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Treatment variation related to comorbidity and complications in type 2 diabetes
A real world analysis

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Abstract

A complex comorbidity status may cause treatment variance interfering with type 2 diabetes (T2D) guideline-confirm therapy and influence the occurrence of complications but evidence on its relationships and alternative treatments are lacking. This study aimed to identify treatment variance and common T2D drug treatment related to comorbid status and the association with comorbidity and complications.

Based on Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) databases, we conducted a retrospective, observational exploratory study including 7123 T2D patients without microvascular-, macrovascular complication. We explored patterns of comorbid status and drug treatment and its relation to the development of complications within 4-year period. Analysis was performed by two-step cluster analysis and nonlinear canonical correlation analysis.

64.9% had at least one other chronic disease and 61.7% of T2D patients were treated with >1 glucose lowering drugs. 15.8% developed microvascular complications and 6.5% had ischemic heart disease or cerebrovascular complications. 82.2% of the treatment patterns were identified among T2D patients with 1 or no comorbidity while 14.4% was identified in patients with ≥2 comorbidities. Combination treatment such as, sulfonylurea or dipeptidyl peptidase-4 inhibitors combined with metformin were observed. Occurrence of microvascular- or/and macrovascular complication and its relation to comorbidity and treatment pattern was not identified.

In conclusion, as number of comorbidity increased with both type of comorbidity (diabetes related-, unrelated) present, common treatment patterns were less or not identified. More treatment variance was observed in patient's groups that had developed complications.

Abbreviations: ATC = anatomical therapeutic chemical, DPP4i = dipeptidyl peptidase 4 inhibitor, MET = metformin, SU = sulfonylurea, T2D = type 2 diabetes, TZD = thiazolidinedione.

Keywords: cluster analysis, comorbidity, drug treatment, non-linear canonical correlation analysis, type 2 diabetes

1. Introduction

The increasing burden imposed by complex comorbidity status in terms of effective diabetes care may influence treatment quality by increasing variance in such care.[1] 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.[2] In addition, it has been reported that patients with T2D have more chronic diseases than the diabetes-free population.[3] For instance, in Korea, patients in all age groups with newly detected T2D have a significantly higher prevalence of coronary artery disease and cardiovascular disease compared with the general Korean population.[4] It may be feasible to develop specific treatment guidelines for patients with complex comorbid conditions. Clinical guidelines have recently rendered diabetes care significantly more evidence-based, with the goal of providing effective treatment 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.

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.[5–7] However, standard recommendations are increasingly criticized as contributing to excessive treatment that is sometimes futile. Variations in guideline-recommended treatments have been noted in practice,[8] and several studies have emphasized that current standard diabetes treatment recommendations do not appropriately consider individuals with complex comorbidities.[9,10] The identification of common comorbidity patterns and the explora-

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tion of current treatment status in terms of such comorbidities may improve the approach of management of T2D and associated comorbidities.

Such work would increase our understanding of the current recommendations, and enable policymakers and clinicians to develop specific guidelines for patients with complex comorbidities, eventually improving diabetes care. Exploring the current treatment status of diabetes patients with comorbidities would lead to the identification of patients for whom specific guidelines are required to prevent unnecessary treatment variance that may trigger negative health outcomes. It may be difficult to create a single recommendation for all patients with a certain comorbid condition; variance in treatment decision making in practice may be unavoidable. However, it is necessary to ascertain and discuss 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 our study were to identify comorbidity and drug treatment patterns, and to explore the associations between comorbid status and drug treatment pattern in T2D patients.

2. Methods

2.1. Subjects

We performed a retrospective, observational exploratory study on patients with T2D aged 30 years and older without any 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;[11] 2.2% of the total eligible population was randomly sampled using 1476 strata from the 2002 Korean (nationwide) health insurance database. Cohort was followed up for 11 years, thus to 2013. The database provides detailed information on all of the procedures performed 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.

2.2. Comorbidities

Based on prior studies, 24 chronic diseases recognized as common comorbid conditions among T2D patients were considered in this study.[3,12,13] Among these diseases, number and type of comorbidity and presence of diabetes complications were assessed for further analyses.

