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ORIGINAL ARTICLE

Clinicodemographic Profile and Outcomes of Type 2 Diabetes Mellitus in the Indonesian Cohort of DISCOVER: A 3-Year Prospective Cohort Study

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Abstract

Background. Indonesia is amongst the top 10 countries with the highest prevalence of Type 2 Diabetes Mellitus (T2DM) at 10.8%. However, the distinguishable features of T2DM in Indonesia remain obscure. Therefore, the DISCOVER study aimed to describe the characteristics of T2DM patients, associated vascular complications and treatment in Indonesia.

Methodology. DISCOVER study is a multi-country, multicenter, prospective, cohort study over 3 years. In the present study, the data were collected from 13 sites from clinical practice, hospitals and public health facilities in Indonesia.

Results. A total of 221 subjects were recruited with a mean age of 55.6 ± 9.8 years and body mass index (BMI) of 26.4 ± 4.4 kg/m^2. Over 40% of patients had hypertension and/or hyperlipidemia. The mean duration of T2DM was 58.3 ± 62.0 months while the mean HbA1c levels was 9.2 ± 2%. In total, 82.4% completed the study within a 36-month follow-up period. BMI remained elevated i.e., >25 kg/m^2. A significant reduction was observed in HbA1c levels as compared to baseline (9.2 ± 2% to 8.1 ± 1.8%). T2DM-associated microvascular complications such as peripheral neuropathy, albuminuria and chronic kidney disease were observed in 17.2%. Macrovascular complications including coronary artery disease and heart failure were seen in 26.2% of patients. We also found that more than 70% of patients were on metformin and/or sulfonylurea.

Conclusion.The features of patients with T2DM in Indonesia were high BMI, with hypertension and hyperlipidemia as co-morbidities. Metformin and sulfonylureas were the most common treatment. HbA1c reduction during follow-up did not reach recommended target. Thus, early detection and intervention using available glucose-lowering medications and aggressive management of risk factors and complications are essential to improve outcomes of diabetes management in Indonesia.

Key words: diabetes type 2, vascular complications, real-world study, Indonesia

INTRODUCTION

Type 2 diabetes mellitus (T2DM) affects an estimated 463 million adults aged 20–79 years and is projected to reach 578 million people in 2030. It imposes a significant economic burden on the global healthcare system and the broader global economy. In 2016-2017, the average cost for T2DM outpatients based on National Health Coverage claims was USD 9574 per 7 days of treatment.[1]

There is limited published data on the incidence and prevalence of T2DM in Indonesia. According to the International Diabetes Federation (IDF), Indonesia's national diabetes prevalence is estimated to be 6.2% in 2019 and 10.8% in 2021, placing it among the top 10 countries with the highest prevalence of T2DM and also with the steepest climb.[1]

According to the Basic Health Research (*Riset Kesehatan Dasar*/ RISKESDAS) 2018 in Indonesia, 10.9% of population ≥15 years old have T2DM. Majority of these patients also have acute or chronic complications.[2,3] Hyperglycemia is associated with several potentially life-threatening microvascular and macrovascular complications, including

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heart failure, coronary artery disease (CAD) and chronic kidney disease (CKD).[3] Due to these complications, diabetes poses risks of decreased quality of life and high economic burden, making it a critical chronic disease to address.

Clinical guidelines recommend metformin as the first line glucose-lowering therapy, in conjunction with lifestyle changes. The Indonesian Endocrinologist Society, *Perkumpulan Endokrinologi Indonesia* (PERKENI), recommends several glucose-lowering therapies as the first-line according to the patient's glycated hemoglobin (HbA1c) in conjunction with lifestyle changes.[3] Sustaining glycemic control, in conjunction with the management of comorbidities such as hypertension and hyperlipidemia, continues to be a critical component of effective T2DM treatment. If metformin monotherapy fails, however, guidelines recommend an individualized and patient-centered approach to drug selection based on patient characteristics.[4]

DISCOVER study's primary objective is to characterize the disease management patterns and clinical evolution of T2DM patients initiating a second-line glucose-lowering treatment (add-on or switch) over 3 years. The purpose of this research was to describe baseline data and its changes in 3 years of follow-up on T2DM patients in Indonesia and to discuss the prevalence of cardiorenal complications following the initiation of second-line therapy.

