreements for effective health outcomes (Sidorenkov *et al.,* 2011). Prior studies show that the fulfilment of certain structure of care elements related to health system structure, disease management strategies, incentives and cost-containment systems can be beneficial in enhancing processes and outcomes of T2D care (Renders *et al.,* 2001; Tsai *et al.,* 2005). In addition, results from clinical trials show feasible drug treatment has favorable effects on surrogate and hard outcomes (UK Prospective Diabetes Study Group, 1998a; UK Prospective Diabetes Study Group, 1998b; Turnbull *et al.,* 2009).

It is known that risk factors, such as HbA1c, blood pressure, and lipid levels, need to be checked and monitored to determine whether patients are well treated or adjustments in treatment are needed (AHRQ, 2009; NHS, 2009; NCQA, 2010). Therefore, most T2D guidelines also have recommendations regarding the frequency of such risk factor testing (Nicolucci *et al.*,2006; Wens *et al*., 2007; ADA, 2009; Calvert *et al*.,2009), but the rationale is mostly based on the agreement of experts and its effect as a process indicator on the quality of T2D care is resulted by medication treatment.

The predictive validity on various diabetes complications related to these risk factor levels is recognized by numerous studies (Gilbert *et al.,*1995; Stratton *et al.,* 2000; Baigent *et al.,* 2005). However, some relationships are in

a matter of debate in the management of diabetes and related cardiovascular risk factors. For example, changes in HbA1c may not reflect cardiovascular protection in the long run. In fact, current studies suggest that surrogate outcome measurement should go beyond HbA1c management in the future. In particular, hypoglycemia is recognized as a predictor of macrovascular events, adverse clinical outcomes, and mortality among T2D patients. Considering the substantial morbidity, associated mortality, and decreased the quality of life caused by hypoglycemia, its prevention is an integral part of patient-centered diabetes care along with HbA1c control, as reinforced by clinical practice guidelines. However, it remains surprising that less than 10% of the initiatives included a corresponding hypoglycemia performance measure (Zoungas *et al.*, 2010; Rodriguez-Gutierrez *et al.*, 2016).

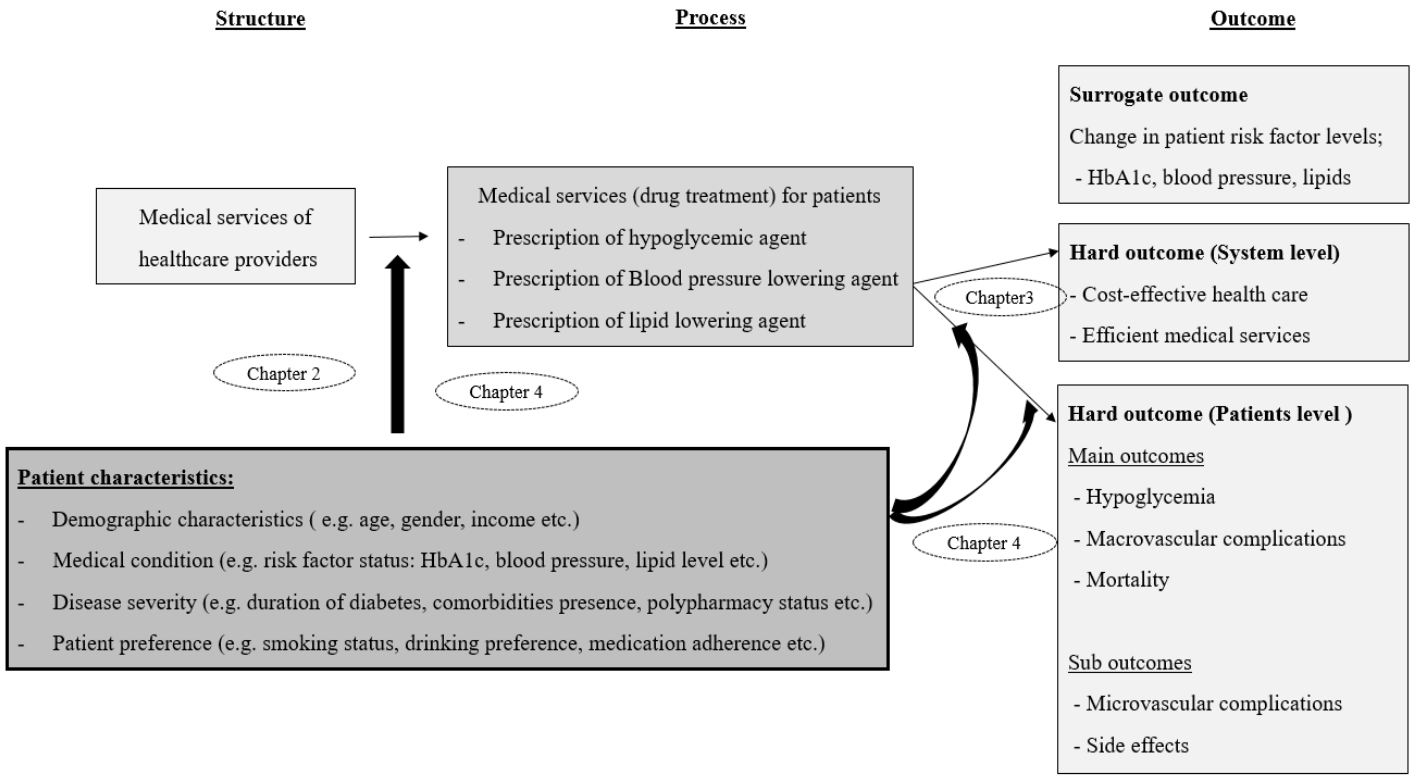

Figure 1-6. The Conceptual framework of the thesis based on the Donabedian model

CHAPTER 2.

Role of Patient and Practice Characteristics in Variance of Treatment Quality in Type 2 Diabetes between General Practices

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Cho YY, Sidorenkov G, Denig P. Role of Patient and Practice Characteristics in Variance of Treatment Quality in Type 2 Diabetes between General Practices. PLoS ONE. 2016;11(11): e0166012 DOI: 10.1371/journal. pone.0166012.

2.1 Introduction

Quality assessment frameworks have been introduced in several countries with the goal to ensure appropriate and evidence-based healthcare for patients (van den Berg *et al.,* 2014). Within such frameworks, guideline recommendations on optimal care are linked to performance measures and accountability processes. Performance measures assess to what extent care is delivered according to guideline recommendations.

When applying such measures in clinical practice, variation in the performance of healthcare providers and institutions is common. For example,

prescribing of preferred drugs by Dutch general practitioners ranged from 35% to 95%, whereas prescribing drug treatment when indicated ranged from 60% to 95% (van den Berg *et al.,* 2014).

Differences in performance may be attributed to the underlying patient population as well as to the healthcare provider and the practice organization. In heterogeneous populations, it is to be expected that healthcare provider's treatment decisions are influenced by differences in patient characteristics. For example, patients with type 2 diabetes (T2D) commonly have multiple conditions and risk factors which may require individualized treatment plans. A recent review concluded that patient characteristics, such as marital status and BMI, affect outcome measures for diabetes but no consistent patterns were observed for process measures (Calsbeek *et al.,* 2016). Previous research indicates that patient characteristics, such as age (Booth *et al.,* 2006; van Hateren *et al.,* 2012), gender (Krämer *et al.,* 2012; Manteuffel *et al.,* 2014), disease duration (Satman *et al.,* 2012), comorbidity presence (Woodard *et al.,* 2011), and level of risk factor control (Parnes *et al.,* 2004; Ab *et al.,* 2009), can all influence prescribing in this population. This may reflect appropriate care, for example, when different treatment regimens are considered for elderly patients (Brown *et al.,* 2003; van Hateren *et al.,* 2011), or intensified treatment is prescribed for patients with more progressed disease states (Chen *et al.,* 2013).

Variance may also be justifiable when there are competing demands (Piette and Kerr, 2006; Pentakota *et al.*, 2012) or when patients are reluctant or unwilling to take specific or more drugs (Mathew *et al*., 2013). In other cases, variance can be non-justifiable, for example, when prescription rates for guideline recommended treatment differ in men and women (Krämer *et al.*, 2012; Manteuffel *et al.*, 2014). Healthcare providers' personal preferences, knowledge and habits can influence treatment decisions. For example, physicians may differ in their preferences for certain types of treatment, or in their reluctance or keenness to prescribe (Greving *et al.*, 2006; Ab *et al.*, 2009; Peyrot *et al.*, 2012). In addition, practice characteristics, such as practice type, size, consultation time, and the presence of support staff have been found to influence prescribing behavior (McGinn *et al.*, 2006; Tahrani *et al.*, 2008). These factors may contribute to non-justifiable variance between practices.

Accounting for patient characteristics causing justifiable differences is important for fair between practice comparisons of treatment quality. The aim of this study is to describe the differences in treatment quality of patients with diabetes between general practices, and identify patient and practice level characteristics that may explain these differences.

2.2 Methods

2.2.1 Study design and setting

A cross-sectional study was conducted to assess treatment quality in 2012 in a large diabetes care group in The Netherlands, which included more than 80% of all general practices in the province of Groningen. Diabetes care groups have been formed after the introduction of bundled payment in 2007 (Campmans-Kuijpers *et al.,* 2013). They are responsible for the organization and provision of diabetes care in accordance with the Dutch clinical practice guidelines.

2.2.2 Study population and data collection

Data were collected from the GIANTT (Groningen Initiative to Analyze Type 2 Diabetes) database. This regional longitudinal database contains anonymized data extracted from electronic medical records of almost all type 2 diabetes mellitus (T2D) patients (<1% opted out) managed in general practice (Voorham *et al.,* 2007). The database includes prescription data, medical history, results from routine laboratory tests and physical examinations. Medical history consists of diagnoses, which are documented in the medical records by means of the International Classification of Primary Care (ICPC) or

short text descriptions which are manually coded. From the 189 general practices in GIANTT, 6 were excluded for having incomplete prescription or diagnostic data. Patients diagnosed with T2D before 1 January 2012 were selected. Patients with incomplete follow-up in 2012, and patients with missing or invalid onset dates for diabetes were excluded.

2.2.3 Outcomes: treatment measures

Treatment quality was defined as current treatment status, that is, if a patient was treated or not with guideline recommended drug treatment, similar to many of the prescribing measures currently in use in The Netherlands (Instituut voor Verantwoord Medicijngebruik, 2015).

Study focused on whether any drug treatment was prescribed for eligible patients, and whether the recommended drug class was prescribed for three common risk factors. This includes treatment in T2D patients with (1) any glucose-lowering drug, (2) any lipid-lowering drug in patients with an additional diagnosis of dyslipidemia, vascular comorbidity or nephropathy, and (3) any blood pressure-lowering drugs in patients with an additional diagnosis of hypertension, vascular comorbidity or nephropathy. Within the above defined patients the recommended drug classes comprised of treatment with (1)

metformin, (2) statins, and (3) drugs acting on renin-angiotensin-aldosterone system (RAAS-blockers).

A patient was considered as being treated when a prescription was recorded within the last 4 months of the 2012, taking into account that a prescription can be issued for a maximum period of 3 months in the Netherlands.

2.2.4 Explanatory variables

To explain the differences in treatment between practices, the following patient level characteristics were included as dichotomous variables: age (≥70 years for glucose lowering treatment, ≥80 years for blood pressure and lipid lowering treatment), gender, duration of diabetes (≥2 years), overweight (ICPC T82, T83), history of cardiovascular comorbidity (ICPC K74-K77, K84, K99.1, left ventricular hypertrophy, coronary artery bypass graft, percutaneous transluminal coronary angioplasty), history of peripheral vascular comorbidity (ICPC K89-K92, peripheral bypass, percutaneous transluminal angioplasty), diabetes complications (K99.6, F83, N94.2), nephropathy (ICPC U90, U99.1, U99.2, U99.3, dialysis, or kidney transplantation), history of malignancy (ICPC A79, B72-B74, D74-D77, F74.1, H75.1, K72.1, L71.1, N74, R84, R85, S77, T71, U75-U77, X75-X77, Y77, Y78), history of psychological disorders (P70-P80, P85, P98, P99), treatment with 5 or more other chronic drug classes (ATC codes starting with A, B, C, H, L, M, N, R, excluding antihypertensive, glucose-

regulating, and lipid-regulating drugs), treatment with 3 or more glucose lowering drug classes, treatment with 4 or more blood pressure lowering drug classes, and treatment with 2 or more lipid lowering drug classes.

The cutoff levels for age were based on the Dutch guideline (NHG standard, 2013) where less stringent treatment targets are recommended for elderly patients. The cutoff level for diabetes duration was chosen to distinguish patients who were recently diagnosed with T2D (diabetes duration < 2 years) from those having diabetes for a longer period (≥ 2 years). The cutoff levels for the number of chronic medications and numbers of glucose, blood pressure, and lipid lowering medication were chosen to indicate the burden of being on high numbers of drug classes unrelated to the outcome of interest (e.g. the variable determining treatment with 3 or more glucose lowering drug classes was not used in the models where outcome was defined as treatment with glucose-lowering drugs or metformin).

The following general practice level characteristics were included in order to explain potentially non-justifiable differences in treatment between practices: number of diabetes patients per practice, presence of educated diabetes assistant, and practice type (solo or group).

2.2.5 Statistical analyses

The treatment quality rates were described at practice level as mean percentages with standard deviation, or median percentages with interquartile ranges. Descriptive statistics were also used to describe the distribution of patient characteristics across general practices.

Multilevel logistic regression analysis was conducted for each of the six treatment measures separately (using Stata 14.1, Special Edition and SPSS 23 version) to assess the proportion of variance that is attributed to general practice level and the proportion of this variance that can be explained by patient and practice characteristics. Two level random intercept models were estimated with patients at level 1 nested within general practices at level 2. In these models the probability for the treatment outcome can vary across practices but the effect of the patient characteristics is assumed to be the same (fixed) for all practices.

First, the proportion of variance in treatment at practice level was estimated in an empty multilevel model. Second, multilevel univariate analyses were conducted for each patient and practice level explanatory variable. Next, three multivariate models were built using backwards selection for including variables that were potentially associated with the treatment measure ($p < 0.2$); (i) model 1, with patient level characteristics only, (ii) model 2, with general

practice characteristics only, (iii) model 3, with patient and practice characteristics together.

The pseudo R^2 measure was used to estimate what part of the variance at practice level could be explained by including patient and general practice characteristics (Lovaglio *et al.,* 2011; Snijders *et al.,* 2011). For this, the percentages reduction in pseudo R^2 were calculated for each model compared to the empty model, expressing the part of the practice level variance that can be explained by the included characteristics.

2.3 Results

A cohort of 24,628 T2D patients managed in 183 general practices was eligible, after excluding 974 patients for incomplete follow-up and 27 patients for missing or invalid diabetes onset dates. Of the 183 general practices, 90.7% had a diabetes assistant and 45.4% were practices with a single general practitioner (Table 2-1). The median number of T2D patients per practice was 122 with a range from 15 to 480 patients. The proportion of patients with comorbidity, hypertension, dyslipidemia and overweight, varied widely across the practices (Table 2-1). Among the eligible patients, 75.3% of patients were

treated with glucose-lowering drugs, 73.7% with lipid-lowering drugs, and 87.8% with blood pressure-lowering drugs.

Considerable differences (IQR 9.5-13.9) were observed in these treatment rates between general practices (Table 2-2). The between practice variance in the empty multilevel model was 7.5% for glucose-lowering treatment, 3.6% for metformin, 3.1% for lipid-lowering treatment, 10.3% for statins, 8.6% for blood pressure-lowering treatment, and 3.9% for RAAS-blockers (Table 2-3). The models including all the characteristics (model 3) are presented in Table 2-4 reflecting the effect sizes of the associations between the included characteristics and treatment outcomes.

For glucose lowering drugs, patient and practice characteristics together reduced the practice level variance with 1.4%, and thereby explained 19.0% of the observed practice level variance in treatment (Table 2-3). Each of the tested patient characteristics explained less than 2% of the variance in the univariate analyses (Supplemental Material 2-1). Together, patient characteristics explained only 3.3% of the variance. Practice characteristics, in turn, explained 15.5% of the variance. For metformin, adjusting for patient characteristics reduced the practice level variance with 0.3% thereby explaining 7.5% of the variance in treatment. In the univariate analyses age of patient and use of ≥5 chronic drugs were the characteristics that explained the most of the practice level variance. Practice characteristics did not explain any practice level variance in treatment with metformin.

For lipid-lowering drugs and statins, patient and practice characteristics together reduced the practice level variance with 0.6% each, and thereby explained 20% and 6% of this variance respectively (Table 2-3). Age, treatment with 3 or more glucose-lowering drugs, and number of patient with T2D per practice explained between 2.9% and 5.8% of the variance in treatment with lipid-lowering drugs in the univariate analyses (Supplemental Material 2-1). Together, patient characteristics explained 9.9% of the variance in treatment with lipid-lowering drugs and 0.3% of the variance in treatment with statins. Practice characteristics explained 8.3% and 6.0% of the variance respectively.

For blood pressure-lowering drugs and RAAS-blockers, patient and practice characteristics together reduced the practice level variance with 2.1% and 0.5% respectively, and thereby explained 9.9% and 13.4% of this variance (Table 2-3). A history of psychological comorbidity and number of T2D patients per practice explained 3.7% and 4.3% of the variance in treatment with blood pressure-lowering drugs in the univariate analysis (Supplemental Material 2-1). Together, patient characteristics explained 6.2% of the variance in treatment with blood pressure-lowering drugs and 7.2% of the variance in treatment with RAAS-blockers. Practice characteristics explained 4.3% and 5.9% of the variance.

Table 2-1. Practice and patients' characteristics for the study population

	Number included	%	Median (IQR)	Median (IQR) % or median among practices	Range (Min-Max) among practices
Practice level	183				
Diabetes patients per practice			122.0 (77.0)		15–480
Solo practice (%)	83	45.4			
Practice assistant (%)	166	90.7			
Patient level	24,628				
Gender, female (%)	12,571	51		50.8 (6.3)	20–65.8
Age (years)	24,628		67.0 (17.0)	67.1 (2.7)	59.5–74.0
Diabetes duration (years)	24,628		5.0 (7.0)	6.2 (1.3)	3.8–9.5
History of cardiovascular comorbidity (%)	5,320	21.6		22.2 (14.9)	0.0–46.5
History of peripheral vascular (%)	2,888	11.7		11.1 (8.9)	0.0–56.0
Diabetes complications (%)	2,380	9.7		8.2 (11.4)	0–30.1
History of malignancy (%)	3,281	13.3		13.7 (11.3)	0.0–53.3
History of psychological disorders (%)	2,500	10.2		8.6 (8.3)	0.0–36.9
Hypertension (%)	12,345	50.1		51.2 (31.7)	1.6–88.2
Dyslipidemia (%)	4,747	19.3		14.6 (19.0)	0.0–79.5
Nephropathy (%)	1,275	5.2		3.3 (6.0)	0.0–30.1
Overweight (%)	11,526	46.8		50.0 (26.6)	3.5–83.1
≥5 chronic drugs (%)	6,916	28.1		26.9 (9.7)	12.4–45.7
≥3 glucose lowering drugs (%)	2,568	10.4		10.5 (6.1)	0.0–20.9
≥2 lipid lowering drugs (%)	753	3.1		2.8 (2.5)	0.0–12.8
≥4 blood pressure lowering drugs (%)	2,939	11.9		11.8 (5.3)	0.0–32.1

Table 2-2. Proportion of patients treated and the between practice differences in treatment rate

Treatment measure	Patients with treatment indication	Patients receiving treatment	%	Median percentage among practices [IQR]	Range among practices (min–max)
Glucose-lowering drugs	24628	18547	75.3	77.9 (13.9)	39.1–95.7
Metformin	18547	15572	83.9	84.7 (7.5)	60.2–100
Lipid-lowering drugs	10272	7567	73.7	74.3 (13.2)	43.8–100
Statins	7567	7375	97.5	98.6 (3.7)	66.7–100
Blood pressure-lowering drugs	15369	13487	87.8	90.4 (9.5)	55.6–100
RAAS-blockers*	13487	10590	78.5	80.4 (10.2)	45.3–100

* RAAS-blockers: renin-angiotensin-aldosterone system blockers

Table 2-3. Proportion and reduction of variance in treatment attributed to practice level

	Variance at practice level (%)*			
	Glucose-lowering drugs		Metformin	
	proportion	reduction	proportion	reduction
Empty model: crude practice level variance	7.5		3.6	
Model 1: including patient characteristics only	7.3	0.2	3.3	0.3
Model 2: including practice characteristics only	6.4	1.1	3.6	0
Model 3: including patient and practice characteristics**	6.1	1.4	3.3	0.3
	Lipid-lowering drugs		Statins	
	proportion	reduction	proportion	reduction
Empty model: crude practice level variance	3.1		10.3	
Model 1: including patient characteristics only	2.8	0.3	10.2	0.1
Model 2: including practice characteristics only	2.9	0.2	9.6	0.7
Model 3: including patient and practice characteristics**	2.5	0.6	9.6	0.7
	Blood pressure-lowering drugs		RAAS-blockers	
	proportion	reduction	proportion	reduction
Empty model: crude practice level variance	8.5		3.9	
Model 1: including patient characteristics only	6.7	1.8	3.8	0.1
Model 2: including practice characteristics only	8.2	0.3	3.7	0.2
Model 3: including patient and practice characteristics**	6.4	2.1	3.4	0.5