Comorbidities were defined as diabetes-related or diabetes-unrelated diseases (Supplementary Digital Content 1, http://links.lww.com/MD/C491, Table that illustrates comorbid diseases with ICD-10 codes). Conventionally,[14,15] diabetes-related diseases, such as hypertension, dyslipidemia, or atherosclerosis, are chronic conditions that represent part of the overall pathophysiological risk profile similar to diabetes and/or are known to be associated with its complications. Conversely, diabetes-unrelated diseases, such as musculoskeletal diseases or psychiatric diseases, are conditions either not directly related to or with an ambiguous association to diabetes pathogenesis or diabetes management.[2,14,15]

During follow up, 6 diabetes-related diseases were additionally assessed as diabetes complications. Of these 6 diabetes

complications, 3 were microvascular (neuropathy, retinopathy, nephropathy) and 3 were macrovascular complications (peripheral vascular disease, ischemic heart disease, 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).

2.3. Drug treatment

Number and type of glucose lowering drugs, presence of lipid lowering drugs, and blood pressure lowering drugs were assessed. We evaluated 5 categories of glucose-lowering drugs (metformin [MET], sulfonylureas [SU], thiazolidinediones [TZD], dipeptidyl peptidase 4 inhibitors [DPP4i], insulin) (Supplementary Digital Content 2, http://links.lww.com/MD/C491, Table that illustrates ATC codes of drug treatments). Prescriptions for 90 days or longer 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.

2.4. Statistical analyses

Descriptive statistics were calculated for age, sex, 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.[16,17] The analysis proceeds in 2 steps: preclustering 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.[18,19] 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 with other clusters (separation).[17] The average silhouette coefficient is the average of all cases of the following calculation for each individual case: $(B - A)/\max(A, B)$.[20] 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. Positive silhouette (range from −1 to +1) indicates 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,[21] 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.

Nonlinear 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.[22] 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.[23] In this study, we used nonlinear canonical correlation analysis to examine the relationships among 4 sets of variables. Age and sex were entered into the first set and the baseline comorbidity was 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. All of the analyses were conducted using SPSS (Version 25.0, IBM, Armonk, NY) software.

3. Results

3.1. Characteristics of comorbidities and drug treatment status

In total 7123 T2D patients were included for analysis (Supplementary Digital Content 3, http://links.lww.com/MD/C491, figure that shows the flow chart of the selection of the study population). 64.9% had at least one other chronic disease at baseline (Table 1). At follow-up, the proportions of comorbid patients had increased to 84.1% (≥1 disease) and 49.5% (≥2 disease). 88.2% T2D patients with ≥1 comorbidities had only diabetes related disease while 8.2% had both, diabetes related- and unrelated disease at baseline. T2D patients with both type of comorbidities increased to 20.2% after 4 years at follow up. In case of treatment, 61.7% of T2D patients were treated with >1 glucose lowering drugs and most of the T2D patients with indication (diagnosed with dyslipidemia, hypertension) were treated with lipid lowering-, blood pressure lowering drugs at baseline (79.8% and 91.6%, respectively). Within 4 years,

Patient characteristics.

Characteristic	N	%
Baseline ('09)		
N	7123	100.0
Sex, male	4081	57.3
Age, ≥65 y	2149	30.2
Number of comorbidity, ≥1	4622	64.9
Number of comorbidity, ≥2	1613	22.6
Type of comorbidity*, diabetes-related only	4080	88.2
Type of comorbidity*, both[†]	381	8.2
Number of glucose lowering drug in use, >1	4394	61.7
Presence of lipid lowering drug treatment,[‡] yes	1796	79.8
Presence of blood pressure lowering drug treatment,[§] yes	3066	91.6
Follow up ('13)		
Number of comorbidity, ≥1	5993	84.1
Number of comorbidity, ≥2	3521	49.5
Type of comorbidity*, diabetes-related only	4589	76.6
Type of comorbidity*, both[†]	1213	20.2
Presence of microvascular complication, ≥1	1126	15.8
Retinopathy	154	2.2
Nephropathy	336	4.7
Neuropathy	733	10.3
Presence of macrovascular complication, ≥1	1125	15.8
Peripheral vascular disease (PVD)	746	10.5
Cerebrovascular disease	158	2.2
Ischemic heart disease	308	4.3