METHODS

DISCOVER is a 3-year multi-country, multi-center, prospective, cohort study. The study was approved by each participating institution's Institutional Review Board (IRB). A signed informed consent form was obtained from each participant.

For the Indonesian cohort, a total of 221 patients were recruited randomly from 13 sites throughout the country's 8 provinces from January 2015 - October 2019. These sites were selected on the basis of the proportion of patients in primary, secondary, tertiary, private or state owned health care facilities. The study population consisted of patients aged 18 years and above with a diagnosis of T2DM, and who were initiating a second-line glucose-lowering therapy. Patients with previous T2DM diagnosis were also included if they had micro- or macrovascular complications. Macrovascular complications include heart failure, coronary artery disease, and diabetic foot while microvascular complications include chronic kidney disease and peripheral neuropathy events. Excluded in the study were patients who were pregnant, those undergoing dialysis, had renal transplant and those who received injectable agents as first-line therapy or traditional regimen.

Medical records were reviewed for patient demographics, clinical characteristics and glucose-lowering treatment. Laboratory results, as well as history of complications or related procedures were noted during the initial clinical visit and subsequent regular clinical visits at 6, 12, 24 and 36 months. Complications were diagnosed and classified by the investigators who were practicing physicians at the respective study centress and were validated by 2 different investigators as per the patient's medical record.

The demographic variables such as patient's baseline characteristics, treatment patterns, HbA1c level, fasting blood glucose (FBG) and postprandial glucose (PPG), lipid profile, body weight, body mass index (BMI), blood pressure, cardiorenal outcomes and hospitalization events were described using descriptive statistics. As appropriate, descriptive data were presented as frequencies (percentages), means (standard deviations [SD]) and medians (interquartile ranges [IQR]). The data were analyzed using Graphpad v5 software. The baseline and follow-up data were compared statistically using repeated measure ANOVA.

For sample size calculation, statistical software, 'G*Power version 3.1.9.2' was used taking the prevalence of T2DM in the Indonesian population to be 10.8%. The sample size also considered other factors such as follow-up time of 36 months, complications and mortality rate. Considering all these factors and keeping 80% power and 5% significance, the sample size was estimated to be 285.

RESULTS

The Indonesia DISCOVER study program enrolled a total of 221 patients from 13 sites in Indonesia, including primary care centers (8.3%), general/community hospital (50%), and university/teaching hospital (25%). The clinical sites were Endocrinology (38.5%), Internal Medicine (30.8%) and General Practitioner practices (20.8%). Public hospital/ health center accounted for 61.5% of cases. Of 221 patients at baseline, 182 (82.4%) completed the study during the 36 months follow-up period, 5.9% of patients died and 8.6% were lost to follow-up. Cardiovascular disease accounts for 50% of these deaths. Reasons for discontinuation in the study include withdrawal of consent (2.3%) and other reasons (0.9%). Table 1 shows the baseline demographics i.e., age, gender, ethnicity, working status, medical history, health insurance coverage and diabetes-related complications. All participants were Indonesians (Asian) with a mean age of 55.6 ± 9.8 years. Among them, 56.6% were females. Over 40% of patients had comorbidities such as hypertension and/or hyperlipidemia.

The initial BMI was 26.4 ± 4.4 kg/m^2 and remained elevated throughout the follow-up period, i.e., >25 kg/m^2. The mean duration of T2DM was 58.3 ± 62.0 months with HbA1c levels of 9.2 ± 2% at baseline. There was a significant reduction in HbA1c, FBG and PPG during follow-up as compared to baseline (p<0.05). However, the mean HbA1c level (8.0 ± 1.8) did not reach the American Diabetes Association (ADA) recommended target of 7%.[3] Unfortunately, more than 40% of data were missing for HbA1c and PPG. Other clinical characteristics such as systolic and diastolic