* Pseudo R^2 for the two level fixed effect random intercept models
** Model 3 included the variables with the effect size from Table 2-4

Table 2-4. Effect sizes of the association between the characteristics and treatment outcomes as described in model 3 in the methods (all selected variables are included into the models)

Model	Treatment with glucose-lowering drugs (n = 24628)	Treatment with metformin (n = 18547)	Treatment with lipid-lowering drugs (n = 10272)	Treatment with statins (n = 7567)	Treatment with blood pressure-lowering drugs (n = 15369)	Treatment with RAAS-blockers (n = 13487)
Age	0.76 (0.71–0.81)	0.55 (0.50–0.60)	0.37 (0.33–0.41)	NA	0.68 (0.60–0.77)	0.77 (0.69–0.86)
Female gender	0.81 (0.76–0.86)	0.75 (0.69–0.82)	0.73 (0.67–0.80)	0.83 (0.62–1.11)	1.08 (0.98–1.19)	0.80 (0.73–0.87)
Diabetes duration	3.16 (2.97–3.38)	0.57 (0.51–0.63)	1.08 (0.97–1.20)	NA	NA	1.37 (1.25–1.51)
Hypertension	0.92 (0.86–0.99)	1.15 (1.05–1.25)	NA	NA	NA	NA
Dyslipidemia	NA	NA	NA	NA	NA	NA
Nephropathy	0.83 (0.72–0.96)	NA	NA	NA	NA	NA
Overweight	1.35 (1.27–1.45)	1.09 (0.99–1.18)	NA	NA	1.34 (1.21–1.49)	1.23 (1.12–1.34)
Cardiovascular comorbidity	NA	0.87 (0.79–0.96)	NA	NA	NA	NA
Peripheral vascular comorbidity	NA	0.84 (0.74–0.95)	NA	NA	NA	NA
Diabetes complications	1.14 (1.02–1.27)	0.87 (0.76–0.99)	0.83 (0.73–0.95)	NA	0.86 (0.74–1.00)	NA
Malignancy	0.87 (0.80–0.95)	0.87 (0.78–0.98)	0.81 (0.72–0.91)	0.77 (0.54–1.11)	NA	NA
Psychological disorder	0.81 (0.74–0.90)	NA	0.77 (0.67–0.88)	NA	0.61 (0.53–0.70)	0.81 (0.71–0.92)
≥5 chronic drugs	NA	0.61 (0.55–0.66)	NA	0.82 (0.60–1.10)	1.29 (1.15–1.44)	0.73 (0.67–0.80)
≥3 glucose-lowering drugs	NA	NA	1.39 (1.18–1.64)	NA	1.41 (1.17–1.70)	1.11 (0.97–1.29)
≥2 lipid-lowering drugs	1.53 (1.25–1.89)	1.31 (1.02–1.68)	NA	NA	NA	1.28 (0.98–1.63)
≥4 blood pressure-lowering drugs	1.36 (1.23–1.51)	NA	1.42 (1.25–1.61)	NA	NA	NA
Solo practice	NA	NA	0.86 (0.75–0.99)	NA	NA	NA
Assistant presence	0.72 (0.54–0.95)	NA	NA	1.54 (0.87–2.71)	NA	NA
Number of T2DM patients per practice	0.99 (0.99–0.99)	NA	0.99 (0.99–0.99)	NA	0.99 (0.99–0.99)	0.99 (0.99–0.99)

NA implies that characteristic was not included in the model since it was either an inclusion criterion or a part of the treatment measure

2.4 Discussion

Considerable between practice differences in treatment with glucose-lowering, lipid-lowering, blood pressure-lowering drugs, and RAAS-blockers (IQR ranges of 10% or more) in T2D patients were observed. Smaller between practice differences in treatment were observed in treatment with metformin and statins (IQR ranges less than 8%). Not more than 10% of the observed differences, however, could be attributed to practice level, indicating that a significant part of the differences may be due to random variance. Of these differences attributed to practice level, between 6% and 25% could be explained by the patient and practice level characteristics included in this study. Patient characteristics explained almost 10% of the differences in lipid-lowering treatment compared to less than 10% for the other treatments. Practice characteristics explained more than 15% of the differences in glucose-lowering treatment compared to less than 10% for the other treatments.

Several studies have described differences in treatment rates between general practices, showing sometimes wide ranges (Gulliford *et al*., 2005; Hansen *et al*., 2007; Simmons *et al*., 2014; Hira *et al.*, 2015; National Health Service, 2016). One study looked at between practice differences in treatment with glucose-lowering drugs in Danish patients, and found a two-fold difference in prescription rate between the 10 and 90 percentile (Hansen *et al.*,

2007) compared to a 1.4-fold difference in this study when calculated for these percentiles (data not shown). Another study looked at the differences in treatment with lipid-lowering and blood pressure-lowering drugs in the UK patients with diabetes and hypertension (Gulliford *et al.,* 2005). This study found the IQRs for treatment with lipid-lowering drugs of 11 and for blood pressure-lowering drugs of 8, which are slightly smaller in comparison to the IQRs of around 13 and almost 9 observed in this study. Thus, it appears that the practice variation observed among Dutch general practices is lower for glucose-lowering drugs and similar for blood pressure-lowering drugs to that observed previously in other countries.

A recent review looking at patient characteristics associated with diabetes performance indicators did not find any consistent impact of demographics, complications, comorbidity, geography or care-seeking behavior (Calsbeek *et al*., 2016). They included only studies addressing monitoring of risk factors, for which there may be few justified reasons not to conduct such monitoring. For prescribing treatment, patient characteristics altogether explained at least 10% of the between practices differences for treatment with lipid-lowering drugs, but less than 10% for the treatment with blood pressure-lowering drugs and glucose-lowering drugs. For differences in treatment with lipid-lowering drugs but also with metformin, the patients' age was relevant, implying that age of a patient influences the practitioners' decisions to prescribe (Gnavi *et al.*, 2007). Since age-based prescribing in this case may be considered justified (Heart

Protection Study Collaborative Group, 2002; Shepherd *et al*., 2002; Inzucchi *et al*., 2014), this supports an age-stratified assessment of these treatment rates. For treatment with lipid-lowering drugs, the concomitant use of 3 or more glucose-regulating drugs explained 3% of the between practice variance. This suggests that there is a higher probability of receiving lipid-lowering drugs in patients with more severe diabetes. Since poor metabolic control is seen as an additional risk factor, starting statins is usually justified in such patients (Nederlands Huisartsen Genootschap, 2012). For metformin the concomitant use of 5 or more chronic drugs explained almost 7% of the variance. There seemed to be a shift from metformin to alternative treatment, including insulin, in patients with polypharmacy. This could be due to more complications and intolerability issues in these patients. On the other hand, the comorbidities and diabetes complications included in this study could not explain the between practice differences. These findings imply that the role of co-medication and comorbidity in explaining between practice variance should be further investigated. Especially, more information is needed about other factors, such as disease severity, drug intolerance and medication adherence.

Practice characteristics explained at least 15% of the between practices differences for treatment with glucose-lowering drugs, and less than 10% for treatment with lipid-lowering and blood pressure-lowering drugs. Between practice differences in health care quality of patients with diabetes and the role of patient and practice characteristics in these differences were examined

previously (Krein *et al.,* 2002; Dijkstra *et al.,* 2004; O'Connor, 2008). These studies, however, focused mainly on differences in monitoring of risk factors or differences in risk factor outcomes between practices. Similar to the findings of this study, they showed that the relatively small proportion (1-12%) of differences in quality of care can be attributed to differences between practitioners or practices (Krein *et al*., 2002; Dijkstra *et al.,* 2004; O'Connor, 2008; Calsbeek *et al*., 2016;). The number of T2D patients per practice was the most relevant practice characteristic in this study, which explained between 5% and 13% of the treatment variance for glucose-lowering drugs, lipid-lowering drugs, blood pressure-lowering drugs, and RAAS-blockers. A lower probability of being treated in practices with a higher number of T2D patients was observed. One explanation could be that these practices are more active in screening for diabetes, and therefore have more patients not yet in need of treatment (Janssen *et al.,* 2008; Van den Bruel, 2015). An alternative explanation is that the practice organization in large practices may be insufficient to provide optimal care. Although there is some evidence that practice size may negatively influence quality of care, this finding is not consistent (Ng CW *et al.,* 2013). Of the other practice characteristics, the presence of a physician's assistant explained some additional variance in treatment with statins, and RAAS-blockers, where it seemed that these drugs are more prescribed in practices with an assistant. This is in line with a finding in the UK, where prescribing of blood pressure and lipid lowering drugs was more guideline concordant in patients

assessed by a project nurse (Mohammed *et al.,* 2012). Surprisingly, a lower probability of being treated with glucose-lowering drugs in practices employing physician's assistant was observed. One explanation could be that the physicians' assistants are more consistent with guidelines resulting in fewer prediabetes patients per practice that may remain untreated if considered diabetic (Janssen *et al*., 2008). Overall, it appears that such general practice characteristics can only in part explain differences in treatment rates.

The study was based on data from the large general practice database containing a wide range of patient characteristics, treatment and comorbidity data. More than 90% of the differences in treatment between practices, however, remained unexplained. Part of this might be caused by the variance in other patient and practice level characteristics that were not able to include in this study, e.g. intolerance or unwillingness of patients for taking specific or additional drug treatment, severity of disease, visit frequency or practice location (Hong *et al.,* 2010). Because of the cross-sectional design, present study could not include the level of HbA1c, cholesterol, or blood pressure in the models. Instead study restricted all models to patients with an indication for treatment. The comorbidity data in medical records are known to be incomplete (Botsis *et al*., 2010), which would result in underestimating their influence on between practice variance. However, the comorbidity data in this study were enriched by manually coding text descriptions, resulting in higher comorbidity rates compared with that observed in a previous general practice study

conducted in The Netherlands (Struijs *et al.*, 2006). Moreover, practices with poor registration levels were excluded from this analysis. Finally, no data were available on practitioner level characteristics, such the physician's knowledge or attitudes. Given the observed variance at practice level, there is a need to explore other, unmeasured practice or practitioner characteristics (Hong *et al.*, 2010; Kralewski *et al.*, 2015).

Measuring the quality of treatment at practice level is part of various quality improvement initiatives (van Althuis *et al*., 2015; Health & Social Care Information Centre, 2016; National Committee of Quality Assurance, 2016). In several countries external parties, such as insurance companies or professional organizations, use quality assessment to reward health care providers who meet predefined standards of quality. For fair assessment it is important to know whether the observed differences in quality of treatment between healthcare providers may be attributed to practice level, and to what extent they can be explained by differences in the underlying patient population. In such cases, either case-mix adjustment or stratification can be recommended (Calsbeek *et al*., 2016). The findings of this study imply that the tested treatment measures are only to a small degree affected by differences in the underlying patient population. This study only supports to include age as a relevant patient characteristic to reduce justifiable differences in treatment rates with lipid-lowering drugs. Other patient characteristics either do not explain the between practice difference in treatment or do not justify these differences. Of

practice characteristics, This study found that the number of T2D patients per practice and presence of a physician's assistant may explain differences in treatment rates. This and also other modifiable practice characteristics should be identified and explored in future studies.

Supplemental Material 2-1. Proportion of variance in treatment attributed to practice level with percentage reduction compared to empty model (%)

Model	Treatment with glucose-lowering drugs		Treatment with metformin		Treatment with lipid-lowering drugs		Treatment with statins		Treatment with blood pressure-lowering drugs		Treatment with RAAS-blockers	
	Variance at practice level	% explained variance	Variance at practice level	% explained variance	Variance at practice level	% explained variance	Variance at practice level	% explained variance	Variance at practice level	% explained variance	Variance at practice level	% explained variance
Empty	7.53		3.60		3.13		10.26		8.55		3.89	
Age included	7.56	-0.40	3.39	5.83	3.01	3.83	10.2	0.58	8.53	0.23	3.85	1.03
Gender included	7.54	-0.13	3.54	1.67	3.08	1.60	10.06	1.95	8.55	0.00	3.79	2.57
Diabetes duration included	7.48	0.66	3.52	2.22	3.13	0.00	10.26	0.00	8.57	-0.23	3.83	1.54
Hypertension included	7.52	0.13	3.60	0.00	3.14	-0.32	10.27	-0.10	NA	NA	NA	NA
Dyslipidemia included	7.53	0.00	3.60	0.00	NA	NA	NA	NA	8.61	-0.70	3.91	-0.51
Nephropathy included	7.52	0.13	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Overweight included	7.51	0.27	3.64	-1.11	3.15	-0.64	10.24	0.19	8.63	-0.94	3.96	-1.80
Cardiovascular comorbidity included	7.61	-1.06	3.67	-1.94	NA	NA	NA	NA	NA	NA	NA	NA
Peripheral vascular comorbidity included	7.53	0.00	3.65	-1.39	NA	NA	NA	NA	NA	NA	NA	NA
Diabetes complication included	7.64	-1.46	3.64	-1.11	3.11	0.64	10.12	1.36	8.48	0.82	3.90	-0.26
Malignancy included	7.48	0.66	3.66	-1.67	3.09	1.28	10.48	-2.14	8.48	0.82	3.88	0.26
Psychological disorder included	7.45	1.06	3.61	-0.28	3.11	0.64	10.25	0.10	8.23	3.74	3.85	1.03
≥5 chronic drugs included	7.54	-0.13	3.36	6.67	3.16	-0.96	10.18	0.78	8.49	0.70	3.90	-0.26
≥3 glucose-lowering drugs included	NA	NA	NA	NA	3.04	2.88	10.25	0.10	8.42	1.52	3.89	0.00
≥2 lipid-lowering drugs included	7.50	0.40	3.61	-0.28	NA	NA	NA	NA	8.52	0.35	3.86	0.77
≥4 blood pressure-lowering drugs included	7.48	0.66	3.58	0.56	3.10	0.96	10.25	0.10	NA	NA	NA	NA
Solo practice	7.31	2.92	3.60	0.00	3.12	0.32	10.03	2.24	8.56	-0.12	3.88	0.26
Assistant presence	7.25	3.72	3.60	0.00	3.13	0.00	9.64	6.04	8.55	0.00	3.82	1.80
Number of T2DM patients per practice	6.54	13.15	3.62	-0.56	2.95	5.75	10.28	-0.19	8.18	4.33	3.66	5.91
Model 1: patient characteristics	7.28	3.32	3.33	7.50	2.82	9.90	10.23	0.29	8.02	6.20	3.61	7.20
Model 2: practice characteristics	6.36	15.54	3.62	-0.56	2.87	8.31	9.64	6.04	8.18	4.33	3.66	5.91
Model 3: patient and practice	6.10	18.99	3.33	7.50	2.50	20.13	9.64	6.04	7.70	9.94	3.37	13.37

NA implies that characteristic was not included in the model since it was either an inclusion criterion for or part of the treatment measure

CHAPTER 3.

Relationship of Type 2 Diabetes Therapy, Comorbidity, and Complications

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Relationship of Type 2 Diabetes Therapy, Comorbidity, and Complications

3.1 Introduction

The increasing burden in terms of effective diabetes care imposed by complex comorbidity status may influence treatment quality by increasing variance (Conwell *et al.*, 2008). Previous studies examining chronic conditions in patients with type 2 diabetes (T2D) found associations among increasing numbers of comorbidities, higher health-service utilization, and impaired physical functioning (Struijs *et al.*, 2006). In addition, it has been reported that patients with T2D have more chronic diseases than the diabetes-free population (Alonso-Moran *et al.*, 2015). For instance, in Korea, patients in all age groups with newly detected T2D were reported to have a significantly higher prevalence of coronary artery disease and cardiovascular disease compared to the general Korean population (Koo *et al.*, 2014). It might be feasible to develop

specific treatment guidelines for T2D patients with complex comorbid conditions. Clinical guidelines have rendered T2D care significantly more evidence-based, with the goal of providing effective therapy and reducing treatment variation. However, it remains unclear how to successfully identify the principal targets of interventions in complex comorbid patients and how to establish appropriate treatment guidelines in such patients.

Metformin is recommended as the first-line drug for controlling glucose levels in T2D patients. In addition, use of renin-angiotensin-aldosterone-system (RAAS) blockers to lower blood pressure, and of statins to lower lipid levels, are recommended for the prevention of further vascular complications (European Heart Journal, 2013; NICE, 2015; ADA,2016). Nevertheless, standard recommendations are increasingly criticized as contributing to excessive treatment that is sometimes futile. Variations in guideline-recommended treatments have been noted in practice (Cho *et al.*, 2016), and several studies have emphasized that current standard T2D treatment recommendations do not appropriately consider individuals with complex comorbidities (Kerr *et al.*, 2007; Woodard *et al.*, 2011). The identification of common comorbidity patterns and the exploration of current treatment status in terms of such comorbidities may improve the approach of management of T2D and associated comorbidities. This would increase our understanding of the current recommendations, and enable policymakers and clinicians to develop specific guidelines for patients with complex comorbidities. It may be difficult

to create a single recommendation for all T2D patients with a certain comorbid condition; variance in treatment decision making in practice may be unavoidable. However, it is necessary to ascertain and discuss a patient's current treatment status, because the number of available treatment options is becoming increasingly intricate and current guidelines rely principally on individual physician decision making.

The objectives of this study were to identify comorbidity and drug treatment patterns, and to explore the associations between comorbid status and drug treatment pattern in T2D patients.

3.2 Methods

3.2.1 Subjects

A retrospective, observational exploratory study was performed on patients with T2D aged 30 years and older without microvascular- or macrovascular diabetes complications using the South Korean 2009 and 2013 National Health Insurance Service-National Sample Cohort (NHIS-NSC) databases. Baseline data on demographic factors, comorbidity clusters and drug treatment clusters were obtained from the 2009 NHIS-NSC database. Comorbidity status was followed up in 2013. The NHIS-NSC is a population-

based cohort established by the NHIS of South Korea (Lee *et al.*, 2017); 2.2% of the total eligible population was randomly sampled using 1,476 strata from the 2002 Korean (nationwide) health insurance database. The cohort was followed up for 11 years, thus to 2013. The database provides detailed information on performed procedures and prescription drugs used, as well as diagnostic codes and personal information. The study was approved by the Institutional Review Board of Seoul National University.

3.2.2 Comorbidities

Number and type of comorbidity and presence of diabetes complication were assessed. 14 chronic diseases and 6 diabetes complications identified in prior studies (Barnett *et al.*, 2012; Alonso-Moran *et al.*, 2015) were considered (Supplementary Material 3-1). Among the 14 diseases, 6 were diabetes-related diseases and 8 were diabetes-unrelated disease. Diabetes-related diseases were those that (overall or in part) exhibited pathophysiological risk profiles similar to that of diabetes (Piette *et al.*, 2006). In follow up, 6 diabetes complications were considered along with 14 chronic diseases. 6 diabetes complications included both microvascular and macrovascular complications; retinopathy, neuropathy, nephropathy, peripheral vascular disease (PVD), ischemic heart disease, and cerebrovascular disease. Comorbidity records were extracted from

the NHIS-NSC database; the data had been encoded according to the International Classification of Disease (10th revision; ICD-10).

3.2.3 Drug treatment

Number and type of glucose lowering drugs, presence of lipid lowering drugs and blood pressure lowering drugs were assessed. 5 categories of glucose-lowering drugs, 4 categories of blood pressure-lowering drugs, and 4 categories of lipid-lowering drugs were evaluated (Supplementary Material 3-2). Prescriptions for longer than 90 days were subjected to further analysis. Classification into categories was based on the Anatomical Therapeutic Chemical(ATC) classification codes, which were extracted by reference to the prescription data of the NHIS-NSC database.

3.2.4 Statistical Analyses

Descriptive statistics were calculated for age, gender, comorbidities, drug treatment status and diabetes complications. Two-step cluster analyses were performed to identify groups that were homogeneous in terms of drug treatment and comorbidities including diabetes complications. Non-linear canonical correlation analyses were performed to explore the possible relationships between comorbidities and drug treatment clusters.

Two-step cluster analysis is appropriate when evaluating large datasets that contain categorical information (Zhang *et al.,* 1997; Finch *et al.,* 2015). The analysis proceeds in two steps: pre-clustering of participants into small subclasses, followed by final clustering of subclasses into an appropriate number of clusters determined using the Bayesian information criterion. Within a complex dataset, this technique can detect latent relationships among patients with multiple distinct characteristics (Norusis *et al.,* 2008; Amato *et al.,* 2016).

The average silhouette (a measure of cohesion and separation ranging from –1 to +1) was used to indicate the overall goodness-of-fit. The silhouette is a measure of how similar an object is to its own cluster (cohesion) compared to other clusters (separation) (Zhang *et al.,* 1997). The average silhouette coefficient is the average of all cases of the following calculation for each individual case: (B–A)/max (A, B) (IBM, 2017). A is the distance from the case to the centroid of the cluster to which the case belongs, and B is the minimal distance from the case to the centroid of every other cluster. Euclidean distances are generally calculated. A positive silhouette (range from -1 to +1) indicate that the average distance between cases in a cluster is smaller than the average distance to cases in other clusters, and thus are desirable. As found by Rousseeuw (1987), an average silhouette >0.5 indicates reasonably good partitioning of data. If the silhouette is <0.2, the quality of partitioning is considered poor; a value between 0.2 and 0.5 is considered fair.