* Proportion of T2D patients with diabetes related disease only among patients with at least 1 comorbidity.
[†] Diabetes related and unrelated comorbidity.
[‡] Proportion of T2D patients with dyslipidemia (N=2250) treated with lipid lowering drugs.
[§] Proportion of T2D patients with hypertension (N=3346) treated with blood pressure lowering drugs.

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

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

* Optimal scaling level: single nominal.
[†] Projections of the single quantified variables in the object space.
[‡] Optimal scaling level: multiple nominal.
[§] Projections of the multiple quantified variables in the object space.

15.8% developed microvascular complications and 6.5% had ischemic heart disease or cerebrovascular disease.

3.2. Associations between comorbidities and drug treatment patterns

We identified 7 comorbidity clusters and 20 treatment clusters at baseline and 12 comorbidity clusters at follow-up through two-step cluster analysis with an average silhouette measure of 0.8. In addition, relationships among age, sex, baseline drug treatment clustering, baseline comorbidity clustering, and follow-up comorbidity clustering were assessed by nonlinear canonical correlation analysis and significant associations between comorbidity and drug treatment clusters were identified (Table 2). Our 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 we employed a 2-dimensional design, half of the fit value ([1.081/2]*100 = 54.1%) was the mean proportion of the variation explained by our 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, sex, comorbidity, and drug treatment patterns (Fig. 1, Supplementary Digital Content 4, http://links.lww.com/MD/C491, figure that illustrates difference in relationship of age and sex with comorbidity and treatment clusters). 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 sex were positioned near the center of the plot showing its less or no effect on identifying relationships (Supplementary Digital Content 4, http://links.lww.com/MD/C491, figure that illustrates difference in relationship of age and sex with comorbidity and treatment clusters).

Five groups were identified in terms of similarity among baseline comorbidity, drug treatment, and follow-up comorbidity clustering (Table 3, Fig. 1). 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
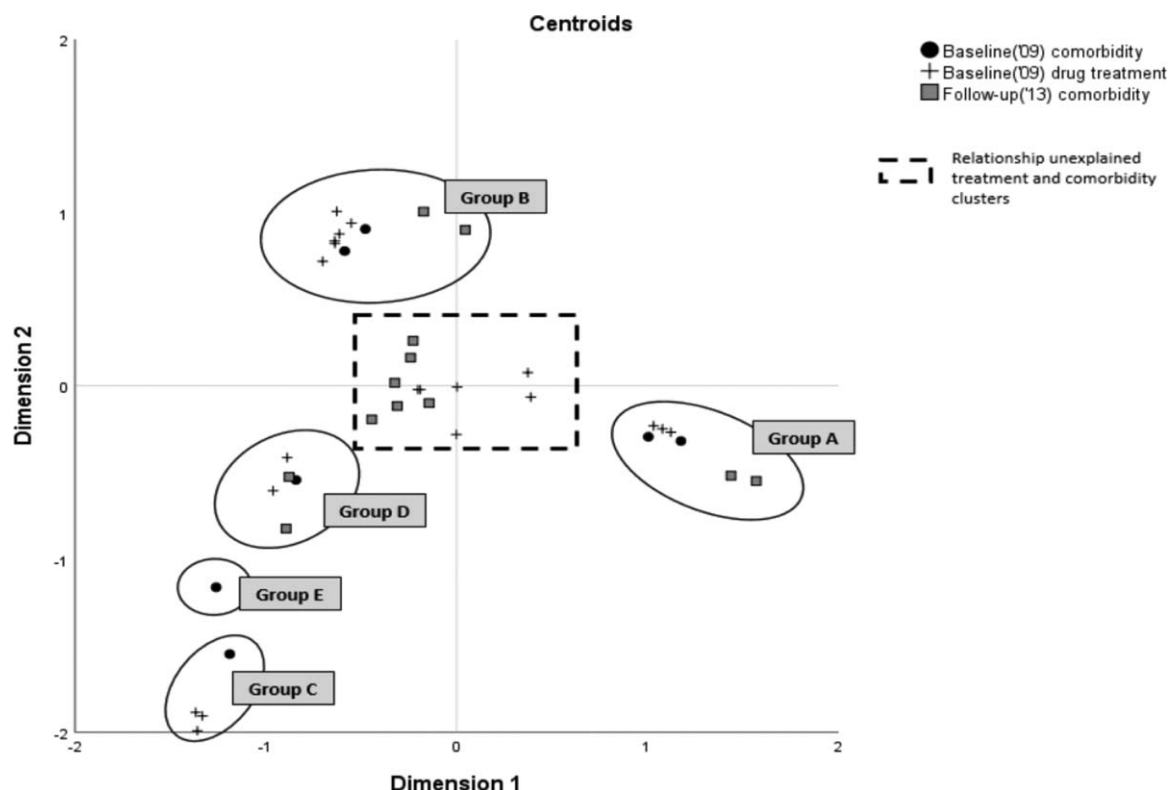
Figure 1. Five groups based on similarity among baseline comorbidity, drug treatment, and follow-up comorbidity clustering.