Table 1. Patient demographics

Parameter, n (%)	n = 221
Sex	
Male	96 (43.4%)
Female	125 (56.6%)
Age, years (Mean±SD)	55.6 ± 9.8
Self-reported ethnicity	
Caucasian	1 (0.5%)
Asian	205 (92.8%)
Arabic	2 (0.9%)
Others	13 (5.9%)
Education level	
No formal education	4 (1.8%)
Primary (1-6 years of education)	41 (18.7%)
Secondary (7-13 years of education)	72 (32.9%)
University/higher education (13+ years)	102 (46.6%)
Not known	2 (0.9%)
Main working status	
Employed	70 (31.8%)
Self-employed	47 (21.4%)
Unemployed	82 (37.3%)
Retired	21 (9.5%)
Not known	1 (0.45%)
Health insurance coverage	
Private	61 (27.6%)
Public/governmental	105 (47.5%)
Mixed	1 (0.5%)
No insurance	54 (24.4%)
Duration of diabetes (months), mean±SD	58.3 ± 62.0
Comorbidities	
Hypertension	97 (43.9%)
Hyperlipidemia	98 (44.3%)
Macrovascular complication	38 (17.2%)
Heart failure	11 (5%)
Coronary artery disease	12 (5.4%)
Diabetic foot	9 (4.1%)
Microvascular complication	58 (26.2%)
Chronic kidney disease	14 (16.2%)
Peripheral neuropathy event	20 (9%)

SD, standard deviation; n, number of patients; %, percentage

blood pressure, weight and lipid profile (total cholesterol, high-density lipoproteins, and low-density lipoproteins) remained the same during follow-up. On the contrary, triglycerides levels were significantly reduced. Table 2 summarizes the clinical characteristics at baseline and follow-up.

Microvascular and macrovascular complications associated with T2DM were observed in 17.2% and 26.2% of patients, respectively. As shown in Figure 1 (A and B), the most common macrovascular complications at 36 months were coronary artery disease and heart failure in 35% and 25%, respectively. On the other hand, peripheral neuropathy contributed to 32% of cases, microalbuminuria in 25% of cases and chronic kidney disease in 20% of cases with microvascular complications. Diabetes-related complications at follow-up were further documented and classified based on the need for hospitalization. There were 6.2% hospitalization events in 6 months, 5.6% in 12 months and 6.4% in 24 months follow-up. A surge of 12.1% of hospitalization events was observed at 36 months of follow-up. The primary reasons for hospitalization were cardiovascular events, diabetic foot and diabetes-related complications, which are shown in Figure 1 (C). Serious infections, cancer, cellulitis and renal failure were included in other reasons.

In terms of medications, approximately 36.7% of patients were started on monotherapy and 13.6% of patients were on combination therapy. We found that more than 70% of patients were on metformin and/or sulfonylurea as a first-line treatment. The combination of metformin and sulfonylurea was the most frequently used second-line therapy, followed by the triple therapy of metformin, sulfonylurea and dipeptidyl peptidase-4 inhibitor (DPP-4i). About 26.7% of patients were on second-line therapy and 11.3% were on triple therapy. During the follow-up period, only 22.7% of patients remained on monotherapy. The most frequently cited reason for switching from first-line to second-line therapy was due to treatment failure. The choice for second-line therapy was based on improved efficacy. Sulfonylureas were the most commonly stopped medication at all follow-up time points, accounting for 6.7%, 8.7%, 8% and 8.4% of the population at 6, 12, 24, and 36 months, respectively, followed by metformin and fixed-dose metformin+DPP-4i. The changes in patients' treatment during the follow-up period of 36 months are shown in Figure 2.

Table 2. Clinical characteristics at baseline and follow-up time points (6, 12, 24, 36 months)