Non-linear canonical correlation analysis allows evaluation of nonlinear relationships among a large number of different sets of variables scaled as either nominal, ordinal, or numerical. This approach analyzes relationships among K sets of variables, searching for commonalities among sets of variables that refer to the same objects (Mooi *et al.,* 2011). The purpose is to determine how similar sets of variables are to each other in a low-dimensional space; between-set similarities are established by simultaneously comparing linear combinations of the variables in each set to those of an unknown set (Frie *et al.,* 2009). In this study, nonlinear canonical correlation analysis was used to examine the relationships among four sets of variables. Age and gender were entered into the first set and the baseline comorbidity were included in the second set. The third set contained the baseline drug treatment clusters, and the fourth set the follow-up comorbidity clusters including diabetes complications.

Two types of sensitivity analyses were conducted. First, random sampled 70% of the study population was considered using two-step cluster analysis. Second, a hierarchical cluster analysis was performed using Ward's method. The F value is used in this method to maximize the differences between clusters significantly. This method is widely used as it minimizes the variance within groups and produces similar-sized clusters (Aldenderfer *et al.,* 1984; Fraley *et al.,* 1998). Hierarchical cluster analysis is especially proper for categorical variables or when the distribution of the variables is not independent. Squared Euclidian Distance is the square root of the sum of squared distances. Since the

Euclidian Distance is squared, it increases the importance of large distances, while weakening the importance of small distances. For binary data, the Squared Euclidean Distance is commonly used. All of the analyses were conducted using SPSS (Ver. 25) software.

3.3 Results

3.3.1 Characteristics of comorbidities and drug treatment status

In total 7,123 T2D patients were included for analysis (Figure 3-1). 64.9% had at least one other chronic disease and 22.6% had two or more comorbid diseases at baseline (Table 3-1). At follow-up, the proportions of comorbid patients had increased to 84.1% (one or more diseases) and 49.5% (two or more diseases). 88.2% T2D patients with 1 or more comorbidities had only diabetes related diseases while 8.2% had both, diabetes related and unrelated diseases at baseline. T2D patients with both type of comorbidities increased to 20.2% at follow up. In case of treatment, 61.7% of T2D patients were treated with 2 or more glucose lowering drugs and most of the T2D patients with indication (diagnosed with dyslipidemia or hypertension) were treated with lipid lowering- or blood pressure lowering drugs at baseline (79.8% and 91.6% respectively). In addition, within 4 years, 15.8% developed 1 or more

microvascular complications and 6.5% had ischemic heart disease or/ and cerebrovascular disease.

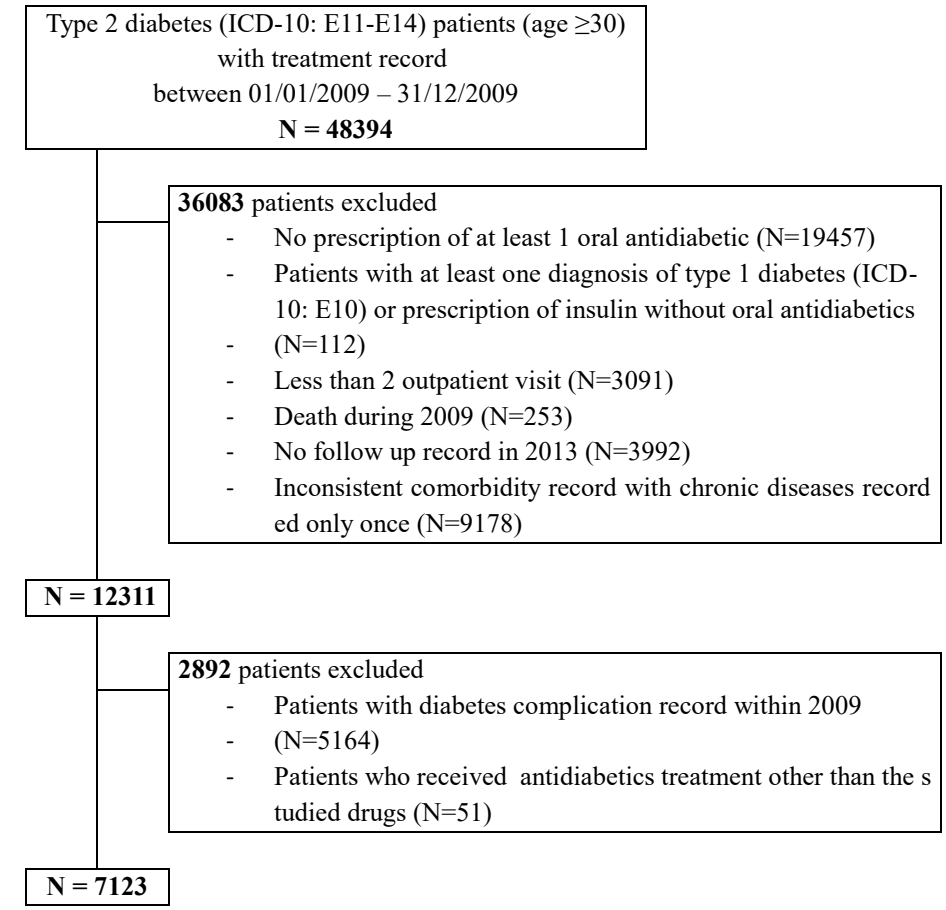


Figure 3-1. Selection of the study population

Table 3-1. Patient characteristics at baseline and follow-up

	N	%
Baseline (’09)		
N	7,123	100.0
Sex, *male*	4,081	57.3
Age, *≥65 years*	2,149	30.2
Number of comorbidity, *1 or more*	4,622	64.9
Number of comorbidity, *2 or more*	1,613	22.6
Type of comorbidity[a], *diabetes-related only*	4,080	88.2
Type of comorbidity[a], *both*[b]	381	8.2
Number of glucose lowering drug in use, *more than 1*	4,394	61.7
Presence of lipid lowering drug treatment[c], *yes*	1,796	79.8
Presence of blood pressure lowering drug treatment[d], *yes*	3,066	91.6
Follow up (’13)		
Number of comorbidity, *1 or more*	5,993	84.1
Number of comorbidity, *2 or more*	3,521	49.5
Type of comorbidity[a], *diabetes-related only*	4,589	76.6
Type of comorbidity[a], *both*[b]	1,213	20.2
Presence of microvascular complication, *1 or more*	1,126	15.8
Retinopathy	154	2.2
Nephropathy	336	4.7
Neuropathy	733	10.3
Presence of macrovascular complication, *1 or more*	1,125	15.8
Peripheral vascular disease(PVD)	746	10.5
Cerebrovascular disease	158	2.2
Ischemic heart disease	308	4.3

[a] Proportion of T2D patients with diabetes related disease only among patients with at least 1 comorbidity; [b] Diabetes related and unrelated comorbidity; [c] Proportion of T2D patients with dyslipidemia (N=2250) treated with lipid lowering drugs; [d] Proportion of T2D patients with hypertension (N=3346) treated with blood pressure lowering drugs;

3.3.2 Associations between comorbidities and drug treatment patterns

7 comorbidity clusters and 20 treatment clusters at baseline and 12 comorbidity clusters at follow-up were identified through two-step cluster analysis with an average silhouette measure of 0.8. In addition, relationships among age, gender, baseline drug treatment clustering, baseline comorbidity clustering, and follow-up comorbidity clustering were assessed by nonlinear canonical correlation analysis and associations between comorbidity and drug treatment clusters were identified (Table 3-2). Results can be considered significant because the eigenvalues were high (0.591 in the first dimension and 0.490 in the second dimension) and the fit value was 1.081 (which can be interpreted as the proportion of explained variance). As a two-dimensional design was employed in this study, half of the fit value [(1.081/2) *100 = 54.1%] was the mean proportion of the variation explained by the model. This means that the variables included in 4 sets explained over half (54.1%) of the variability in the data.

Centroid plots show the relationship among age, gender, comorbidity and drug treatment patterns (Figure 3-2, Supplemental Material 3-3). Difference and similarities among groups were shown by distance between each other and clusters included within the group explained the characteristics of each group. Variables or clusters positioned near the center of the centroid plot without being positioned in the group indicates weak or no effect on identifying

difference or similarities of relationships among groups than other clusters. Age and gender were positioned near the center of the plot showing its less or no effect on identifying relationships (Supplemental Material 3-3).

5 groups were identified in terms of similarity among baseline comorbidity, drug treatment, and follow-up comorbidity clustering (Table 3-3, Figure 3-2). 81.2% of T2D patients were included in Group A and Group B. Group A included 2 baseline comorbidity clusters, 3 drug treatment clusters and 2 follow up comorbidity clusters. Patients had none or 1 diabetes unrelated disease and 82.2% of the treatment patterns was identified. They were treated with MET, SU, MET+SU without lipid or blood pressure lowering drugs at baseline period. Also, 49.6% of follow up comorbidity pattern was identified of this group. Patients were identified to have none or 1 diabetes unrelated disease with no complication existing at follow up. Group B included 2 baseline comorbidity clusters, 6 drug treatment clusters and 2 follow up comorbidity clusters. Patients had 1 or 2 diabetes unrelated- or/and related diseases and 71.8% of them were treated with MET, SU, MET+SU with lipid or blood pressure lowering drugs at baseline period. Also, 48.1% of the patients were identified to have no complication existing at follow up with similar comorbid status as baseline. Group C included 1 baseline comorbidity cluster, 3 drug treatment clusters without identified follow up comorbidity clusters. Patients had 2 diabetes

related diseases and 54.6% of them were treated with MET, SU or MET+SU with lipid and blood pressure lowering drugs at baseline period.

Group D included 1 baseline comorbidity cluster, 2 drug treatment clusters and 2 follow up comorbidity clusters. Patients had more than 2 diabetes related diseases and 14.4% of treatment pattern was identified. They were treated with MET+DPP4i or SU+TZD with lipid lowering drugs and blood pressure lowering drugs at baseline period. 13.3% of follow up comorbidity patterns were identified of this group. Patients were identified to have no complication with diabetes unrelated disease developed compare to baseline period. Group E included 1 baseline comorbidity cluster including patients with 2 or more diabetes related- and unrelated diseases. However, related drug treatment patterns or follow up comorbidity patterns were not identified

Meanwhile, several relationship unexplained treatment clusters were identified. These cluster included; TZD or DPP4i, MET/SU+DPP4i, MET/SU+TZD, MET+SU+TZD, Insulin combined with MET or SU. Also, baseline comorbidity and drug treatment patterns were not identified related to follow up comorbidity clusters including micro- and/or macrovascular complications (Table 3-4, Figure 3-2). These clusters could probable explain the unidentified proportion of baseline treatment pattern and follow up comorbidity patterns.

3.3.3 Sensitivity analyses

Two types of sensitivity analyses were conducted. First, the two-step cluster analysis was conducted with 70% of the study population by random sampling. Results showed similar clustering. With average silhouette measure 0.8, 7 baseline comorbidity, 20 drug treatment and 12 follow up comorbidity clusters were observed and nonlinear canonical correlation analysis showed similar results. Second, a hierarchical cluster analysis was performed using Ward's method (Supplemental Material 3-4). Compared to clusters conducted from two-step analysis, baseline clusters matched 100%, treatment cluster and follow up clusters were average 90% similar. Nonlinear canonical correlation analysis showed similar results.

Table 3-2. Two-dimensional solution (nonlinear canonical correlation analysis) of the relationships among age and gender, baseline drug treatment clustering, baseline comorbidity clustering, and follow-up comorbidity clustering

Set		Loss		Total loss
		Dimension		
		1	2	
1	Age, Gender [a,b]	0.968	0.995	1.963
2	Baseline comorbidity clustering [c,d]	0.127	0.205	0.331
3	Baseline treatment clustering [c,d]	0.202	0.289	0.492
4	Follow up comorbidity clustering [c,d]	0.339	0.550	0.889
Mean loss		0.409	0.510	0.919
Eigenvalue		0.591	0.490	
Fit				1.081

[a] Optimal Scaling Level: Single Nominal;

[b] Projections of the Single Quantified Variables in the Object Space;

[c] Optimal Scaling Level: Multiple Nominal;

[d] Projections of the Multiple Quantified Variables in the Object Space.

Table 3-3. Characteristics of related baseline drug treatment clusters, baseline comorbidity clusters, and follow-up comorbidity clusters

Characteristics	Group A	Group B	Group C	Group D	Group E
N (%)	2,662 (37.4)	3,116 (43.7)	1,131 (15.9)	90 (1.3)	124 (1.7)
Baseline('09) comorbidity (average silhouette = 0.8)*					
Number of Clusters	2	2	1	1	1
Number of comorbidity	None or 1	1 or 2	2	2 or more	2 or more
Type of comorbidity	Diabetes-unrelated	Diabetes-related	Diabetes-related	Diabetes-related	Both
		Both[a]			
Baseline('09) drug treatment (average silhouette = 0.8)*					
Identified treatment patterns related to baseline comorbidity(%)	82.2	71.8	54.6	14.4	Not identified
Number of Clusters	3	6	3	2	Not identified
Number of glucose lowering drugs	1 or 2	1 or 2	1 or 2	2	Not identified
Type of glucose lowering drugs	MET / SU	MET / SU	MET / SU	MET+DPP4i	Not identified
	MET+SU	MET+SU	MET+SU	SU+TZD	
Presence of lipid lowering drugs	No	No / Yes	Yes	Yes	Not identified
Presence of blood pressure lowering drugs	No	No / Yes	Yes	Yes	Not identified
Follow up('13) comorbidity (average silhouette = 0.8)*					
Identified follow up comorbidity patterns related to baseline comorbidity(%)	49.6	48.1	Not identified	13.3	Not identified
Number of Clusters	2	2	Not identified	2	Not identified
Number of comorbidity	None or 1	1 or 2	Not identified	2 or more	Not identified
Type of comorbidity	Diabetes-unrelated	Diabetes-related	Not identified	Diabetes-related	Not identified
		Both		Both	
Type of complication	None	None	Not identified	None	Not identified

* The average silhouette of cohesion and separation; an indication of the overall goodness of fit (>0.2);

[a] Diabetes related and unrelated comorbidity; MET, metformin; SU, Sulfonylureas; TZD, Thiazolidinediones; DPP4i, Dipeptidyl peptidase 4 (DPP-4) inhibitors;

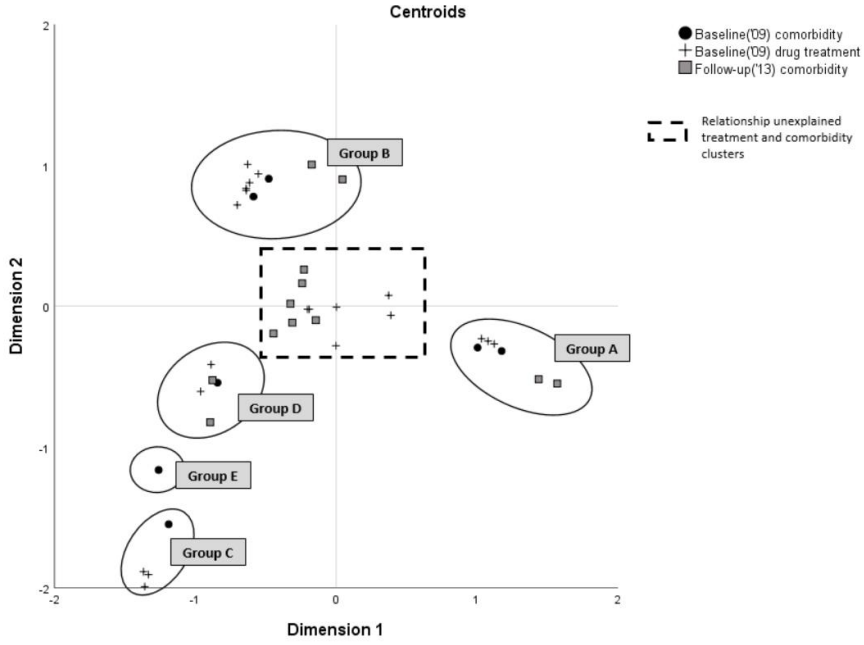


Figure 3-2. 5 groups based on similarity among baseline comorbidity, drug treatment, and follow-up comorbidity clustering

Table 3-4. Relationship unexplained drug treatment and comorbidity clusters

Baseline ('09) treatment				
Type	Number of glucose lowering drugs	Type of glucose lowering drugs	Presence of lipid lowering drugs	Presence of blood pressure lowering drugs
A	1	TZD or DPP4i	Yes	Yes
B	2	MET/SU+DPP4i MET/SU+TZD MET/SU+Insulin	No / Yes	Yes
C	3	MET+SU+TZD	Yes	Yes

Follow up ('13) comorbidity			
Type	Number of comorbidity	Type of comorbidity	Type of complication
A	1 or 2	Diabetes-related	Peripheral vascular disease (PVD)
B	1 or more	Diabetes-related Both[a]	Neuropathy or Retinopathy or Nephropathy
C	2 or more	Diabetes-related Both[a]	Peripheral vascular disease (PVD) and Neuropathy, Cerebrovascular disease, Ischemic heart disease

[a] Diabetes related and unrelated comorbidity; MET, metformin; SU, Sulfonylureas; TZD, Thiazolidinediones; DPP4i, Dipeptidyl peptidase 4 inhibitors;

3.4 Discussion

T2D patients often have other chronic diseases, which greatly burdens diabetes care. Present study found that 64.9% of patients had at least one other chronic disease and 22.6% of patients had two or more diseases before developing any diabetes complications. Especially the proportion of patients with 2 or more chronic disease doubled (49.5%) within 4 years.

In this study, comorbidity patterns and treatment patterns among T2D patients and explored the relationships among baseline comorbid status, drug treatment patterns and occurrence of diabetes complications were identified.

Present study report three main findings. First, results tend to show that as number of comorbidity increased and both type of comorbidities (diabetes unrelated and related disease) were present, common treatment patterns were less or not identified. The primary goal of diabetes treatment is to control blood glucose levels, which if left unchecked, may trigger complications (Lagu *et al.*, 2008; European Heart Journal, 2013; NICE, 2015; ADA, 2016). If metformin is insufficient, the treatment guidelines recommend second-line agents including sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, insulin, SGLT-2 inhibitors, and glucagon-like peptide-1 receptor agonists.

However, guidelines suggest the use of other treatments than metformin if needed in practice setting without recommending specific type of treatment patterns and its effect on outcomes, such as, micro-macrovascular complications. Results show that combination treatment, such as SU or DPP4i combined with MET or SU+TZD, were commonly observed in T2D patients with comorbidities. Recent studies have shown that DPP-4 inhibitors significantly lower the incidence of cardiovascular events (Richter *et al.*, 2008). Moreover, a meta-analysis of initial therapies prescribed for treatment-naive patients with type 2 diabetes found that significantly more patients attained the HbA1c goal of <7% when initially treated with metformin and DPP-4 inhibitors compared to metformin alone (Bailey, 2013).

In this study, MET+DPP4i was identified as treatment pattern in patients with 2 or more diabetes related comorbidity. However, its relation remained unclear in patients with 1 or 2 comorbidities and with patients that had both type of comorbidities, diabetes related and unrelated. Considering the effect of DPP4i presented in prior studies, further studies are necessary to assess the impact of comorbid status on the effect of MET+DPP4i treatment. In addition, TZD reduces insulin resistance and preserves beta cell function, whereas SU increases insulin secretion. So complementary mechanisms may have additive or synergistic effects (Cheng *et al.*, 2005). TZD plus an SU may cause more weight gain than SU alone. However, this may be mitigated by the fact that

TZD-induced fat accumulation is primarily subcutaneous rather than visceral (Rosenstock *et al.,* 2006). In fact, in a 2-year double-blinded trial, the Rosiglitazone Early vs SULfonylurea Titration (RESULT) study compared rosiglitazone with SU monotherapy, SU+TZD reduced the risk of diseases progression. These data suggest that early addition of a TZD to submaximal SU is more effective than SU dose escalation alone. Furthermore, an analysis of resource utilization and cost of care in the RESULT study concluded that TZD plus SU combination therapy is cost effective (Herman WH, *et al*. 2005). Prior randomized control trials which compared HbA1c change between MET+SU and SU+TZD mostly reported no significant between-group difference at 2 years. Thus, TZD plus SU therapy is a reasonable alternative to MET+SU (Hanefeld *et al.,* 2004; Charbonnel *et al.,* 2005). Recent retrospective analysis of the UK General Practice Database (including 91,511 type 2 diabetes patients with a follow-up time of 7.1 years), thiazolidinedione use was associated with over 30% reduction in all-cause mortality compared to metformin (Morgan *et al.,* 2012).