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

Table 3

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

Characteristics N (%)	Group A 2662 (37.4)	Group B 3116 (43.7)	Group C 1131 (15.9)	Group D 90 (1.3)	Group E 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	≥2
Type of comorbidity	Diabetes-unrelated	Diabetes-related Both[†]	Diabetes-related	Diabetes-related	Both
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+SU	MET/SU MET+SU	MET+DPP4i SU+TZD	Not identified
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 Both	Not identified	Diabetes-related Both	Not identified
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).

[†] Diabetes related and unrelated comorbidity; DPP4i = dipeptidyl peptidase 4 (DPP-4) inhibitors, MET = metformin, SU = sulfonylureas, TZD = thiazolidinediones.

Table 4

Relationship unexplained type of 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	Diabetes-related Both*	Neuropathy or retinopathy or nephropathy
C	≥2	Diabetes-related Both*	Peripheral vascular disease (PVD) and neuropathy cerebrovascular disease Ischemic heart disease

* Diabetes related and unrelated comorbidity; DPP4i = dipeptidyl peptidase 4 inhibitors, MET = metformin, SU = sulfonylureas, TZD = thiazolidinediones.

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 >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 with baseline period. Group E included 1 baseline comorbidity cluster including patients with ≥2 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 4, Fig. 1). These clusters could probable explain the unidentified proportion of baseline treatment pattern and follow up comorbidity patterns.

4. Discussion

T2D patients often have other chronic diseases, which greatly burden diabetes care. As it is known that uncontrolled treatment variance affects quality of care, identifying treatment status to provide evidence based adequate monitoring for T2D patients is important. Especially, risk group for diabetes complication, such as T2D patients with comorbidities, should be considered primarily. We found that 64.9% of patients had at least one other chronic disease and 22.6% of patients had ≥2 diseases before developing any diabetes complications. Especially, proportion of patients with ≥2 chronic disease doubled (49.5%) within 4 years.

In this study, we identified comorbidity patterns and treatment patterns among T2D patients and explored the relationships among baseline comorbid status, drug treatment patterns, and occurrence of diabetes complications. We report 5 main findings. Firstly, as number of comorbidity increased and both type of comorbidities (diabetes unrelated-, related disease) were present, common treatment patterns were less or not identified. This shows the increase of treatment variance related to complex comorbid status. The primary goal of diabetes treatment is to control blood glucose levels, which if left unchecked, may trigger complications.[5–7,24] If metformin is insufficient, the treatment guidelines recommend second-line agents including sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, insulin, sodium glucose co-transporter-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. Since it is recognized that uncontrolled variance affects quality of T2D care, it is important to assess the impact of diverse treatment patterns on health outcomes to control the variance.