Parameter	Baseline data (0 months) n = 221	6 months follow-up n = 195	12 months follow-up n = 196	24 months follow-up n = 188	36 months follow-up n = 190	*p*
Weight (kg)	67.4 ± 14.0	67.0 ± 14.1	67.0 ± 14.1	67.2 ± 14.1	67.4 ± 14.5	1.000
BMI (kg/m^2)	26.4 ± 4.4	26.3 ± 4.4	26.3 ± 4.4	26.4 ± 4.5	26.4 ± 4.6	1.000
Systolic BP (mmHg)	127.7 ± 17.2	128.9 ± 17.6	128.4 ± 16.4	129.3 ± 16.9	129.7 ± 19.5	0.278
Diastolic BP (mmHg)	80.6 ± 8.7	80.5 ± 7.8	80.6 ± 7.6	81.2 ± 8.7	81.0 ± 10.0	0.671
HbA1c (%)	9.2 ± 2	7.9 ± 1.7	7.9 ± 1.8	8.1 ± 1.9	8.0 ± 1.8	**<0.01**
Fasting glucose (mg/dL)	176.5 ± 60.3	150.2 ± 52.7	155.4 ± 55.0	162.5 ± 60.2	156.1 ± 51.3	**<0.05**
PPG (mg/dL)	250.0 ± 81.9	208.4 ± 69	212.3 ± 75.4	212.3 ± 75.4	221.1 ± 78.1	**<0.01**
HDL-C (mg/dL)	46.3 ± 12.7	45.6 ± 10.1	48.2 ± 12.3	47.1 ± 12.9	48.7 ± 13.3	0.063
LDL-C (mg/dL)	126.8 ± 39.1	123.2 ± 37.3	124.7 ± 34.6	126.5 ± 39.0	127.7 ± 39.2	0.834
Total cholesterol (mg/dL)	204.9 ± 54.5	196.2 ± 43.0	206.1 ± 50.5	201.0 ± 50.5	194.7 ± 42.2	0.052
Triglycerides (mg/dL)	186.4 ± 182.5	155.8 ± 74.5	177.1 ± 194.2	160.7 ± 81.6	154.7 ± 109.7	**<0.05**

BMI, body mass index; BP, blood pressure; PPG, postprandial glucose; SD, standard deviation; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