Second, treatment and comorbidity patterns were not identified in the group of T2D patients with 2 or more comorbidities or if diabetes unrelated disease was present along with diabetes related diseases. This indicates that T2D patients with 2 or more comorbidities are exposed to higher treatment variance than other T2D patients. Further studies related to effective drug

treatment should be conducted within this group to control the variance that could support effective diabetes care. Treatment patterns which were not specified in any groups including insulin combined with MET or SU could be used in the treatment of this group. Regarding the fact that differences in glucose-lowering treatment are partly explained by complications and intolerances reflecting the polypharmacy associated with complex comorbidities (Cho *et al*., 2016), insulin therapy could be favored in T2D patients with complex comorbid status. In addition, a recent study found that the combination of insulin with oral glucose-lowering drugs provided several potential advantages without compromising glycemic efficacy (Woo, 2017). Further studies should be conducted on T2D patients with these conditions to assess effective diabetes care.

Thirdly, related comorbidity or treatment pattern to occurrence of micro- or macrovascular complications was not identified clearly. This indicates that different treatment patterns in various comorbid status relates to the development of complications. This is reasonable since all of the drug treatments should have an effect on glucose level control and control of glucose level an important factor to development of macrovascular complications. Considering treatment clusters that were identified from this study, further studies would be necessary on assessing the association between identified

treatment clusters and its relation to development of micro-macrovascular disease.

This study had certain strengths. First, this is the first study to define the relationship between comorbidity status and drug treatment in Korean patients with type 2 diabetes. This study outlined possible early approaches for the prevention or management of comorbid conditions in such patients. In addition, identification of associations between comorbidities and treatment status allows us to understand differences and variance in current diabetes care in terms of comorbidities. If the appropriate treatment is lacking or if treatment status is unclear in those with certain comorbidities, our approach identifies potential groups at risk who should be the prime targets of treatment guidance. This study focused on current treatment patterns and identified common treatments. If different treatments were associated with differences in health outcomes in terms of comorbid status, such findings would support the results of this study. Second, this study was able to avoid selection bias, ensuring the accuracy of the descriptive data; interrogated NHIS-NSC databases that are representative of the entire Korean population. Present study studied virtually a representative proportion of all diabetics in a defined geographical area. In addition, the database contained information on primary, specialized, and ambulatory hospital care; and the drugs prescribed. Such detailed descriptions of health problems strengthened the data.

However, this study had certain limitations. First, this study used administrative datasets; this means that the accuracy of the results is critically dependent on the recorded clinical diagnoses, and the accuracy of clinical coding by the NHIS has been disputed. Korean studies comparing diagnoses in claim databases with medical records revealed overall accuracy rates of 72.3% for diabetes, 71.4% for myocardial infarction, and 83.4% for ischemic stroke (Kimm *et al.*, 2012; Park *et al.*, 2013). Thus, study imposed strict subject selection criteria to minimize misclassification and its effects in the present study. Particularly, with comorbidities, only patients with consistent diagnoses to the time of follow-up were considered genuinely comorbid. Another limitation is the selection of medical conditions. Currently, no standard list of major or chronic diseases associated with diabetes is available. Thus, the list of diseases considered may not be complete, but this study included major chronic diseases that are known to be common in diabetics. In addition, comorbidity duration was not assessed. Therefore, comorbidities were considered complications only; no conclusions in terms of potentially modifiable risk factors can be drawn. Future refinements could feature the inclusion of other medical conditions and their durations.

Comorbidity status and its effect on diabetes treatment are a complex phenomenon that we do not yet know how to effectively manage in clinical practice. However, identification of comorbidity clusters and their relationships

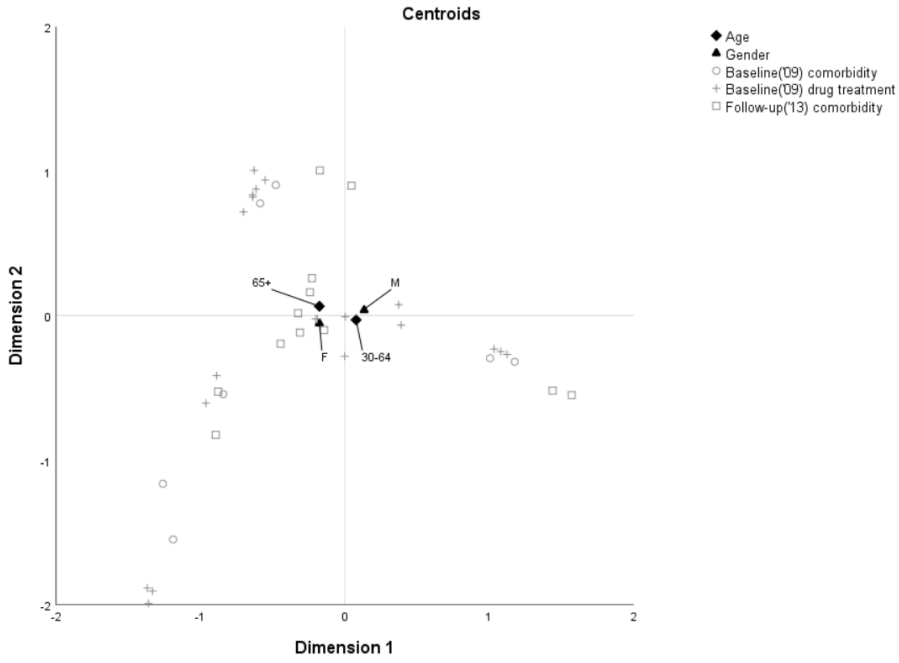
with treatment status enables us to consider patterns of comorbidity in terms of effective treatment that could improve diabetes care.

Supplemental Material 3-1. Chronic disease classification (10th revision; ICD-10)

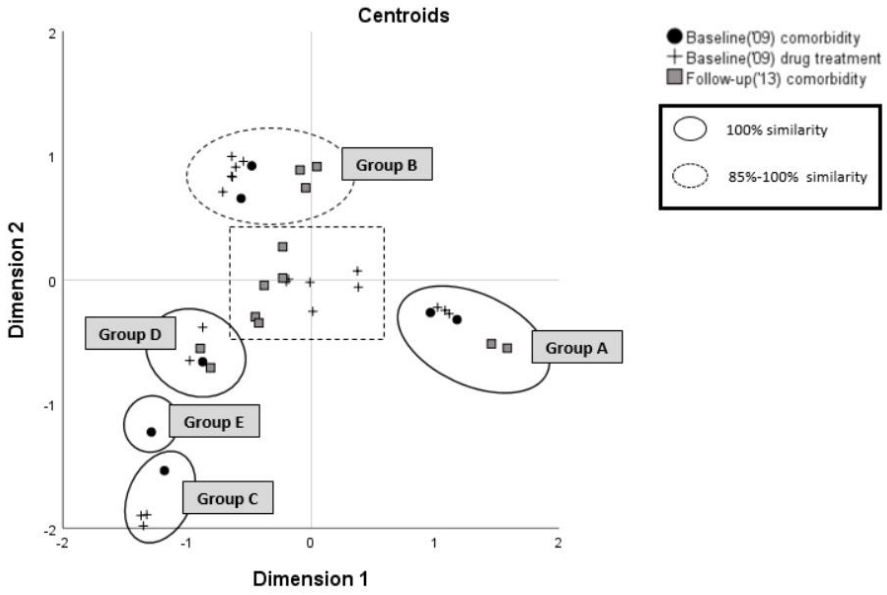
Type of Comorbidity	ICD-10 code
Diabetes-related disease	
Dyslipidemia	E78
Hypertension	I10
Atherosclerosis	I70
Aneurysm	I71-I72
Cardiac disorder	I20,I25, I42, I46-I50
Chronic kidney disease(CKD)	N18
Diabetes-unrelated disease	
Arthritis	M15-M19, M05-M06, M10-M11
Osteoporosis	M81-M82
COPD/Asthma	J44/J45
Anxiety/Depression	F40-F41/F32
Dermatitis	L20–L30
Malignancy	C00-C97
Diabetes microvascular complication	
Neuropathy	G63.2, E11.4–E14.4
Nephropathy	N08.3, E11.2–E14.2
Retinopathy	H28, H36, E11.3–E14.3
Diabetes macrovascular complication	
Ischemic heart disease	I21
Cerebrovascular disease	G45-G46, I60-I69
Peripheral vascular disease (PVD)	173.9, I79.2, E11.5–E14.5

Supplemental Material 3-2. Drug treatment classification (Anatomical Therapeutic Chemical [ATC] classification)

Drug	ATC code
Glucose-lowering drugs	A10
Insulin	A10A
Biguanides (Metformin, MET)	A10BA
Sulfonylureas (SU)	A10BB
Thiazolidinediones (TZD)	A10BG
Dipeptidyl peptidase 4 (DPP-4) inhibitors (DPP4i)	A10BH
Blood pressure-lowering drugs	C03, C07–09
Diuretics	C03
Beta-blockers	C07
Calcium antagonists	C08
ACE inhibitors and angiotensin antagonists (RAAS blockers)	C09
Lipid-lowering drugs	C10
HMG CoA reductase inhibitors (=Statins)	C10AA
Fibrates	C10AB
Bile acid sequestrates	C10AC
Nicotinic acid and derivatives thereof	C10AD



Supplemental Material 3-3. Difference in relationship of age and gender with baseline (2009) comorbidity and treatment clusters, and follow-up (2013) comorbidity clusters



Supplemental Material 3-4. Similarity among baseline comorbidity, drug treatment, and follow-up comorbidity clustering using Ward's method

CHAPTER 4.

The impact of comorbidity on the relationship of metformin-based combination treatment and hypoglycemia, cardiovascular events and all-cause mortality in type 2 diabetes patients

Chapter 4.

The impact of comorbidity on the relationship of metformin-based combination treatment and hypoglycemia, cardiovascular events and all-cause mortality in type 2 diabetes patients

Cho YY, Cho SI. Metformin combined with dipeptidyl peptidase-4 inhibitors or metformin combined with sulfonylureas in patients with type 2 diabetes: A real world analysis of the South Korean national cohort. Metabolism 2018 Mar 9. pii: S0026-0495(18)30081-7. doi: 10.1016/ j.metabol.2018.03.009.

4.1 Introduction

As increasing numbers of type 2 diabetes (T2D) patients develop comorbidities, more patients require multiple glucose-lowering medications to maintain appropriate glucose levels (Turner RC *et al.*, 1999; Mozaffarian *et al.*, 2016). The effective control of glucose levels relates to the management of existing comorbidities and the prevention of diabetes related comorbidities

(Anonymous, 1998; Farzadfar *et al.,* 2011; Garber *et al.,* 2015; Handelsman *et al.,* 2015; Lin *et al.,* 2015; Gallo *et al.,* 2018).

Currently, most guidelines recommend initial MET monotherapy prior to addition of any second-line drug (European Heart Journal, 2013; National Institute for Health and Care Excellence, 2015; American Diabetes Association, 2016; International Diabetes Federation, 2017; Upadhyay *et al.,* 2018), but combination therapy (MET plus additional agent) instituted as soon as possible after T2D diagnosis may improve glycemic control (Stratton *et al.,* 2000; Milligan, 2016). A meta-analysis of 15 randomized controlled trials found that MET combined with other agents significantly improved HbA1c levels and attainment of glycemic goals compared with MET alone (Phung *et al.,* 2014). Unfortunately, while previous studies showed that over a quarter (26%) of all patients switch to combination therapy within 3 years of diabetes diagnosis, 20–30% fail to achieve adequate HbA1c levels (<7.0%) eventually (Riedel *et al.,* 2007).

In many cases the optimal glycemic control is not achieved only by changes in lifestyle and the most part of type 2 diabetic patients needs a pharmacological treatment (American Diabetes Association, 2006). Type 2 diabetes is a progressive condition that requires combination therapy for optimal glycemic control (Turner, 1999). When hyperglycemia appears no longer adequately controlled, addition of a second agent with similar or

different mechanism of action is recommended. The most common combination regimens are SU plus metformin (Inzucchi, 2002; Petri, 2006). The selection of the ideal second-line therapy remains controversial because of personal preferences, costs, and most importantly efficacy and safety issues (Garber *et al.,* 2015). When selecting a class of antihyperglycemic agents for combination therapy, the glucose-lowering efficacy, risk of hypoglycemia, cardiovascular benefits, side effect and cost associated with the drugs are preferentially considered (Bailey *et al.,* 2013; Handelsman *et al.,* 2015; American Diabetes Association, 2015).

Metformin forms the basis of most oral combination therapies in T2D. Metformin provides reduction of body weight and ameliorates lipid abnormalities in obese and non-obese patients: moreover, metformin is effective in reducing C reactive protein (PCR) and lipoprotein a (Lp(a)) in thus improving, at the same time, endothelial dysfunction (Hundal, 2003). Metformin has a positive effect on several CV risk factors and has been shown to reduce cardiac events in overweight subjects with type 2 diabetes (Derosa, 2007).

Options for dual therapy (i.e. add-on) with metformin include oral agents (sulfonylureas, TZDs, DPP-4 inhibitors, SGLT2 inhibitors), injectable glucagon-like peptide 1 (GLP-1) agonists, or basal insulin (Inzucchi *et al.,* 2015).

One historically popular combination is that of metformin plus a sulfonylurea. In 2012, 22.1% of metformin use in the United States was concomitant with that of a sulfonylurea (Hampp *et al.*, 2014). Sulfonylureas (SU) have been popular combination agents for years, while DPP-4 (dipeptidyl peptidase-4) inhibitors have emerged more recently. In Korea, the number of patients with diabetes on combination (dual) therapy steadily increased from 35.0% in 2002 to 44.9% in 2013. Of patients on dual therapy in 2013, 41.7% were treated with SU and 32.5% with DPP-4 inhibitors (Korean Diabetes association, 2016). SUs are not expensive; however, they are known to be associated with weight gain, hypoglycemia, and an increased risk of cardiovascular-related mortality (Riedel *et al*., 2007; Rao *et al*., 2008). Some recent studies have indicated that DPP-4 inhibitors are associated with fewer side effects and improve long-term survival with lower risks of both fatal and nonfatal cardiovascular disease (CVD) events even after a first myocardial infarction, but the data remain conflicting (Morgan *et al.*, 2014; Seong *et al*., 2015; Eriksson *et al*., 2016; Wang *et al*., 2017).

Presently, clinicians have limited guidance when choosing a second agent and the presence of multiple comorbidities adds to the complexity of decision-making in clinical practice (Dailey *et al.*, 2002; Donnan *et al.*, 2002; Gallo *et al*., 2018). It was shown that the comorbidity status significantly impacts diabetes treatment intensification in insufficiently controlled patients (Kerr *et*

al., 2007; Conwell *et al.,* 2008; Lagu *et al*., 2008; Bolen *et al.,* 2008; Woodard *et al.,* 2011). Considering the increase of T2D diabetes patients with complex comorbid status (Lin *et al*., 2015; Mozaffarian *et al.,* 2016), assessing the effect of combination treatment in such T2D patients is warranted.

Aim of this study was to examine the risk of combination therapy with either MET+SU or MET+DPP4i in terms of hypoglycemia, CVD events, and all-cause mortality among T2D patients with comorbid status, using data of the South Korean National Health Insurance Service (NHIS)–National Sample Cohort.

Current guidelines from the American Association of Clinical Endocrinologists and American College of Endocrinology recommend initiating dual therapy (usually with metformin, unless contraindicated or not tolerated, plus a second agent) in patients with entry HbA1c levels >7.5%, and initiating dual or triple therapy with oral glucose-lowering agents in patients with entry HbA1c levels >9.0%.

For decades, antihyperglycaemic agents have been used for the treatment of type 2 diabetes mellitus given their effectiveness and convenience. Metformin (MET) and Sulfonylureas (SU) are time-tested antihyperglycaemic agents that have been administered for more than 50 years. These agents were followed by the introduction of other antihyperglycaemic agents such as glinides (GLN), thiazolidinediones (TZD), alpha-glucosidase inhibitors (AGI),

dipeptidyl peptidase-4 inhibitors (DPP-4I), and sodium–glucose cotransporter-2 inhibitors (SGLT2-I). MET is recognized as the drug of choice for monotherapy unless contraindicated or unwanted side effects occur. SU-induced hypoglycaemia is losing ground to various new agents, but the generic formulae of SU together with MET are cheap and effective. The cardiovascular hazards of several agents are a major concern to physicians and legislating bodies. In choosing antihyperglycaemic agents for dual or triple therapy, the treating physician must keep in mind the health status of the patient, medication side effects, cost, and patient preference.

4.2 Methods

4.2.1 Study population

Korean T2D patients with comorbidities who switched from monotherapy to combination treatment between July 1, 2008 and December 31, 2013 were included. The NHIS–National Sample Cohort was used, a population-based cohort established by the National Health Insurance Service (NHIS) system of South Korea that includes 2.2% of the total eligible population randomly sampled using 1,476 strata (Lee *et al.*, 2017). The database provides detailed information on the procedures performed and drugs prescribed, as well as

diagnostic codes and personal data. From this database, prescription information of diabetes drugs was extracted prescribed to 59,548 T2D patients (ICD-10 codes, E11–14). This is a retrospective cohort study with an exemption of the need for obtaining a written consent and was approved by the Institutional Review Board of the Seoul National University.

4.2.2 Exposure

Patients that initiated combination treatment with either MET+SU or MET+DPP4i between July 1, 2008 and December 31, 2013. Patients with a prior record of at least 3 months of mono therapy and at least 3 months of follow up record were included. The index date was that of combination treatment initiation. At time of the study, the following DPP4 inhibitors were available for T2D patients in South Korea: sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin, and gemigliptin (Kim *et al.,* 2013, Ko *et al.,* 2016).

4.2.3 Main outcomes

The main outcomes of the study were hospital admission or emergency room visit due to hypoglycemia, CVD events, and all-cause mortality. Patients were observed from the index date until: a gap of at least 6 months in filling a prescription for MET+SU or MET+DPP4i; or hypoglycemia; CVD events; all-

cause mortality; or December 31, 2013. The three endpoints were defined as: (1) hypoglycemia (ICD-10 codes: E16.0, E16.1, or E16.2) or diabetes with coma (ICD-10 codes: E10.0, E11.0, E12.0, E13.0, or E14.0), (2) CVD events including myocardial infarction (ICD-10 code: I21), stroke (ICD-10 codes: I63, G45), heart failure (ICD-10 code: I50), unstable angina pectoris (ICD-10 code: I20.0) or cardiovascular-related death, and (3) death from any cause in accordance with previous research (Eriksson *et al.*, 2016).

4.2.4 Sub outcomes

In addition, hospital admission or emergency room visit due to retinopathy (ICD-10 codes: E11.3, E12.3, E13.3, E14.3, H36.0), neuropathy (ICD-10 codes: E11.4, E12.4, E13.4, E14.4, G63.2), or nephropathy (ICD-10 codes: E11.2, E12.2, E13.2, E14.2, N08.3) was assess as additional primary outcomes. Only T2D patients without prior record of retinopathy, neuropathy or nephropathy at combination treatment initiation period were considered for the analysis. (Supplemental Material 4-1). Also, additional outcomes included: diagnosis of obesity (ICD-10 code: E66), hospital admission or emergency room visit due to gastrointestinal side effects, such as, obstipation (ICD-10 code: K59.0, K59.1) and nausea (ICD-10 code: R11), skin adverse event defined as pemphigoid diagnosis (ICD-10 code: L12), as well as pancreatitis (ICD-10 code: K85 K86) and malignant pancreas neoplasm (ICD-10 code: C25).

4.2.5 Covariates

To minimize confounding effects including age, sex, duration of mono treatment, comorbidity status (presence of diabetes unrelated comorbidity / number of diabetes related comorbidity), use of statins, use of low-dose aspirin, use of antihypertensives were subjected to serial statistical adjustment. Diabetes-related comorbidities were defined as being part of the same overall (pathophysiological) risk profile (Kerr *et al.*, 2007), and included hypertension, dyslipidemia, a history of ischemic heart disease, a history of stroke, peripheral vascular disease, neuropathy, nephropathy, retinopathy, and chronic kidney disease. Diabetes-unrelated comorbidities included dermatitis, arthritis, anxiety, depression, chronic obstructive pulmonary disease (COPD), asthma, osteoporosis, and malignancy (Supplemental Material 4-1).

4.2.6 Propensity score matching

To address the issue of confounding, propensity score matching (PSM) was conducted. Propensity scores were calculated and age, sex, duration of mono treatment, diabetes-unrelated comorbidity status, number of diabetes-related comorbidities, use of statins, use of low-dose aspirin, and use of antihypertensives were used as adjusted variables. These variables were chosen based on previous studies of risk factors affecting prescriptions and risk of

diabetes complications. Previous studies indicate that age (Booth *et al.*, 2006), gender (Manteuffel *et al.*, 2014), duration of monotherapy (Ha *et al.*, 2017), prior record of micro- or macrovascular complications (Wilke *et al.*, 2015; Eriksson *et al.*, 2016), presence of comorbidities (Woodard *et al.*, 2011), as well as risk levels and control status, such as, antihypertensive, lipid lowering or aspirin treatment (Li *et al.*, 2016) influence both prescribing practices and the risk of microvascular- or/and macrovascular complications.

4.2.7 Statistical analyses

The baseline characteristics of patients on the two combination treatments were compared using the chi-square test. Time from combination treatment initiation to an outcome event were analyzed using the Kaplan–Meier method. Cumulative incidence curves were created via survival analysis, and the significance of differences between curves were compared by log-rank testing.