Second, our results show that combination treatments such as, SU or DPP4i combined with MET or SU+TZD are treated in T2D patients with comorbidities. In our study, MET+DPP4i was a relative pattern in patients with ≥2 diabetes related comorbidities. 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. Recent studies have shown that DPP-4 inhibitors significantly lower the incidence of cardiovascular events.[25] 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 with metformin alone.[26] 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 the SU increases insulin secretion. So complementary mechanisms may have additive or synergistic effects.[27] 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.[28,29] In fact, 2-year double-blind trial, the Rosiglitazone Early versus SULfonylurea Titration (RESULT) study compared 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.

Third, our results show that not only the number of comorbidities but also presence of diabetes unrelated comorbidity tends to increase treatment variance. In our study, treatment pattern was recognized among T2D patients with ≥2 diabetes related comorbidities while treatments for patient with both type of comorbidities were not identified. It has been suggested that diabetes-related comorbidity enhances cardiovascular risk factor management and unrelated comorbidity may have no impact or have a negative effect on risk factor management and health outcomes.[10,24,30] Microvascular and macrovascular complications often develop concomitantly, as the conditions share risk factors and pathological pathways.[31] However, any relationship between microvascular diseases and diabetes-unrelated diseases is less recognized. In addition, recent studies have shown that retinal disorders are associated with (possibly) depressive symptoms,[32] reduced bone mineral density, and an increased prevalence of osteoporosis.[33] In terms of chronic obstructive pulmonary disease (COPD), Chew et al[34] found that microvascular disease was more common and more severe in patients with than without COPD, increasing the cardiac risk. Our findings support the results of previous studies, and show that it may be necessary to consider treatments and methods for preventing diabetes microvascular complication among T2D patients with diabetes unrelated comorbidity.

Fourth, several combination treatments were identified without or partly being specified in any group. Further studies on such treatments, such as, MET/SU+Insulin or MET+SU+TZD, and its relation to health outcome considering comorbidities could provide insights on treatment alternatives for effective diabetes care. Regarding the fact that differences in glucose-lowering treatment are partly explained by complications and intolerances reflecting the polypharmacy associated with complex comorbidities, insulin therapy could be favored in T2D patients with complex comorbid status.[8] In addition, a recent study found that the combination of insulin with oral glucose-lowering drugs afforded several potential advantages without compromising glycemic efficacy.[35] In a 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), TZD (pioglitazone) combined with MET appeared to provide superior clinical outcomes; all-cause mortality, major adverse cardiovascular events, stroke; compared with the most commonly used regimen, MET+SU, or SU monotherapy.[36]

Lastly, 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 which itself is an important factor in preventing 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.

Our 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. We 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. We 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 our work. Second, we avoided selection bias, ensuring the accuracy of the descriptive data; we interrogated NHIS-NSC databases that are representative of the entire Korean population. We studied virtually all of the 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 our data.

However, our work had certain limitations. First, we used administrative datasets; this means that the accuracy of our 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.[37,38] Thus, we 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. Differences in the study populations would explain our results of the proportion of T2D patients with ≥1 comorbidities slightly differing to prior studies that reported 90.6% and 68.4%, respectively among patients of Irish general practices aged over 18 with type 2 diabetes[13] and 89.7% and 68.2% that included Spanish type 2 diabetes patients.[3] Another limitation is our selection of medical conditions. Currently, no standard list of major or chronic diseases associated with diabetes is available. Thus, the list of diseases we considered may not be complete, but we included all of the 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 the effect thereof on diabetes treatment are complex phenomena that we do not yet know how to effectively manage in clinical practice. However, identification of treatment patterns and their relationships with comorbid status enables us to consider patterns of comorbidity in terms of effective treatment that could improve diabetes care.

Author contributions

Conceptualization: Yeon Young Cho, Sung-il Cho.
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Formal analysis: Yeon Young Cho.
Methodology: Yeon Young Cho, Sung-il Cho.
Supervision: Sung-il Cho.
Writing – original draft: Yeon Young Cho.
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