Cox proportional hazards regression models were applied to estimate the risk of events (hypoglycemia, CVD events, and all-cause mortality) by calculating hazard ratios (HRs) and 95% confidence intervals (CIs) for each outcome. Prior to the analysis, the proportional hazard assumption was assessed by log minus log(LML) survival plot. If the predictor satisfies the proportional hazard (PH) assumption, then the graph of the log minus log(LML) versus log

of survival time graph should result in parallel lines if the predictor is proportional. In addition, Kolmogorov-Type Supremum Test was assessed to check PH for the covariates included for the analysis. PH assumption is satisfied when covariates included for the analysis shows insignificant p-value (Allison, 1995; Klein & Moeschberger, 1997; Therneau & Grambsch, 2000; Kalbfleisch & Prentice, 2002). Propensity scores were calculated by multivariate logistic regression analysis adjusted for age, sex, duration of mono treatment, presence of diabetes-unrelated comorbidities, number of diabetes-related comorbidities, and the use of statins, low-dose aspirin, and antihypertensives. Propensity score mapping featured two-to-one matching between MET+SU and MET+DPP4i patients and their nearest neighbors. Furthermore, considering reports concerning an increased hospitalization risk in heart failure patients treated with DPP4 inhibitors, analyses were also performed excluding patients with heart failure (AB *et al.*, 2009; Upadhyay *et al.*, 2018). All analyses were performed using SAS ver. 9.4. All statistical tests were two-sided and $p<0.05$ was deemed significant.

4.2.8 Sensitivity analysis

As sensitivity analysis, an intention-to-treat (ITT) approach was adopted and performed. This analysis included not only T2D patients that fit the inclusion criteria (Switch from monotherapy to MET+SU or MET+DPP4i and

continued the same treatment till the occurrence of the event or the end of the follow up period) but also T2D patients that had subsequent switches or treatment interruption or discontinuation during the follow up period.

ITT analysis is largely considered as the gold standard for estimating the mastery of the intervention in RCTs. Since this analysis includes subjects who were unfit for the inclusion criteria of the study or failed to receive any treatment after randomization when evaluating the effects of study outcomes, it supports the main analysis and conserves the proportion in prognostic factors comprised by randomization, which is crucial for invalidating selection bias and rendering causation (Heritier *et al.,* 2003; Abraha *et al.,* 2010; Yelland *et al.,* 2015).

The idea of ITT analysis can support the limitation of the studies that use observational data which is the underlined influence of potential confounding factors to the outcomes (Stampfer, 2008). In applying the ITT principle to observational data, subjects that initiate the exposure (in this study, combination treatment) are considered as they were in that initially exposed group, regardless of their later behavior, such as, discontinuation or switch of exposures.

4.3 Results

Of the 59,548 T2D patients in the NHIS–National Sample Cohort, 5,693 who started either MET+SU or MET+DPP4i during the study period and had at least one diabetes-related comorbidity were included for further analysis (Figure 4-1). Of the 5,693 eligible patients, 3,767 (66.2%) initiated MET+SU treatment, and 1,926 (33.8%) switched to MET+DPP4i during the study period (Table 4-1). Patients in the MET+DPP4i group were younger than patients in the MET+SU group, but no sex difference was apparent. After an average of 21 months (1.8 years) of monotherapy, second-line regimens were added. In comparison, the treatment costs of MET+DPP4i were significantly higher than the costs of MET+SU ($p<0.0001$). A mean of 2.6 comorbid diseases was present at the time of combination therapy initiation and 34.9% of patients had both diabetes-related and -unrelated comorbidities regardless of the type of treatment. Hypertension and dyslipidemia were the two most frequent comorbidities. The comorbidity status stratified by the two treatment groups is presented in Table 4-1 and Supplemental Material 4-2.

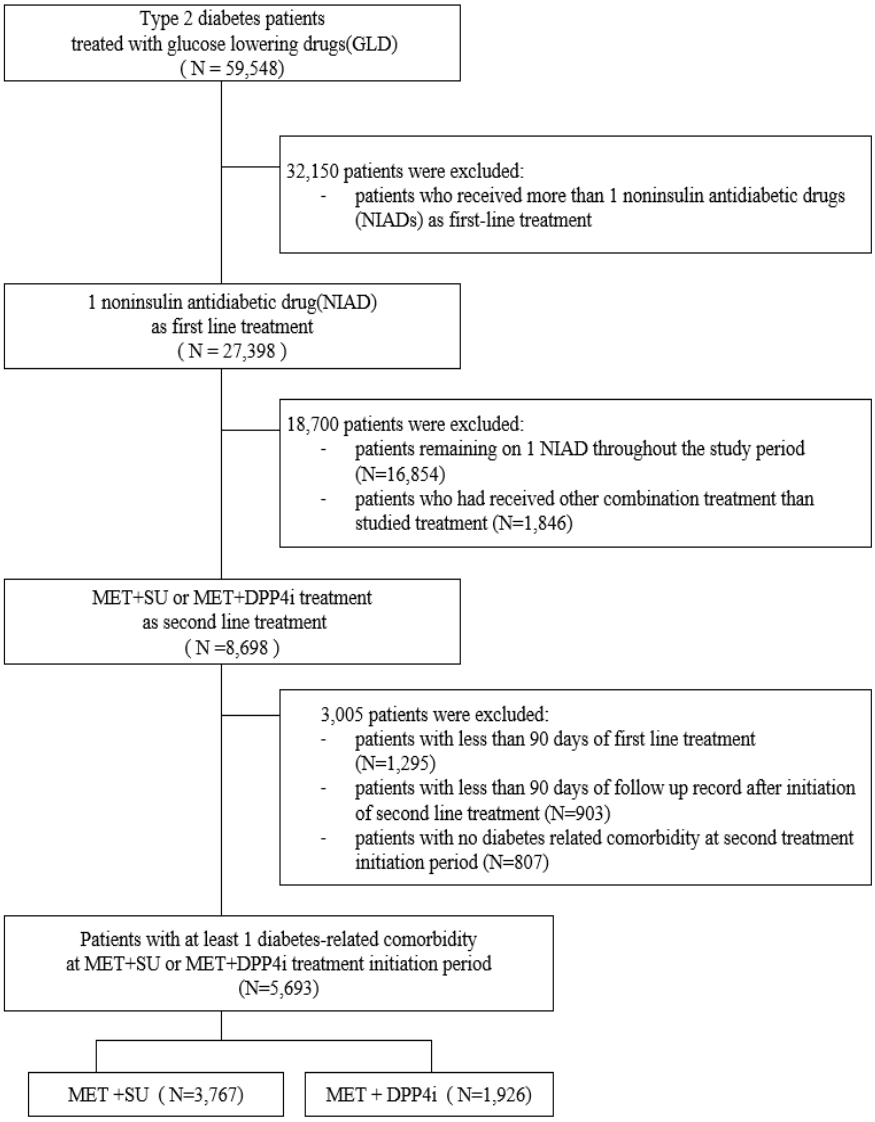


Figure 4-1. Selection of the study population

Table 4-1. Baseline characteristics of patients initiated on either sulfonylurea(SU) or DPP-4 inhibitor (DPP4i) in combination with metformin

	All patients			
	Total	MET + SU	MET +DPP4i	P-value*
Number of patients, N	5,693	3,767	1,926	
65 and over, n(%)	2,200(38.6)	1,570(41.7)	630(32.7)	<.0001
Male, n(%)	3,025(53.1)	1,997 (53.0)	1,028(53.1)	0.80
Duration of monotherapy (months), mean(SD)	21.1(14.8)	20.4(14.6)	22.5(15.1)	0.05
Number of comorbidity, mean(SD)	2.6(1.5)	2.6(1.5)	2.7(1.5)	0.10
Number of diabetes-related comorbidity[a], mean(SD)	2.2(1.1)	2.1(1.1)	2.2(1.2)	0.10
Presence of diabetes-unrelated comorbidity[b]	1,985(34.9)	1,291(34.3)	694(36.0)	0.20

* chi-square test; $p<0.05$

a. dyslipidemia, hypertension, ischemic heart disease (unstable angina, myocardial infarction, heart failure, atrial fibrillation), stroke (hemorrhagic, ischemic, transitory ischemic attack), peripheral vascular disease(PVD), retinopathy, nephropathy, chronic kidney disease(CKD); b. dermatitis, arthritis, COPD, osteoporosis, asthma, depression, anxiety, malignancy; c. myocardial infarction, unstable angina, angina pectoris, heart failure, atrial fibrillation; d. (hemorrhagic, ischemic) stroke, transitory ischemic attack; MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor.

Table 4-1. Baseline characteristics of patients initiated on either sulfonylurea(SU) or DPP-4 inhibitor (DPP4i) in combination with metformin *(continued)*

	All patients			
	Total	MET + SU	MET +DPP4i	P-value*
Prevalence of Comorbidities n(%)				
Hypertension	3,913(68.7)	2,664(70.7)	1,249(64.9)	<.0001
Dyslipidemia	4,290(75.4)	2,669(70.9)	1,621(84.2)	<.0001
History of Ischemic heart disease[c]	918(16.1)	595(15.8)	323(16.8)	0.34
History of Stroke[d]	781(13.7)	537(14.3)	244(12.7)	0.10
Peripheral vascular disease (PVD)	729(12.8)	523(13.9)	206(10.7)	0.0005
Neuropathy	575(10.1)	380(10.1)	195(10.1)	0.97
Nephropathy	655(11.5)	379(10.1)	276(14.3)	<.0001
Retinopathy	362(6.4)	213(5.7)	149(7.7)	0.002
Chronic kidney disease (CKD)	85(1.5)	54(1.4)	31(1.6)	0.60
Dermatitis	682(12.0)	489(13.0)	193(10.0)	0.001
Arthritis	240(4.2)	139(3.7)	101(5.2)	0.005
Osteoporosis	474(8.3)	290(7.7)	184(9.5)	0.02
Chronic obstructive pulmonary disease (COPD)	97(1.7)	59(1.6)	38(2.0)	0.26
Asthma	382(6.7)	267(7.0)	115(5.9)	0.11
Anxiety	492(8.6)	312(8.2)	180(9.3)	0.18
Depression	228(4.0)	135(3.6)	93(4.8)	0.02
Malignancy	175(3.1)	101(2.7)	74(3.8)	0.02
Treatments, n(%)				
Antihypertensives	3,387(59.5)	2,347(62.3)	1,040(54.0)	<.0001
Statins	2,448(43.0)	1,470(39.0)	978(50.8)	<.0001
Low dose aspirin	1,719(30.2)	1,172(31.1)	547(28.4)	0.04

* chi-square test; $p<0.05$

a. dyslipidemia, hypertension, ischemic heart disease (unstable angina, myocardial infarction, heart failure, atrial fibrillation), stroke (hemorrhagic, ischemic, transitory ischemic attack), peripheral vascular disease(PVD), retinopathy, nephropathy, chronic kidney disease(CKD); b. dermatitis, arthritis, COPD, osteoporosis, asthma, depression, anxiety, malignancy; c. myocardial infarction, unstable angina, angina pectoris, heart failure, atrial fibrillation; d. (hemorrhagic, ischemic) stroke, transitory ischemic attack; MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor.

Prior to analysis, proportional hazard (PH) assumption was assessed by log minus log(LML) survival plot. Assumption was satisfied as the graphs were parallel without crossing each other (Supplementary Material 4-3). Also PH assumption was satisfied for the covariates included in the analysis resulting from Kolmogorov-Type Supremum Test (Supplementary Material 4-3).

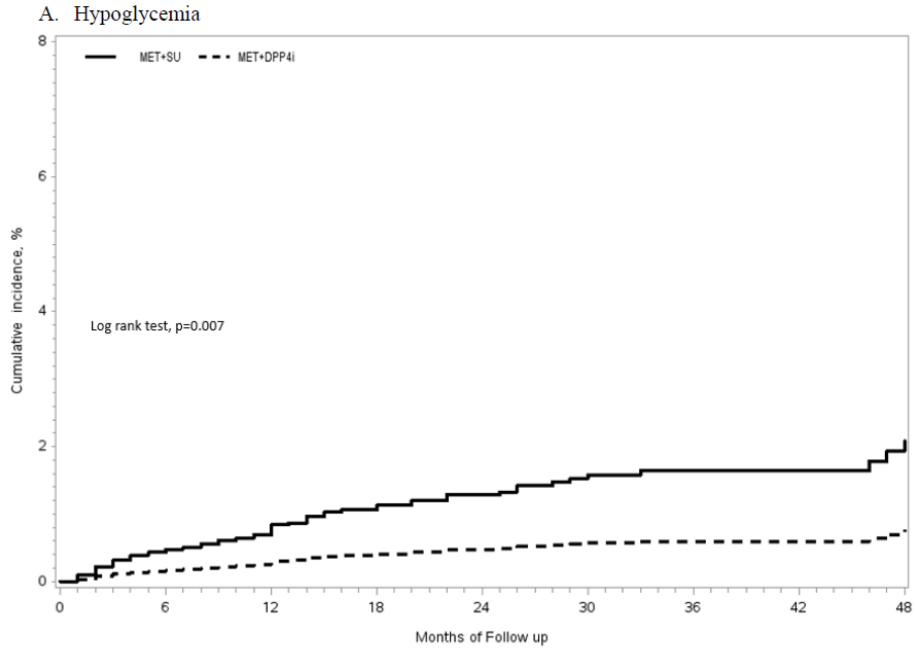
A total of 57 hypoglycemia cases, 263 CVD events, and 113 all-cause mortalities were identified during the follow-up period (Figure 4-2). In unmatched patient comparisons, the unadjusted HRs (95% CIs) associated with MET+DPP4i compared with MET+SU were 0.36 (0.17–0.76) for hypoglycemia, 0.67 (0.50–0.89) for CVD events, and 0.55 (0.34–0.90) for mortality (Table4-2). After adjustment, the values for hypoglycemia and CVD events remained significant. After propensity score matching (2:1) of 3,777 patients, the HRs (95% CIs) associated with MET+DPP4i compared with MET+SU were 0.32 (0.12–0.81) for hypoglycemia, 0.75 (0.54–1.05) for CVD events, and 0.56 (0.32–0.98) for all-cause mortality. In patients without known heart failure, MET+DPP4i significantly reduced the risk for hypoglycemia, CVD events, and all-cause mortality compared to the MET+SU treatment group. Supplemental Material 4-4 presents the analyses stratified by the DPP4 inhibitor prescribed.

The ITT analyses yielded similar results with hazard ratios (95% CI) of 0.53 (0.30-0.95), 0.73 (0.57-0.94), and 0.61 (0.36-1.02) for hypoglycemia,

CVD events and all-cause mortality, respectively. Details are shown in Supplemental Material 4-5.

In addition, Table 4-2 presents the results from univariate analyses of the individual variables used in the multivariate-adjusted survival analyses for each health outcome. Presence of diabetes-unrelated comorbidities and the number of diabetes related comorbidities were associated with an increased risk for CVD events and all-cause mortality. As the type and number of comorbidities were significant risk factors for both CVD events and all-cause mortality, analyses were repeated for subgroups categorized by the presence of diabetes-unrelated comorbidities and the number of diabetes-related comorbidities (Figure 4-3, Supplemental Material 4-6). After adjustment, MET+DPP4i significantly lowered the risk of CVD events in patients with only diabetes related comorbidities.

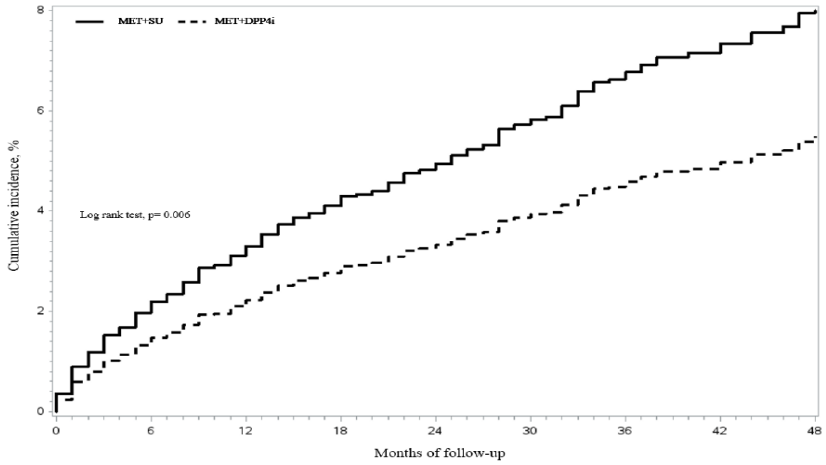
No significant differences in microvascular complications, retinopathy, neuropathy or nephropathy was observed between two treatments (Supplemental Material 4-7). There was no increased occurrence of pemphigoid in patients treated with MET+DPP4i; however only very few cases were reported in total (0.4% vs 0.5%). Equivalently, no differences in pancreatic complications (pancreatitis or pancreatic cancer) and gastrointestinal complications were observed.



Outcome	treatment	Event / Person-years	Number at risk (person / month)								
			0	6	12	18	24	30	36	42	48
Hypoglycemia	MET+SU	49 / 7,740	3767	3460	2929	2467	1982	1545	1149	863	564
	MET+DPP4i	8 / 3,155	1926	1692	1311	1026	805	632	363	258	172

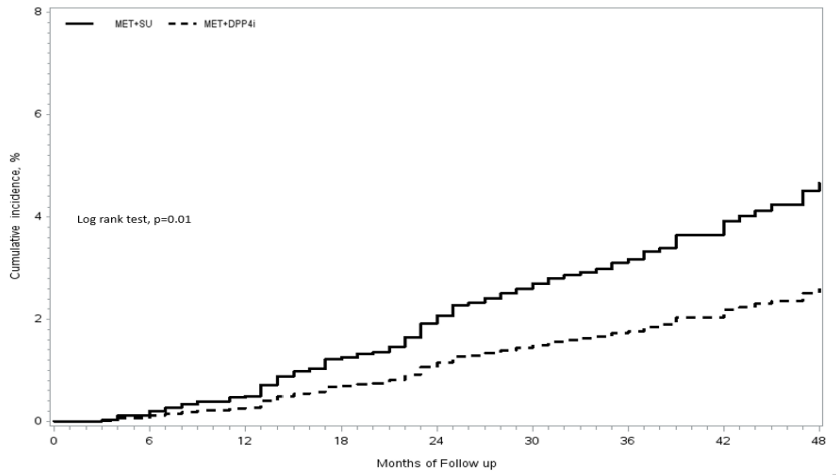
Figure 4-2. Cumulative incidences (%) of (A) hypoglycemia, (B) CVD events, and (C) all-cause mortality

B. CVD events



Outcome	Treatment	Events / Person-years	Number at risk (person / month)								
			0	6	12	18	24	30	36	42	48
CVD events	MET+SU	202 / 7,552	3767	3406	2869	2405	1921	1488	1099	822	533
	MET+DPP4i	61 / 3,097	1926	1676	1284	1000	783	607	347	250	166

C. All-cause mortality



Outcome	treatment	Event / Person-years	Number at risk (person / month)								
			0	6	12	18	24	30	36	42	48
All-cause mortality	MET+SU	93 /7,820	3767	3483	2962	2507	2014	1577	1175	884	575
	MET+DPP4i	20 /3,169	1926	1700	1317	1033	811	636	366	261	173

Figure 4-2. Cumulative incidences (%) of (A) hypoglycemia, (B) CVD events, and (C) all-cause mortality *(continued)*

Table 4-2. Hazard ratios (HRs) for main health outcomes among patients treated with MET+DPP4i versus MET+SU

	Hypoglycemia		CVD events		All-cause mortality	
	HR	95% CI	HR	95% CI	HR	95% CI
MET+DPP4i vs MET+SU						
Unadjusted	0.36	0.17-0.76	0.67	0.50-0.89	0.55	0.34-0.90
Adjusted[a]	0.39	0.18-0.83	0.72	0.54-0.97	0.64	0.39-1.05
Propensity score matched[b]	0.32	0.12-0.81	0.75	0.54-1.05	0.56	0.32-0.98
Without patients with prior heart failure history [c]	0.40	0.19-0.85	0.72	0.54-0.97	0.59	0.36-0.98
Age (65 and older)	3.07	1.73-5.46	2.35	1.80-3.06	5.31	3.35-8.43
Gender (female)	0.67	0.39-1.14	0.89	0.69-1.15	0.54	0.37-0.80
Duration of monotherapy (per months)	0.99	0.97-1.01	0.98	0.97-0.99	1.00	0.98-1.02
Presence of diabetes unrelated comorbidity (yes)	1.46	0.84-2.54	1.32	1.02-1.72	2.00	1.35-2.96
Number of diabetes related comorbidity (per disease)	1.19	0.96-1.49	1.39	1.25-1.53	1.21	1.03-1.43
Antihypertensives (yes)	-	-	0.89	0.68-1.16	1.22	0.80-1.85
Statins (yes)	-	-	0.90	0.70-1.16	0.58	0.38-0.88
Low dose aspirin (yes)	-	-	1.19	0.91-1.54	0.85	0.56-1.28

a. Adjusted for age gender, duration of mono treatment, comorbidities type (unrelated), number of diabetes related comorbidity, Antihypertensives (excl. hypoglycemia), Statins (excl. hypoglycemia), low dose aspirin (excl. hypoglycemia);
b. Matched by age gender, duration of mono treatment, comorbidities type (unrelated), Antihypertensives (excl. hypoglycemia), Statins (excl. hypoglycemia), low dose aspirin (excl. hypoglycemia); c. excluding patients with prior heart failure (HF) record (N=109); CVD, cardiovascular disease; MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor.

A. CVD events

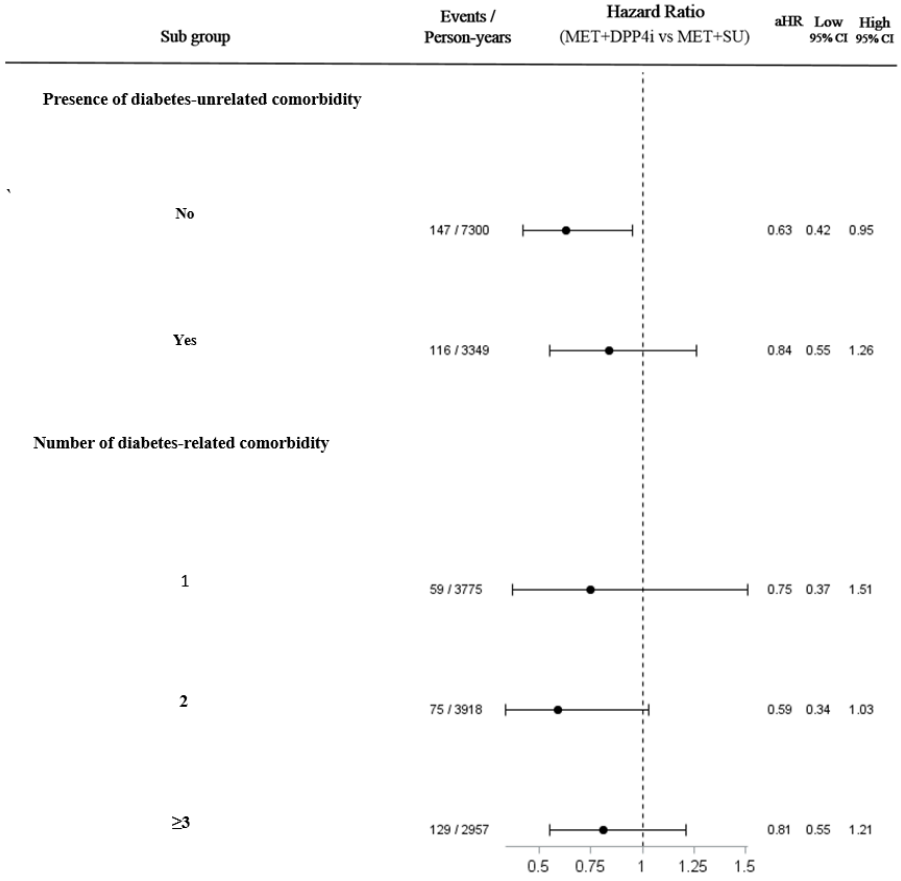


Figure 4-3. Subgroup analysis of the risks of (A) CVD events and (B) all-cause mortality in patients treated with MET+DPP4i versus MET+SU (adjusted Cox proportional hazard regression analyses) according to the presence of diabetes-unrelated comorbidities and number of diabetes-related comorbidities

B. All-cause mortality

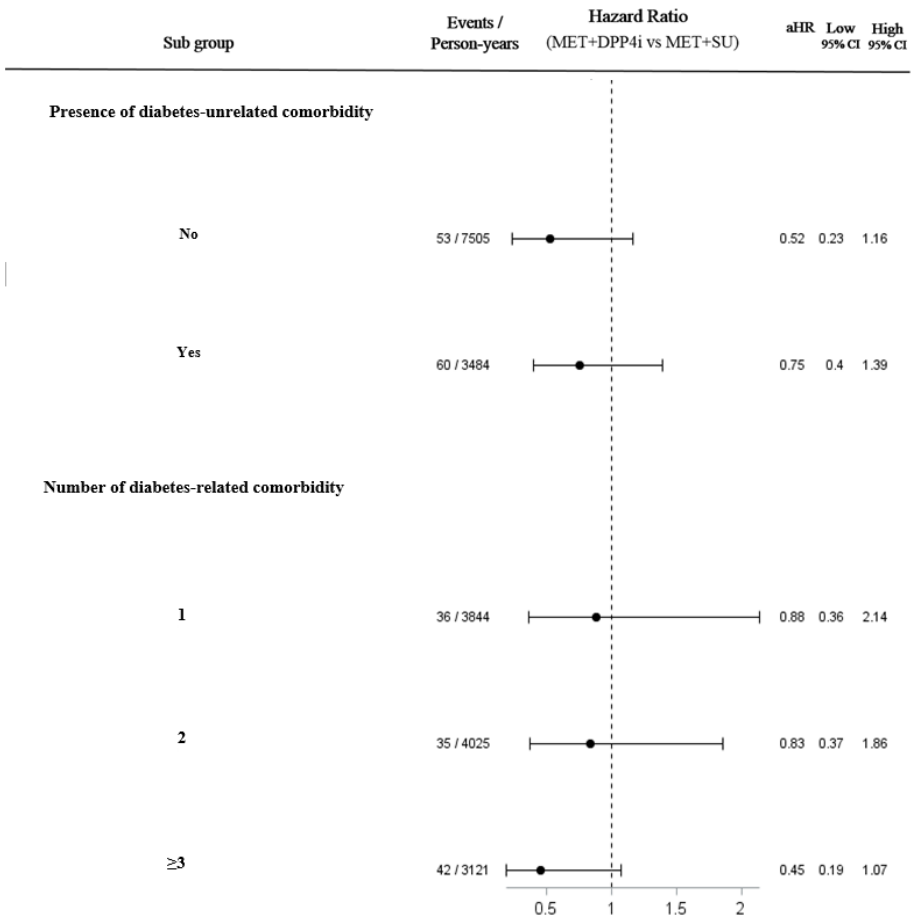


Figure 4-3. Subgroup analysis of the risks of (A) CVD events and (B) all-cause mortality in patients treated with MET+DPP4i versus MET+SU (adjusted Cox proportional hazard regression analyses) according to the presence of diabetes-unrelated comorbidities and number of diabetes-related comorbidities *(continued)*

4.4 Discussion

Most research comparing SU and DPP4 inhibitor treatment did not consider the comorbid status of the patients. This study aimed to compare combination treatment with either MET+SU or MET+DPP4i in terms of hypoglycemia, CVD events, and all-cause mortality among T2D patients with comorbid status. This study report three major findings. First, MET+DPP4i was associated with lower risks of hypoglycemia, CVD events, and all-cause mortality than MET+SU. After adjustment and propensity score matching, the point estimates of all observed outcomes indicated similar associations. Second, the type and number of comorbidities were significant risk factors for both CVD events and all-cause mortality. Third, the efficacy of MET+SU and MET+DPP4i varied in T2D patients with complex comorbidities. Compared to MET+SU, MET+DPP4i tended to be more favorable in patients with an increasing number of diabetes related comorbidities when considering all-cause mortality and significantly lowered the risk for CVD events in patients with only diabetes related comorbidities.

Direct comparisons with previous studies are limited by differences in populations and databases, but part of the findings is in line with previous work. A recent meta-analysis showed that MET+DPP4i treatment significantly

lowered the relative risk of CVD events and all-cause mortality compared with MET+SU (Mishriky *et al.*, 2015). Furthermore, the ongoing randomized Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA) trial, which compared addition of linagliptin versus glimepiride to metformin therapy in T2D patients, showed that the DPP4 inhibitor was associated with significantly fewer CVD events (1.5% vs. 3.3%, p=0.0213) and fewer cases of hypoglycemia (7% vs. 36%, p<0.0001) (Gallwitz *et al.*, 2012). Similarly, a nationwide Swedish study showed that MET+DPP4i was associated with significantly lower risks of mortality and CVD events than was MET+SU (Eriksson *et al.*, 2016). Comparable data were also obtained by the Clinical Practice Research Datalink in the UK (Morgan *et al.*, 2014) and in a nationwide Danish study of T2D patients without any prior history of CVD (Mogensen *et al.*, 2014). However, contrasting results also exist and few prior studies focused on high-risk groups and their outcomes. A study using the Taiwan National Health Insurance database found no differences in CVD risk when various second-line anti-diabetic agents, such as DPP4 inhibitors or SU, were added to MET (Chang *et al.*, 2015). Scirica *et al.* (2013) reported that saxagliptin neither increased nor decreased the risk of ischemic events (compared with placebo) among T2D patients at high risk of CVD events and Green et al. (Green *et al.*, 2015) found similar results using sitagliptin, another DPP-4 inhibitor. Among patients with

T2D and established CVD events, addition of sitagliptin to the usual treatment did not appear to affect the risk of major adverse CVD events.

Present study found that metformin-based combination treatment with SU had an increased risk of hypoglycemia compared to combination treatment with a DPP4 inhibitor and the data further supports the observed association of an increased CVD event risk with MET+SU treatment when compared to MET+DPP4i treatment (Eriksson *et al.,* 2016; Morgan *et al.,* 2014). This study did not observe an increased risk for pancreatic cancer when comparing MET+SU treatment when compared to MET+DPP4i treatment, which is in line with other studies (Gokhale *et al.,* 2014; Zhao *et al.,* 2017). Previous Korean analyses using the Health Insurance Review & Assessment Service database also indicated that MET+SU was associated with a higher CVD risk than MET+DPP4i (Seong *et al.*, 2015; Ha *et al.,* 2017). Results are consistent with these studies while adding additional information. Unlike previous Korean studies, study identified hypoglycemia as a health outcome due to the reported association with SUs (Zhao *et al.,* 2012; Scirica *et al*., 2013; White *et al.,* 2013; Eriksson *et al.,* 2016). Moreover, analysis was focused on patients with at least one diabetes-related comorbidity in addition to diabetes and maximized comparability between the second-line drug types prescribed to explore the effects of type and numbers of comorbidities on treatment outcome. Previous studies indicated that comorbidities may either increase or decrease treatment

intensification in insufficiently controlled patients (Lagu *et al.,*2008; Vitry *et al.,* 2010) and studies have suggested that the types of comorbidities should be considered to elucidate these relationships further (Kerr *et al.,* 2007; Lagu, *et al*., 2008). In this study, type and number of comorbidities were significant risk factors for CVD events and all-cause mortality. T2D patients with only diabetes related comorbidities showed a significantly lower risk of CVD events when receiving MET+DPP4i as compared to MET+SU treatment. Next, subgroup analysis indicated that MET+DPP4i treatment was also associated with relatively lower risks of CVD events and all-cause mortality with an increasing number of diabetes related morbidities when compared with MET+SU treatment. The possible pathophysiologic correlate has been proposed previously: SU receptors are also present in cardiac cells and binding of SUs leads to inhibition of ATP-sensitive potassium channels, thereby impairing the cell's ability to survive short-term ischemia, which may translate to a higher CVD event risk (Abdelmoneim *et al*., 2012; Eriksson *et al.*, 2016). On the other hand, DPP-4 inhibitors were shown to possess protective vascular properties through off-target effects (Goto *et al.,* 2013; Rosenstein *et al.,* 2016).

The results of this study underline that the comorbid status of a T2D patient should be considered when choosing a second line diabetes therapy in clinical practice, with DPP4 inhibitors being associated with a more favorable outcome than SUs. However, currently there is limited evidence concerning the risk of

treatment combinations for hypoglycemia, CVD events and all-cause mortality in comorbid T2D patients and additional studies are necessary to confirm the results. Furthermore, it may be of interest to evaluate if dose effects of the treatment combinations can be observed for CVD events and all-cause mortality.

Meanwhile, the current clinical trial evidence includes a number of therapies in patients with long-standing diabetes, and permits assessment of the effect of intensive glycemic control on microvascular outcomes. Evidence from ADVANCE (Patel *et al.,* 2008; Zoungas *et al.,* 2014) and VADT (Duckworth *et al.,* 2009) indicate long-term benefits of intensive glycemic control on microvascular outcomes. UK Prospective Diabetes Study (1998) presented the fact that intensive blood glucose control by SU substantially decreased the risk of microvascular complications. Similar to the UK Prospective Diabetes Study (UKPDS), significant benefits were noted on microvascular complications by The Steno-2 Study (Pedersen & Gæde, 2003). Also several studies report direct or potential beneficial effects of DPP4i on all microvascular diabetes-related complications (Fadini *et al.,* 2010; Matsubara *et al.,* 2013; Poncina *et al.,* 2014). Meanwhile, combination of metformin and either sulfonylurea or DPP4i showed similar glycemic effectiveness among drug-naïve Korean T2D patients (Lee *et al.,* 2013). Also, study of direct comparison between MET+SU and MET+DPP4i presented no difference in rate of microvascular event. This study

was conducted on 3,746 T2D patients on oral mono- or oral dual anti-diabetic combination therapy and was followed up for 24 months for microvascular events (Gitt *et al.,* 2013).

This study has certain strengths. It uses representative population-based cohort data of the South Korean National Sample Cohort; thereby representing real-world clinical practice settings (Lee *et al*., 2017; Kim *et al.,* 2017). Additionally, this study specifically investigated comorbid T2D patients which allowed us to determine the impact of comorbidities in the comparison of DPP4 inhibitors and SU combined with metformin. Nevertheless, this study also has limitations. First, this was a retrospective cohort analysis and events were ascertained from health insurance claims data. Recent Korean studies comparing diagnoses from claims databases with those from medical records reported overall accuracies of 72.3% for diabetes, 71.4% for myocardial infarction, and 83.4% for ischemic stroke (Kimm *et al*., 2012; Park *et al*., 2013). Second, sample size was relatively small as the study maximized the comparability between the second-line drug types to explore the effect of comorbidities on treatment outcomes. Additional long-term follow-up involving more patients is needed to explore the relationship between different second-line glucose-lowering drugs and the risks of hypoglycemia, CVD events, and all-cause mortality in T2D patients with complex comorbidities. Another limitation may be the withdrawal rate. Furthermore, there was only limited data

concerning dose titration within the treatment groups and hypoglycemia in patients where doses had to be down-titrated as well as uncoded hypoglycemia may have been missed.

In conclusion, it was found that type 2 diabetes patients with complex comorbidities who received MET+DPP4i as second-line treatment were at a lower risk of hypoglycemia, CVD, and all-cause mortality compared with those receiving MET+SU. In addition, comorbidity type and number may influence the effects of combination treatment involving glucose-lowering drugs with MET+DPP4i being associated with more favorable outcomes. While the causal relationship needs to be further elucidated, results of this study and those of other observational studies should be considered in clinical practice when choosing combination treatments for comorbid T2D patients.

Supplemental Material 4-1. List of diagnoses and their corresponding codes

Diagnosis or procedure	Corresponding codes (ICD-10[a])
Primary outcomes - main	
Hypoglycemia	E16.0-E16.2, E10.0, E11.0, E12.0, E13.0, E14.0
Cardiovascular events	
Myocardial infarction, Unstable angina, Heart failure	I21, I20.0, I50
Cerebrovascular diseases	I63
Transient cerebral ischemic attacks	G45
Primary outcomes - additional	
Retinopathy	E11.3, E12.3, E13.3, E14.3, H36.0
Neuropathy	E11.4, E12.4, E13.4, E14.4, G63.2
Nephropathy	E11.2, E12.2, E13.2, E14.2, N08.3
Secondary outcomes	
Obesity	E66
Obstipation, nausea	K59.0, K59.1, R11
Pemphigoid	L12
Pancreatitis, pancreas cancer	K85, K86, C25

[a]ICD-10, International Classification of Diseases, 10th revision; [b]ATC, Anatomical Therapeutic Chemical.

Supplemental Material 4-1. List of diagnoses and their corresponding codes *(continued)*

Diagnosis or procedure	Corresponding codes (ICD-10[a])
Covariates	
Hypertension	I10 and/or ATC[b] codes C02–C03, C07–C09
Dyslipidemia	E78 and/or ATC codes C10
Peripheral vascular disease(PVD)	173.9, I79.2, E11.5 – E14.5
Retinopathy	E11.3, E12.3, E13.3, E14.3, H36.0
Neuropathy	E11.4, E12.4, E13.4, E14.4, G63.2
Nephropathy	E11.2, E12.2, E13.2, E14.2, N08.3
Chronic kidney disease	N18
Dermatitis	L20–L30
Arthritis(incl. gout)	M05-M06, M10-M11
Osteoporosis	M81-M82
Chronic obstructive pulmonary disease (COPD)	J44
Asthma	J45
Anxiety	F40-F41
Depression	F32
Malignancy	C00-C97

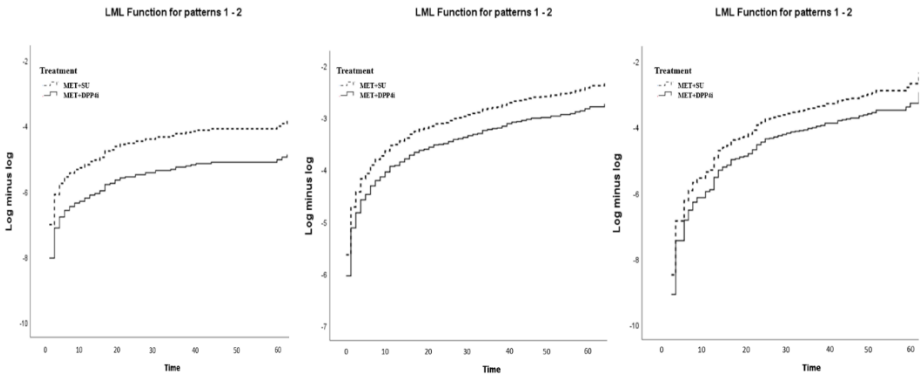
[a]ICD-10, International Classification of Diseases, 10th revision; [b]ATC, Anatomical Therapeutic Chemical.

Supplemental Material 4-2. Propensity Score Matched (2:1) baseline characteristics of patients initiated on either sulfonylurea(SU) or DPP-4 inhibitor (DPP4i) in combination with metformin

	Propensity Score Matched patients (2:1)		
	MET + SU	MET +DPP4i	Total
Number of patients, N	2,518	1,259	3,777
65 and over, n(%)	1,055 (46.8)	539 (45.6)	1,594 (46.4)
Male, n(%)	1,3472(53.3)	665(52.8)	2,007(53.1)
Duration of mono treatment (months), mean(SD)	19.8(14.3)	19.9(13.8)	19.8(14.2)
Number of comorbidity, mean(SD)	2.6(1.4)	2.6(1.4)	2.6(1.4)
Number of diabetes related comorbidity[a], mean(SD)	2.1(1.1)	2.1(1.1)	2.1(1.1)
Presence of diabetes unrelated comorbidity[b]	840(33.4)	421(33.4)	1,261(33.4)
Prevalence of Comorbidities n(%)			
Hypertension	1,803(71.6)	876(70.0)	2,679(70.9)
Dyslipidemia	1,761(69.9)	975(77.4)	2,736(72.4)
History of Ischemic heart disease[c]	400(15.9)	202(16.0)	602(15.9)
History of Stroke[d]	354(14.1)	142(11.3)	496(13.1)
Peripheral vascular disease (PVD)	340(13.5)	116(9.2)	456(12.1)
Neuropathy	248(9.9)	102(8.1)	350(9.3)
Nephropathy	236(9.4)	146(11.6)	382(10.1)
Retinopathy	136(5.4)	72(5.7)	208(5.5)
Chronic kidney disease (CKD)	31(1.2)	19(1.5)	50(1.3)
Dermatitis	319(12.7)	106(8.4)	425(11.3)
Arthritis	81(3.2)	60(4.8)	141(3.7)
Osteoporosis	188(7.5)	126(10.0)	314(8.3)
Chronic obstructive pulmonary diseases(COPD)	39(1.6)	31(2.5)	70(1.9)
Asthma	171(6.8)	67(5.3)	238(6.3)
Anxiety	195(7.7)	101(8.0)	296(7.8)
Depression	79(3.1)	51(4.1)	130(3.4)
Malignancy	70(2.8)	35(2.8)	105(2.8)
Treatments, n(%)			
Antihypertensives	1,603(63.7)	775(61.6)	2,378(63.0)
Statins	885(35.2)	457(36.3)	1,342(35.5)
Low dose aspirin	769(30.5)	393(31.2)	1,162(30.8)

a. dyslipidemia, hypertension, ischemic heart disease (unstable angina, myocardial infarction, heart failure, atrial fibrillation), stroke (hemorrhagic, ischemic, transitory ischemic attack), peripheral vascular disease(PVD), retinopathy, nephropathy, chronic kidney disease(CKD); b. arthritis, COPD, osteoporosis, asthma, depression, anxiety, malignancy; c. myocardial infarction, unstable angina, angina pectoris, heart failure, atrial fibrillation;
d. (hemorrhagic, ischemic) stroke, transitory ischemic attack; MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor;

Supplementary Material 4-3. Proportional Hazards (PH) assumption analysis of main outcomes



Kolmogorov-Type Supremum Test for Proportional Hazards Assumption			
Variable	P value		
	Hypoglycemia	CVD event	All-cause mortality
Treatment	0.3770	0.1170	0.7760
Age	0.7660	0.7810	0.3710
gender	0.6100	0.1650	0.1950
Duration of monotherapy	0.4780	0.5760	0.6240
Presence of diabetes-unrelated comorbidity	0.8660	0.1030	0.2270
Number of diabetes-related comorbidity	0.7000	0.6440	0.0510
Statins	0.7380	0.3590	0.5980
Antihypertensives	0.4960	0.3540	0.5620
Low dose aspirin	0.3280	0.2980	0.8120

Supplemental Material 4-4. Hazard ratios (HRs) for patients treated with MET+DPP4i versus MET+SU (DPP4i type specific)

	Events / Person-years	Unadjusted HR(95% CI)	Adjusted[a] HR(95% CI)	Propensity score matched[b] HR(95% CI)	Without patients of prior HF[C] HR(95% CI)
Hypoglycemia (N=57)					
MET+SU	49 / 7740	1.00	1.00	1.00	1.00
MET+Sitagliptin	6 / 2046	0.42(0.18-0.98)	0.45(0.19-1.06)	0.30(0.09-0.97)	0.43(0.18-1.00)
MET+Vildagliptin	2 /884	0.34(0.08-1.41)	0.37(0.09-1.52)	0.47(0.11-1.94)	0.36(0.09-1.46)
MET+Linagliptin	0 / 170	N/A[d]	N/A	N/A	N/A
MET+Saxagliptin	0 / 55	N/A	N/A	N/A	N/A
CVD events (N=263)					
MET+SU	202 / 7552	1.00	1.00	1.00	1.00
MET+Sitagliptin	37 / 2015	0.63(0.45-0.90)	0.68(0.48-0.97)	0.72(0.48-1.08)	0.66(0.46-0.95)
MET+Vildagliptin	20 / 857	0.85(0.53-1.34)	0.89(0.56-1.41)	0.97(0.58-1.62)	0.92(0.58-1.46)
MET+Linagliptin	3 / 170	0.43(0.14-1.34)	0.51(0.16-1.60)	0.24(0.03-1.72)	0.51(0.16-1.60)
MET+Saxagliptin	1 / 55	0.49(0.68-3.47)	0.59(0.08-4.26)	0.84(0.12-6.03)	0.62(0.09-4.41)
All-cause mortality (N=113)					
MET+SU	93 / 7820	1.00	1.00	1.00	1.00
MET+Sitagliptin	17 / 2059	0.69(0.41-1.16)	0.81(0.48-1.36)	0.66(0.36-1.23)	0.73(0.42-1.27)
MET+Vildagliptin	2 / 885	0.20(0.05-0.79)	0.23(0.06-0.93)	0.25(0.06-1.04)	0.24(0.06-0.96)
MET+Linagliptin	0 / 170	N/A	N/A	N/A	N/A
MET+Saxagliptin	1 / 55	2.88(0.40-21.02)	3.14(0.43-23.01)	4.36(0.59-32.15)	3.14(0.43-23.0)

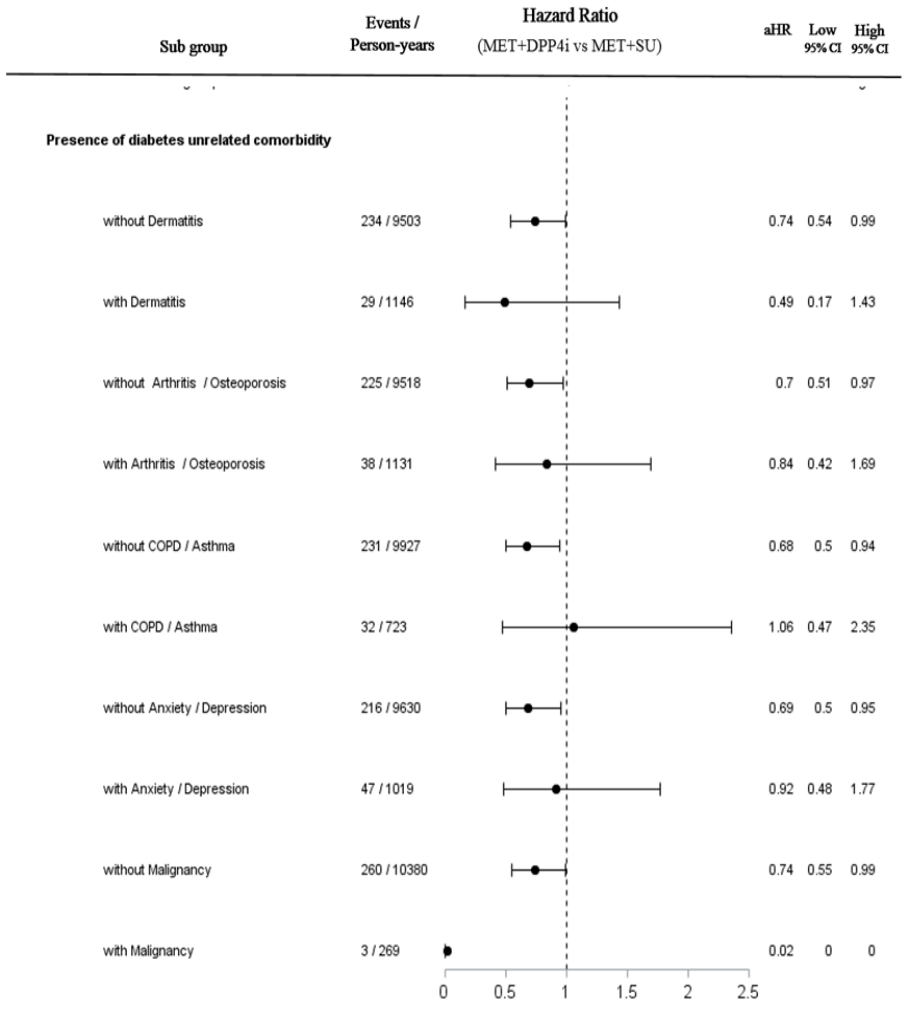
a. Adjusted for age gender, duration of monotherapy, comorbidities type (unrelated), number of diabetes-related comorbidity, antihypertensives (excl. hypoglycemia), statins (excl. hypoglycemia), low dose aspirin (excl. hypoglycemia);
b. Matched by age gender, duration of monotherapy, comorbidities type (unrelated), antihypertensives (excl. hypoglycemia), statins (excl. hypoglycemia), low dose aspirin (excl. hypoglycemia);
CVD, cardiovascular disease; MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor;
c. patients with prior heart failure (HF, n=109) record; d. not analyzed;

Supplemental Material 4-5. Hazard ratios (HRs) of Intent-To-Treat (ITT) analysis for main health outcomes among patients treated with MET+DPP4i versus MET+SU

Intent-To-Treat (ITT) analysis	Hypoglycemia		CVD events		All-cause mortality	
	HR	95% CI	HR	95% CI	HR	95% CI
MET+DPP4i vs MET+SU						
Unadjusted	0.49	0.27-0.86	0.68	0.53-0.87	0.52	0.31-0.87
Adjusted[a]	0.53	0.30-0.95	0.73	0.57-0.94	0.61	0.36-1.02
Age (65 and older)	3.48	2.15-5.65	2.53	2.02-3.17	5.03	3.13-8.07
Gender (female)	0.81	0.52-1.27	0.83	0.67-1.04	0.51	0.34-0.77
Duration of mono treatment (per months)	0.99	0.98-1.01	0.99	0.98-1.00	1.00	0.99-1.02
Presence of diabetes unrelated comorbidity (yes)	1.09	0.89-1.32	1.35	1.23-1.47	2.09	1.39-3.13
Number of diabetes related comorbidity	1.31	0.83-2.07	1.26	1.01-1.57	1.24	1.05-1.47
Antihypertensives (yes)	-	-	0.90	0.72-1.14	1.20	0.78-1.85
Statins (yes)	-	-	0.92	0.74-1.14	0.55	0.35-0.85
Low dose aspirin(yes)	-	-	1.15	0.92-1.44	0.86	0.56-1.32

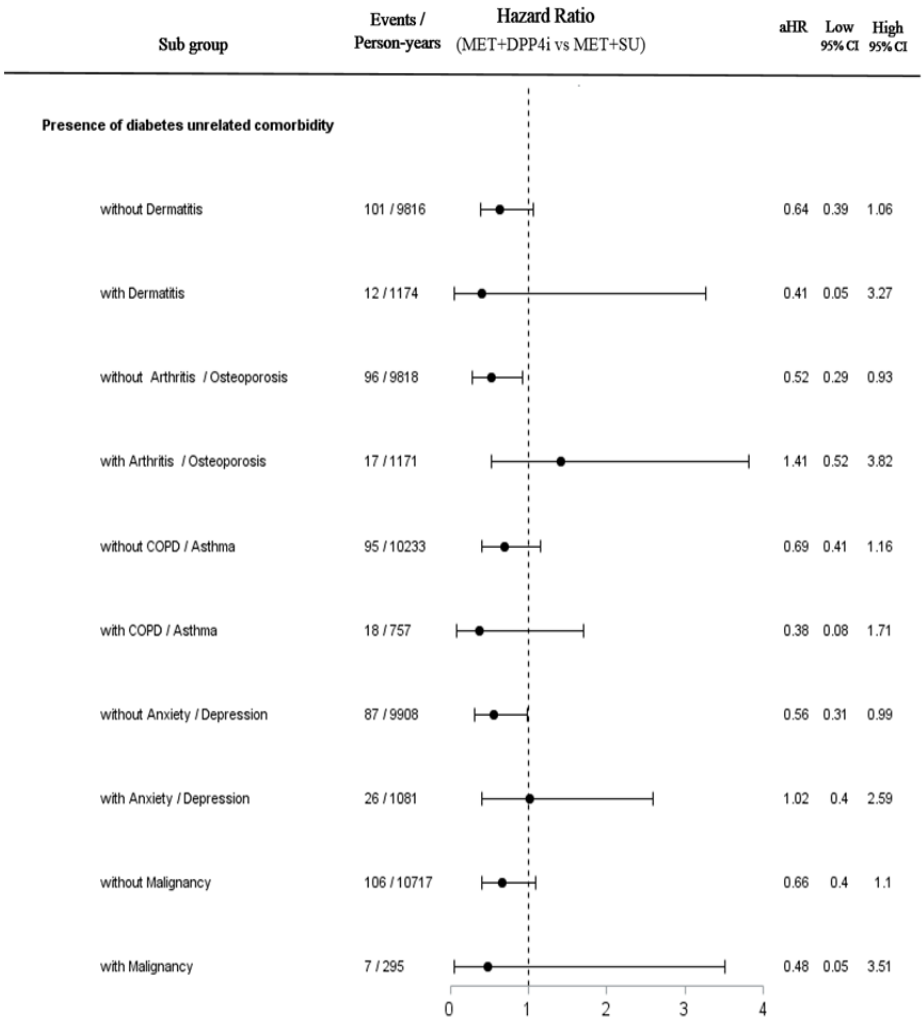
a. Adjusted for age gender, duration of mono treatment, comorbidities type (unrelated), number of diabetes related comorbidity, Antihypertensives (excl. hypoglycemia), Statins (excl. hypoglycemia), low dose aspirin (excl. hypoglycemia);

A. CVD events



Supplemental Material 4-6. Subgroup analysis of the risks of (A) CVD events and (B) all-cause mortality in patients treated with MET+DPP4i versus MET+SU (adjusted Cox proportional hazard regression analyses) according to the presence of each diabetes-unrelated comorbidities

B. All-cause mortality



Supplemental Material 4-6. Subgroup analysis of the risks of (A) CVD events and (B) all-cause mortality in patients treated with MET+DPP4i versus MET+SU (adjusted Cox proportional hazard regression analyses) according to the presence of each diabetes-unrelated comorbidities *(continued)*

Supplemental Material 4-7. Hazard ratios (HRs) for additional health outcomes (microvascular complications, side effects) among patients treated with MET+DPP4i versus MET+SU

A. Main outcomes

	Retinopathy[1)] (N=53)		Neuropathy[2)] (N=63)		Nephropathy[3)] (N=14)		All[4)] (N=91)	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
MET+DPP4i vs MET+SU								
Unadjusted	0.90	0.50-1.64	0.72	0.41-1.28	0.91	0.28-2.89	1.09	0.70-1.70
Adjusted[a]	0.86	0.47-1.58	0.76	0.43-1.35	0.96	0.30-3.11	1.02	0.72-1.75
Propensity score matched[b]	0.83	0.33-1.63	0.76	0.45-1.65	1.08	0.37-4.39	1.03	0.77-2.24
Without patients with prior heart failure history [c]	0.86	0.47-1.58	0.67	0.37-1.23	1.06	0.32-3.50	1.02	0.72-1.76

1) excluding patients with prior retinopathy record (N=362); 2) excluding patients with prior neuropathy record (N=575); 3) excluding patients with prior nephropathy record (N=655); 4) excluding patients with prior record of retinopathy or neuropathy or nephropathy record (N=1331); a. Adjusted for age gender, duration of mono treatment, comorbidities type (unrelated), number of diabetes related comorbidity, Antihypertensives (excl. hypoglycemia), Statins (excl. hypoglycemia), low dose aspirin (excl. hypoglycemia); b. Matched by age gender, duration of mono treatment, comorbidities type (unrelated), Antihypertensives (excl. hypoglycemia), Statins (excl. hypoglycemia), low dose aspirin (excl. hypoglycemia); c. excluding patients with prior heart failure (HF) record (N=109); CVD, cardiovascular disease; MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor.

B. Sub outcomes

	Obstipation / Nausea (N=50)		Pemphigoid[1)] (N=14)		Pancreatitis / Pancreas cancer[2)] (N=42)	
	HR	95% CI	HR	95% CI	HR	95% CI
MET+DPP4i vs MET+SU						
Unadjusted	1.00	0.81-1.24	1.01	0.32-3.25	0.91	0.44-1.88
Adjusted[a]	0.98	0.79-1.22	0.86	0.27-2.82	0.88	0.43-1.83
Propensity score matched[b]	0.94	0.73-1.21	1.02	0.20-5.26	0.76	0.33-1.78
Without patients with heart failure history [c]	1.00	0.81-1.24	1.09	0.32-3.73	0.92	0.44-1.91

1) excluding patients with prior pemphigoid record (N=9); 2) excluding patients with prior pancreatitis or pancreas cancer record (N=50); a. Adjusted for age gender, duration of mono treatment, comorbidities type (unrelated), number of diabetes related comorbidity, Antihypertensives (excl. hypoglycemia), Statins (excl. hypoglycemia), low dose aspirin (excl. hypoglycemia); b. Matched by age gender, duration of mono treatment, comorbidities type (unrelated), Antihypertensives (excl. hypoglycemia), Statins (excl. hypoglycemia), low dose aspirin (excl. hypoglycemia); c. excluding patients with prior heart failure (HF) record (N=109); CVD, cardiovascular disease; MET, metformin; SU, sulfonylurea; DPP4i, dipeptidyl peptidase-4 inhibitor.

CHAPTER 5.

OVERALL DISCUSSION

Chapter 5.

Overall Discussion

The purpose of this thesis was to identify the association between demographic factors and diabetes treatment variation and its impact on health outcome.

According to three studies, this thesis was able to establish (1) the variation in T2D drug treatment among medical practitioners at the patient level, (2) the relationship between comorbidity clusters and the drug treatment pattern of T2D patients and (3) the association between T2D treatment variance and health outcome while considering comorbidity status.

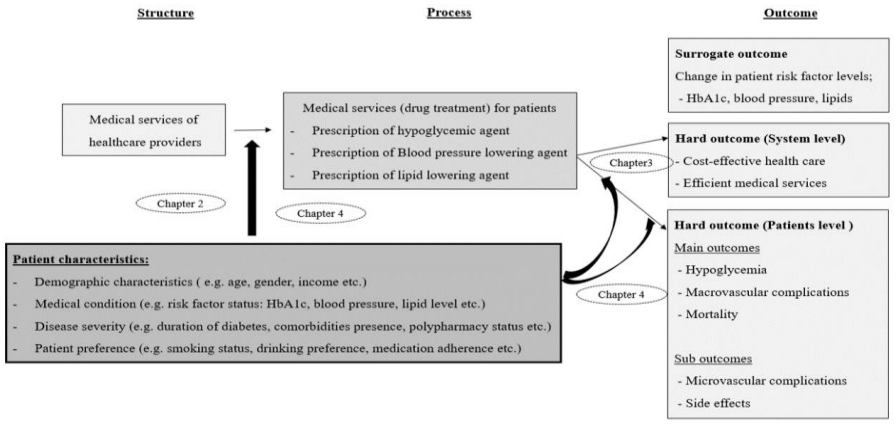


Figure 5-1. Research model

Based on these facts, this thesis aimed to provide evidence for more efficient clinical T2D treatment guidelines which will ultimately support the prevention of complications in T2D patients, reduce mortality, and reduce the medical burden on the national level.

5.1 Variation in T2D Oral Drug Treatment Explained at the Patient Level

In the first study, considerable between practice differences was observed in treatment with glucose-lowering, lipid-lowering, blood pressure-lowering drugs, and RAAS-blockers (IQR ranges of 10% or more) in T2D patients. Of these differences attributed to the practice level, between 6% and 20% was possibly explainable by the patient and practice level characteristics included in the study. In particular, patient characteristics explained 10% of the differences in lipid-lowering treatment and practice characteristics explained more than 15% of the differences in glucose-lowering treatment compared to less than 10% for the other treatments. Patients' age was relevant, implying that age of a patient influences the practitioners' decisions to prescribe. This supports the need of an age-stratified assessment of these treatment rates and approach in future guidelines. For treatment with lipid-lowering drugs, the concomitant use of 3 or more glucose-regulating drugs explained 3% of the between practice variance. This suggests that there is a higher probability of receiving lipid-lowering drugs in patients with more severe diabetes. Since poor metabolic control is seen as an additional risk factor, starting statins is usually justified in such patients. For metformin the concomitant use of 5 or more chronic drugs explained almost 7% of the variance. There seemed to be a shift

from metformin to alternative treatment, including insulin, in patients with polypharmacy. This could be due to more complications and intolerability issues in these patients. On the other hand, the comorbidities and diabetes complications included in this study could not explain the between practice differences. These findings imply that the role of co-medication and comorbidity in explaining between practice variance should be further investigated.

Since Korea is not based on a general practice (GP) system and there is little cohort data of general practices available, the possibility to assess practice characteristics through the GIANTT database revealed unique facts that can be useful for improving the quality of health care providers in Korea. The GIANTT project is a regional initiative of healthcare professionals and researchers focused on the primary care of T2D patients in the province of Groningen, the Netherlands (Voorham *et al.,* 2007; Denig, 2013). More than 20,000 patients with T2D have received information about the project and were given the opportunity to anonymously collect medical data. The ultimate goal of the GIANTT project is to improve the quality of care provided to T2D patients. To achieve this goal, the GIANTT project provides expertise and technical support to organizations to continuously monitor diabetes management based on routinely reported data. Also, the project also uses

evidence-based quality indicators (processes and outcome indicators) to provide benchmark reports on participating diabetes and primary care facilities.

In addition, using GIANTT database, first study was able to identify practice characteristics that could associate with variance in diabetes treatment. Practice characteristics explained at least 15% of the between practices differences for treatment with glucose-lowering drugs. The number of T2D patients per practice was the most relevant practice characteristic in the study, which explained between 5% and 13% of the treatment variance for glucose-lowering drugs, lipid-lowering drugs, blood pressure-lowering drugs. The lower probability of being treated in practices with a higher number of T2D patients was observed. One explanation could be that these practices are more active in screening for diabetes, and therefore have more patients not yet in need of treatment (Janssen *et al*. 2008; Van den Bruel, 2015). An alternative explanation is that the practice organization in large practices may be insufficient to provide optimal care. The presence of a physician's assistant explained some additional variance in treatment with statins, and RAAS-blockers, where it seemed that these drugs are more prescribed in practices with an assistant.

5.2 Relation of Comorbidity Status and Variance in T2D Drug Treatment

In the second study, comorbidity patterns and treatment patterns among T2D patients was identified and the relationships among baseline comorbid status, drug treatment patterns and occurrence of diabetes complications were explored. Especially, this study focused onT2D patients without history of microvascular-, macrovascular complication to explored possible relationship between comorbid status, drug treatment and its relation to the development of complications to assess existences of treatment pattern and its difference to other clusters that did not develop complications within 4-year period.

This study report three main findings. First, results show that as number of comorbidity increased and both type of comorbidities (diabetes unrelated- and related disease) were present, common treatment patterns were less or not identified. The primary goal of diabetes treatment is to control blood glucose levels, which if left unchecked, may trigger complications (Lagu *et al.*, 2008; European Heart Journal, 2013; NICE, 2015; ADA, 2016). If metformin is insufficient, the treatment guidelines recommend second-line agents including sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, insulin, SGLT-2 inhibitors, and glucagon-like peptide-1 receptor

agonists. However, guidelines suggest the use of other treatments than metformin if needed in practice setting without recommending specific type of treatment patterns and its effect on outcomes, such as, micro-macrovascular complications. Results show that combination treatment, such as SU or DPP4i combined with MET or SU+TZD, were commonly observed in T2D patients with comorbidities. Recent studies have shown that DPP-4 inhibitors significantly lower the incidence of cardiovascular events (Richter *et al.*, 2008). Moreover, a meta-analysis of initial therapies prescribed for treatment-naive patients with type 2 diabetes found that significantly more patients attained the HbA1c goal of <7% when initially treated with metformin and DPP-4 inhibitors compared to metformin alone (Bailey, 2013). In this study, MET+DPP4i was identified as treatment pattern in patients with 2 or more diabetes related comorbidity. However, its relation remained unclear in patients with 1 or 2 comorbidities and with patients that had both type of comorbidities, diabetes related and unrelated. Considering the effect of DPP4i presented in prior studies, further studies are necessary to assess the impact of comorbid status on the effect of MET+DPP4i treatment.

Second, treatment and comorbidity patterns were not identified in the group of T2D patients with 2 or more comorbidities or if diabetes unrelated disease was present along with diabetes related diseases. This indicates that T2D patients with 2 or more comorbidities are exposed to higher treatment

variance than other T2D patients. Further studies related to effective drug treatment should be conducted within this group to control the variance that could support effective diabetes care. Treatment patterns which were not specified in any groups, such as, insulin combined with MET or SU could be used in the treatment of this group. In terms of insulin, findings are similar to those of a previous study showing that differences in glucose-lowering treatment are partly explained by complications and intolerances reflecting the polypharmacy associated with complex comorbidities (Cho *et al*., 2016). In addition, a recent study found that the combination of insulin with oral glucose-lowering drugs provided several potential advantages without compromising glycemic efficacy (Woo, 2017). Further studies should be conducted on T2D patients with these conditions to assess effective diabetes care. Thirdly, related comorbidity or treatment pattern to occurrence of micro- or macrovascular complications was not identified clearly. This indicates that different treatment patterns in various comorbid status relates to the development of micro- and macrovascular complications. Considering treatment clusters that were identified from this study, further studies would be necessary on assessing the association between identified treatment clusters and its relation to the development of micro-macrovascular disease.

5.3 Association between T2D drug treatment variance and health outcome

Finally, to translate the findings of the first two studies to clinical practice, a third study targeting the association of T2D treatment variation and health outcome in comorbid T2D patients was conducted. Aim of this study was to examine the risk of combination therapy with either MET+SU or MET+DPP4i in terms of hypoglycemia, CVD events, and all-cause mortality among T2D patients with comorbid status. This study focused on comorbid patients since in real life more and more diabetes patients have one or more comorbidities while being treated for diabetes. The analysis focused on patients with at least one diabetes-related comorbidity in addition to diabetes. Previous studies indicated that comorbidities may either increase or decrease treatment intensification in insufficiently controlled patients (Lagu *et al.*, 2008; Vitry *et al.*, 2010) and studies have suggested that the types of comorbidities should be considered to elucidate these relationships further (Kerr *et al.*, 2007; Lagu *et al*., 2008).

This study report three major findings. First, MET+DPP4i was associated with lower risks of hypoglycemia, CVD events, and all-cause mortality than MET+SU. Second, the type and number of comorbidities were significant risk

factors for both CVD events and all-cause mortality. Third, the efficacy of MET+SU and MET+DPP4i varied in T2D patients with complex comorbidities. Compared to MET+SU, MET+DPP4i tended to be more favorable in patients with an increasing number of diabetes related comorbidities when considering all-cause mortality and significantly lowered the risk for CVD events in patients with only diabetes related comorbidities. The results of this study underline that the comorbid status of a T2D patient should be considered when choosing a second line diabetes therapy in clinical practice, with DPP4 inhibitors being associated with a more favorable outcome than SUs. While the causal relationship needs to be further elucidated, results of the study and those of other observational studies should be considered in clinical practice when choosing combination treatments for comorbid T2D patients.

5.4 Necessity and Perspective towards Customized T2D Guidelines in Clinical Setting

Evolving and actualizing customized care strategies can be particularly challenging for health care providers who have to deal with various patient conditions with limited time and resources beyond diabetes (Raz *et al.*, 2013).

Nowadays, there are a lot of T2D treatments available in clinical settings and there should be more licenses. Does this broad range of arms provide more flexibility to healthcare providers in planning individualized T2D therapies, or does it make the decision making process more complicating by augmenting options? For experts like diabetologists and endocrinologists, the answer is no doubt. However, for many primary care health care providers who have to develop simultaneously in many medical disciplines, wider choices can sometimes be a threat.

The choice of antidiabetic drug combinations becomes even more difficult considering the age of the patient, the duration of diabetes, cognitive and socioeconomic status of the patient, patient preference, compliance and life expectancy, risk for hypoglycemia, the presence of microvascular and macrovascular diabetic complications, the presence of complications such as cardiovascular or renal failure (Qaseem *et al.*, 2012).

Guidelines have been continuously updated to meet the need for advances in T2D treatment, response to criticism, or a more practical and personalized approach (Schernthaner *et al.,* 2010; Ceriello *et al.,* 2012). Although these guidelines tend to include recommendations for establishing personalized blood glucose targets according to phenotype and "empirically" coordinating appropriate drugs to the proper patient, there is no convincing evidence to prove such an approach. These "less normative" guidelines have been viewed as failing to provide sufficient guidance to overwhelmed health care providers when trying to pair the fine differences among the increasing number of antidiabetic medications to the subtle of each patient's predilection and medical characteristics.

Not all possible drug choices are supported by a meta-analysis of randomized controlled trials (RCTs). Also, it is an entirely different idea to implement and evaluate the efficacy of interventions that was conducted in the context of a structured clinical testing environment since in reality variation in structural resources, patient compliance, and socio-demographic and cultural differences exists and influences the outcome of interventions.

Thus, converting RCT results into real-world situations is not a simple process. It is therefore understandable that there are reports that several clinicians are embarrassed by the patient's optimal strategy (Inzucchi *et al.,* 2012). At the same time, however, the long-term need for implementation of

clinical guidelines as evidence-based algorithms is not surprising (Qaseem *et al.*, 2012).

Therefore, to preform effective personalized T2D care in clinical settings while more hard evidence of effective treatment methods become available, health care providers would need guidance by well-structured and practical summary of evidence that outlines a safe and effective process for efficient T2D treatment.

5.5 Role of Customized Guidelines on the Path to Personalized T2D Care

Personalization of T2D care will lead to greater quality of life compared to the one-sized standardized treatment strategy. A recent study compared the proportion of cardio metabolic well-controlled T2D patients that its treatment was based on a simple-personalized approach which was mainly costumed by age and additional health status, versus the one-sized standardized approach based on the general Dutch guideline (Boels *et al.,* 2017). Results showed that T2D patients treated with a customized treatment strategy showed more well-controlled cardio-metabolic condition.

Personalized T2D treatment relates to better 'evidence-based' performance rates in clinical settings. Both T2D patients and diabetes care providers will benefit from these customized strategies. In fact, insurance policy fellowship may also experience less thwarting and greater transparency. Another study sought to examine the cost-effectiveness of individualized glycemic control protocol compared with uniformly applied guideline based approach for the U.S. population with T2D (Laiteerapong *et al.,* 2018). Results showed that individualized approach path saved $13 547 per affected role compared with uniform control, primarily due to lower medication. Personalized approach slightly reduced life expectancy due to an increase in

complications but fewer hypoglycemic events and fewer medications produced more QALYs (16.68 vs. 16.58).

Considering the facts, customized care with guideline based treatment algorithm would be a valuable base for both T2D patients and health care providers. For example, recent ADA and Dutch guidelines show algorithm for determining the target HbA1c considering disease or demographic characteristics (Boels *et al.* 2017). Also algorithm based on patients' characteristics was presented by the Italian Association of Medical Diabetologists (AMD) (Gallo *et al.*, 2015). In case of the AMD algorithm which is online-based, its accessibility and easy to use algorithm was developed for a purpose to guide health care providers in the decision making of personalized treatment plan and lessening clinical inertia by supporting optimization in a timely manner.

The importance of personalized T2D care is growing and several algorithm-based guidelines have been born and continuously updated due to advances in the treatment, or to meet the need for a more specific, individualized approach. However, developing evidence-based algorithm that confines treatment options will need more evidence than is accessible at this present time. Moreover, evidence-based personalizing T2D care will expect enhanced cooperation and co-management among health care providers for better patient treatment in diverse disciplines.

Since evidence-based standardized guidelines have notably improved the quality of diabetes management as a first revolution in diabetes care, customized guidelines based on algorithmic care would be a useful tool not only for translating evidence of personalized T2D care into action in clinical settings but also support active communication among health care providers for better personalized T2D care (Figure 5-2).

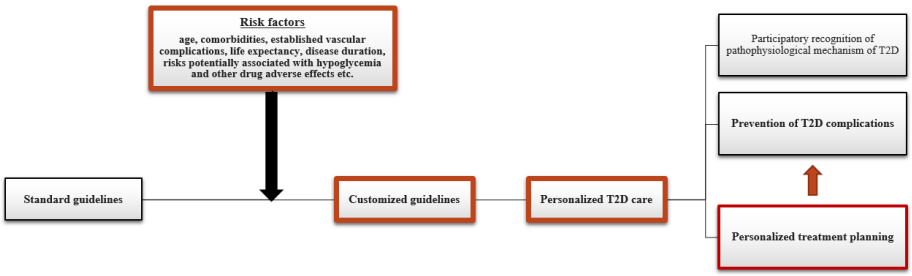


Figure 5-2. Role of customized guidelines on the path to personalized T2D care

5.6 Implications for Future T2D Treatment and Research

The purpose of this thesis was to provide evidence for developing better T2D treatment protocols that would effectively control variation in T2D treatment and eventually improve the quality of T2D care. Thesis included studies that focused on 1) identifying demographic factors that affect treatment variance and 2) analyzing the effect of comorbidity on variation while exploring treatment alternatives and 3) assessing its association with health outcomes.

The first study showed that T2D treatment variance within guideline recommended drug therapy exist among healthcare providers and that this variance is partly explained by patient characteristics. Age appears to be an important determinant when a T2D treatment plan is chosen in clinical practice. The results of this research supports the notion to include age as a relevant patient characteristic in T2D guidelines. While other patient characteristics may play an important role, overall they did not justifiably explain the between practice variance in treatment. Thus, further studies on modifiable patient characteristics are necessary.

The second study directly explored the relationship between comorbidity status and drug treatment in Korean T2D patients. If the appropriate treatment is lacking or if treatment status is unclear in those with certain comorbidities,

the approach aimed to identify potential groups at risk who should be the prime targets of treatment guidance. Identification of associations between comorbidities and treatment status allow us to understand that adherence to guideline-based drug treatment decreases as complexity of comorbidity status grows. Study outlined the increased use of combination treatment in clinical setting and the stressed the necessity to identify the effect of treatment on health outcomes considering comorbid status to avoid increase in uncontrolled treatment variance that would influence the quality of T2D care. The approach for T2D patients with diabetes-unrelated comorbidity to prevent macrovascular complications. In addition,

Ultimately, the third study found that T2D patients with complex comorbidities who received MET+DPP4i as second-line treatment were at a lower risk of hypoglycemia, CVD events, and all-cause mortality compared with those receiving MET+SU. Importantly, comorbidity type and number impacted the effects of combination treatment with MET+DPP4i being associated with more favorable outcomes. Comorbidity status and the effect thereof on diabetes treatment are complex phenomena and we just started grasping its impact on clinical practice. However, identification of comorbidity clusters and their relationships with treatment status enables us to consider patterns of comorbidity in terms of effective treatment that could improve diabetes care

Future quality care of T2D patients should be customized by age and comorbid status. While the causal relationship needs to be further elucidated, the results of this thesis provided evidence that patient's age and comorbidity status ought to be considered in T2D guidelines. This could limit unnecessary treatment variance, decrease the occurrence of complications, reduce mortality and eventually lower the medical burden on the national level.

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ABSTRACT (KOREAN)

국문초록

연구배경

당뇨 관리의 질적 향상은 표준화된 치료지침에 대한 임상에서의 높은 순응도와 의료제공자간의 낮은 치료의 변이에 근거한다. 이러한 치료의 변이는 사망률과 이환율에 영향을 미치므로 변이에 영향을 미치는 요인을 파악하고 해당 요인으로 인해 발생하는 변이에 대한 관리방안을 마련하는 것이 중요하다. 특히, 당뇨병 관리의 주된 행위인 약물 치료의 변이는 환자 치료의 질 차이를 나타내는 지표이기 때문에 치료 변화에 영향을 미치는 환자의 특성을 확인하고 건강 결과와의 관계를 확인함으로써 부정적 건강 결과(합병증 발생, 사망 등)를 예방하는 방안을 지속적으로 마련하는 것이 필요하다. 더욱이, 당뇨병 환자의 타 질환의 이환은 당뇨병 비질환자 대비 약 2-3 배 높고 이러한 동반 질환의 유무는 환자의 수준에서 당뇨 관리를 위한 치료 과정 및 결과에 영향을 미치며 나아가 질병부담 증가의 주

요인이 되므로 동반질환을 고려하여 당뇨병 치료행태의 변이를 파악하고 그를 통해 보다 적절한 치료방안을 마련하는 것이 당뇨 치료의 질 향상에 중요하다. 따라서 본 연구는 (1) 당뇨병 약물 치료의 변이에 영향을 미치는 환자의 특성을 확인하고, (2) 동반질환 군집을 파악하고 해당 군집과 약물치료 행태의 상관성을 확인하였으며. (3) 동반 질환을 고려한 약물 치료의 변이와 심혈관 질환의 연관성을 분석하였다.

연구방법

첫번째 연구목표에 대해서 본 연구는 네덜란드 그로닝헨(Groningen) 지역의 당뇨병 환자에 대한 데이터를 포함한 GIANTT 데이터 베이스를 활용하여 183 개 의원의 24,628 명의 제 2 형 당뇨환자에 대한 단면 연구를 구성하였으며 다단계 로지스틱 회귀분석을 통해 환자특성에 따른 약물치료 행태의 변이를 파악하고자 하였다. 약물의 경우, 혈당강하제 전체와 메트포르민(metformin), 지질강하제 전체와 스타틴(statins), 그리고 혈압강하제 전체와 안지오텐신 전환효소 억제제(ACEi or ARB)의

치료행태를 파악하였으며 변이에 영향을 미치는 환자특성으로는 연령, 성별, 당뇨병 유병기간, 동반질환, 다중약물 복용여부 등이 고려되었고 의원특성으로는 의원의 당뇨환자 규모, 의원형태(단독, 협업), 당뇨관리 특화 보조인력 유무 등이 분석에 포함되었다.

두번째 세부 연구 목표에 대해서 본 연구는 2009 년, 2013 년 건강보험공단의 표본코호트 데이터베이스를 이용하여 후향적 관찰연구를 구성하였다. 대상자는 만 30 세 이상의 당뇨병 합병증을 동반하지 않은 제 2 형 당뇨환자 7,123 명이었으며 이들에 대해 14 개 주요 만성질환과 6 개의 당뇨합병증 유병률을 파악하였으며 이단계 군집분석을 통해 동반질환 군집분석, 혈당강하제, 지질강하제, 혈압강하제 치료행태에 대한 군집분석을 실시하였고 해당 군집에 대한 약물치료패턴의 상관성을 비선형적 정준상관분석을 통해 파악하였다.

세번째 세부 연구 목표에 대해서 본 연구는 건강보험공단의 표본코호트 데이터 베이스를 이용한 후향적 코호트 연구를 구성하였다. 2008 년 7 월 1 일부터 2013 년 12 월 31 일까지 단일요법에서 메트포르민 + 설폰효소제 병합요법 (MET + SU) 또는

메트포르민 + DPP4 억제제 (MET + DPP4i)로 전환하고 당뇨병 관련 동반질환을 1 개 이상 동반한 3,693 명의 제 2 형 당뇨 환자를 대상으로 각 병합요법에 따른 저혈당, 심혈관질환 이환, 그리고 사망에 대한 위험도의 차이를 확인하였으며 생존분석과 성향점수매칭(propensity score matching)을 이용하여 분석을 실시하였다. 본 학위논문연구는 서울대학교 윤리위원회 (IRB No. E1801/002-002) 의 검토 및 승인을 받았으며 건강보험공단 (NHIS-2015-2-030)의 DB 이용 승인을 받았다.

연구결과

본 연구는 세가지 연구목표에 따른 아래의 연구결과를 확인하였다.

첫째, 당뇨병 관리지침에 근거한 약물치료행태 이행의 의원간 변이(IQR 9.5-13.9)를 확인하였으며 환자와 의원의 특성이 치료 약물군에 따라 변이의 6%-20%를 설명하였다. 환자 특성 중 연령, 다중약물복용이 가장 유의한 변이의 요인으로 나타났으며 의원의 당뇨병 환자 수가 의원 특성 중 가장 큰 변이의 요인으로 나타났다.

둘째, 7 개 와 12 개의 동반질환군집, 20 개의 치료행태군집을 확인하였으며 실루엣 스코어 0.8 로 군집 간 유의한 비유사성을 확인하였다. 세가지 군집변수를 가지고 비선형 정준상관분석 실시한 결과 5 개의 그룹이 파악되었으며 3 가지 주요 연구결과를 확인하였다. 첫째, 동반하는 질환수가 증가하고, 당뇨 관련, 비관련 동반질환을 모두 동반한 당뇨환자 그룹일수록 치료 패턴 확인이 어려웠다. 이는 동반 질환이 2 개이상인 환자군이 여러가지 치료 행태가 비슷한 비율로 이루어지고있는 치료의 변이가 높은 환자군임을 의미한다. 둘째, 군집분석 결과 다수의 병합요법 패턴이 확인되었으며 SU, DPP4i 와 TZD (티아졸리딘디온)이 포함된 병합요법이 주로 확인되었다. 마지막으로 대혈관합병증 발생군집의 동반질환패턴 및 치료 패턴을 확인하지 못하였다. CENTROID PLOT 의 중앙에 가깝게 위치함에서도 확인할 수 있듯이 특정 동반질환군집이나 치료 패턴 군집에 크게 연관성이 확인되지 않았다.

셋째, 동반질환을 고려한 제 2 형 당뇨병 환자에 대해 MET+DPP4i 병합요법으로 치료를 행한 경우 MET+SU 대비 저혈당, 심혈관질환 이환, 사망에 대한 위험도가 각 0.39 (0.18–0.83), 0.72 (0.54–0.97), 그리고 0.64 (0.39–1.05)으로 MET+DPP4i 치료행태가 부정적

건강결과에 대한 위험도가 MET+SU 에 대비하여 낮은 것으로 파악되었다. 성향점수 매칭(propensity score matching) 분석에서도 유사한 결과가 도출되었다. 또한, 동반질환의 종류와 수가 저혈당, 심혈관질환 이환, 사망에 대한 위험도 증가의 유의한 위험요인으로 파악되었고 동반질환의 종류와 수에 따른 하위집단분석 (subgroup analyses) 에서도 MET+DPP4i 치료행태가 MET+SU 대비 부정적 건강결과에 대한 위험도가 낮은 것으로 나타났다.

결론

본 연구는 당뇨병 관리지침에 근거한 약물치료행태 이행의 의원간 변이를 확인하였으며 환자특성 중 연령이 가장 큰 치료변이의 요인이면서 임상에서의 치료변이의 존재를 정당화할 수 있는 요소로서 앞으로의 당뇨 치료지침 마련 시 연령이 고려된 치료지침을 마련하는 것이 당뇨 치료의 질을 보다 정확하게 파악할 수 있는 방안이 될 것임을 확인하였다. 아울러 이외의 환자특성 및 의원특성은 치료변이에 영향을 미치지 않거나 정당화 될 수 없는 변이를 야기하는 요인들로서 이들에 대해서는 지속적인 모니터링 및 해당 요인들로

인한 치료변이를 최소화할 수 있는 치료대안이 마련의 필요성을 제안한다.

또한 본 연구는 제 2 형 당뇨군의 동반질환 군집 및 약물치료 행태의 패턴을 사정하고, 동반질환 군집과 약물치료 패턴의 상관성을 확인함으로서 현재 당뇨치료에 있어 환자특성이 복잡해질수록 표준화된 치료패턴 파악이 어려움을 확인하였다.

임상에서의 치료의 변이는 존재할 수 밖에 없다. 그러나 이러한 치료의 변이는 건강결과에 영향을 미치며 나아가 당뇨관리의 질 향상에 영향을 미침으로, 불필요한 변이에 대한 관리방안마련은 당뇨관리의 질 향상 및 질병부담 감소에 중요한 과제이다.

마지막으로, 이 연구는 당뇨치료에 있어 MET+DPP4i 병합요법이 MET+SU 에 대비하여 저혈당, 심혈관질환 이환 및 사망에 미치는 위험도가 낮으며 동반질환의 수와 종류가 이러한 부정적 건강결과의 위험도 증가에 위험요인임을 확인하였다. 치료방법의 차이가 건강결과와 연관성이 있음을 확인함으로써 약물 단일요법 이외에 최근 증가추세에 있는 병합요법에 대해서도 표준화된 치료지침 마련이 필요함을 본 연구는 제안하며 동반질환의 수와 종류 또한

당뇨 치료의 질 향상을 위한 지침개발에 고려되어야 함에 대한 근거를 마련하였다.

주요어: 제 2 형 당뇨, 치료의 질, 약물치료, 변이, 역학, 위험요인, 동반질환, 대혈관 합병증, 생존분석, 이단계 군집분석, 비선형 정준상관분석

학 번: 2012-30645