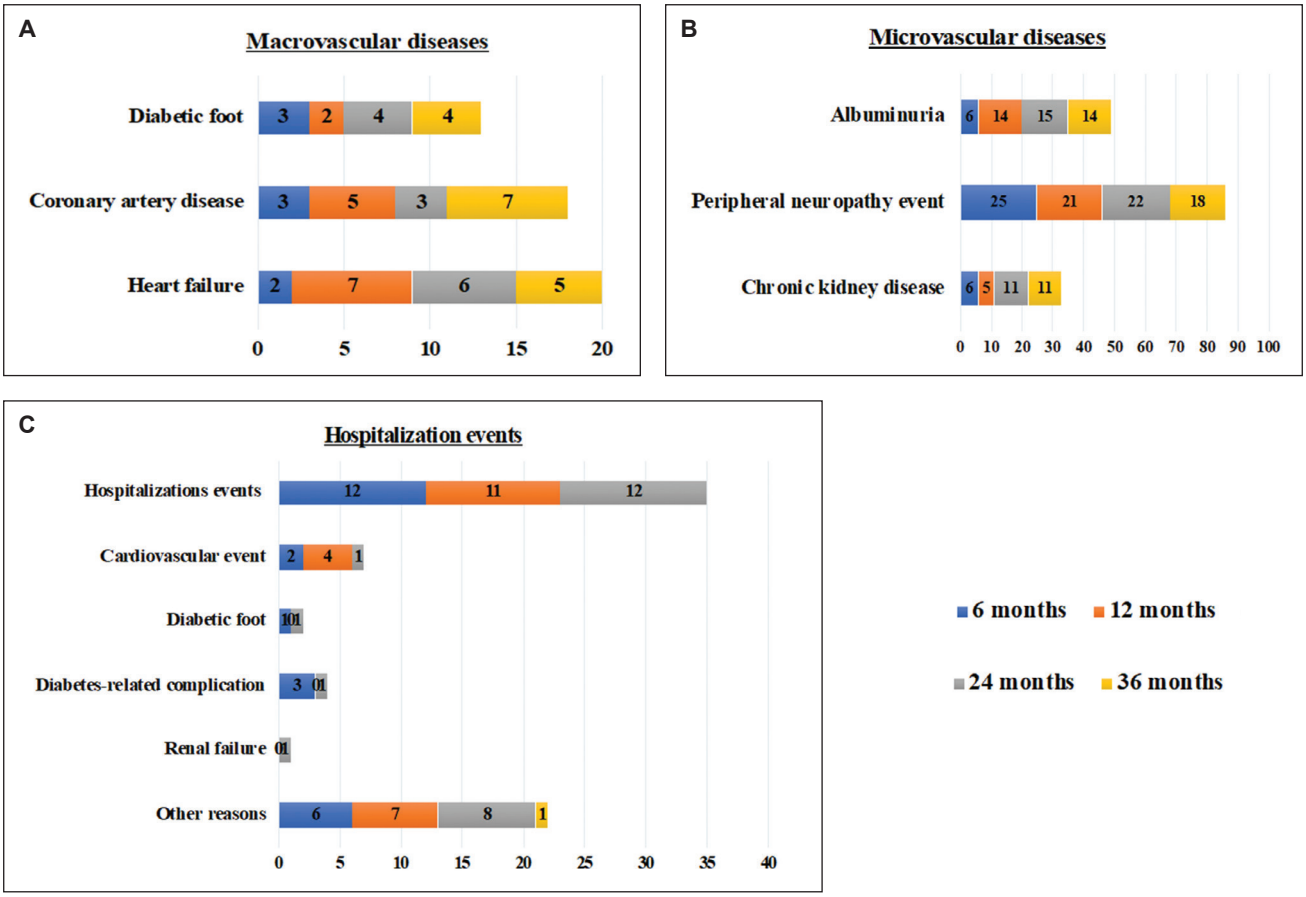

Figure 1. Diabetes-related complications during a follow-up period of 36 months. Side bar-graphs depict the frequencies of participants affected with diabetes-related complications including **(A)** Macrovascular diseases, **(B)** Microvascular diseases, and **(C)** hospitalization events during a follow-up period of 36 months.

DISCUSSION

DISCOVER is a global research programme that assessed the characteristics, treatment and outcomes of T2DM patients after initiating second-line glucose-lowering therapy. This is the first of Indonesia's DISCOVER study from 13 clinical sites representing primary and secondary care in rural and urban locations with different treatment cost resources. This observational study gives a broad picture of the real-world management of patients with T2DM in Indonesia, with different backgrounds, ethnicities and socioeconomic status.

Compared to the whole DISCOVER study, the patients in the Indonesian cohort were younger (55.6 ± 9.8 vs 57.5 ± 12), majority were female (566 vs 47.3%), with lower BMI (26.4 ± 4.4 vs 29.4 ± 6) but higher HbA1c (9.2 ± 2 vs 8.4 ± 1.7).[5] The mean BMI of patients w 26.4±4.4 kg/m^2 which can be classified as overweight or obese. In a study by Cholil et al., a similar mean BMI (25.4 ± 4.2 kg/m^2) was observed among T2DM patients in Indonesia.[6]

Several studies have shown the presence of other medical conditions such as hypertension and dyslipidemia among patients with T2DM.[6-8] The present study demonstrated that T2DM patients in Indonesia had systolic blood pressure of 127.7 ± 17.2 mmHg and diastolic blood pressure of 80.6 ± 8.7 mmHg, which can be classified as pre-hypertension and were stable over 3 years. Additionally, we observed that the mean lipid parameters were elevated over a three-year follow-up period, indicating that most patients had dyslipidemia.[4,5,9]

Monitoring the HbA1c level is recommended to aid in treatment decisions in T2DM patients. The risk for T2DM complications increases linearly with HbA1c levels making glycemic control critical.[10] Some studies indicate that aggressively lowering HbA1c levels increases the rate of hypoglycemia, possibly increasing the risk of cardiovascular events. Compliance with HbA1c testing was low in Indonesia due to the price and unavailability in some provinces. After 3 years of follow-up, mean HbA1c levels decreased significantly but did not reach the target (8.0 ± 1.8%). In several DISCOVER studies, the patients who were started on second-line therapies had a mean HbA1c level that was also above target and remained consistently high even after changing therapies.[5,10,11] The study population's glycemic control was unsatisfactory based on Diabcare 2008 and 2012. Only about one-third of patients met the ADA's recommended HbA1c and FPG targets and were above the recommended PPG levels.[6,12] This indicates that a sizable proportion of patients had suboptimal glycemic control and delayed treatment intensification, increasing their risk of microvascular and macrovascular complications.[13]

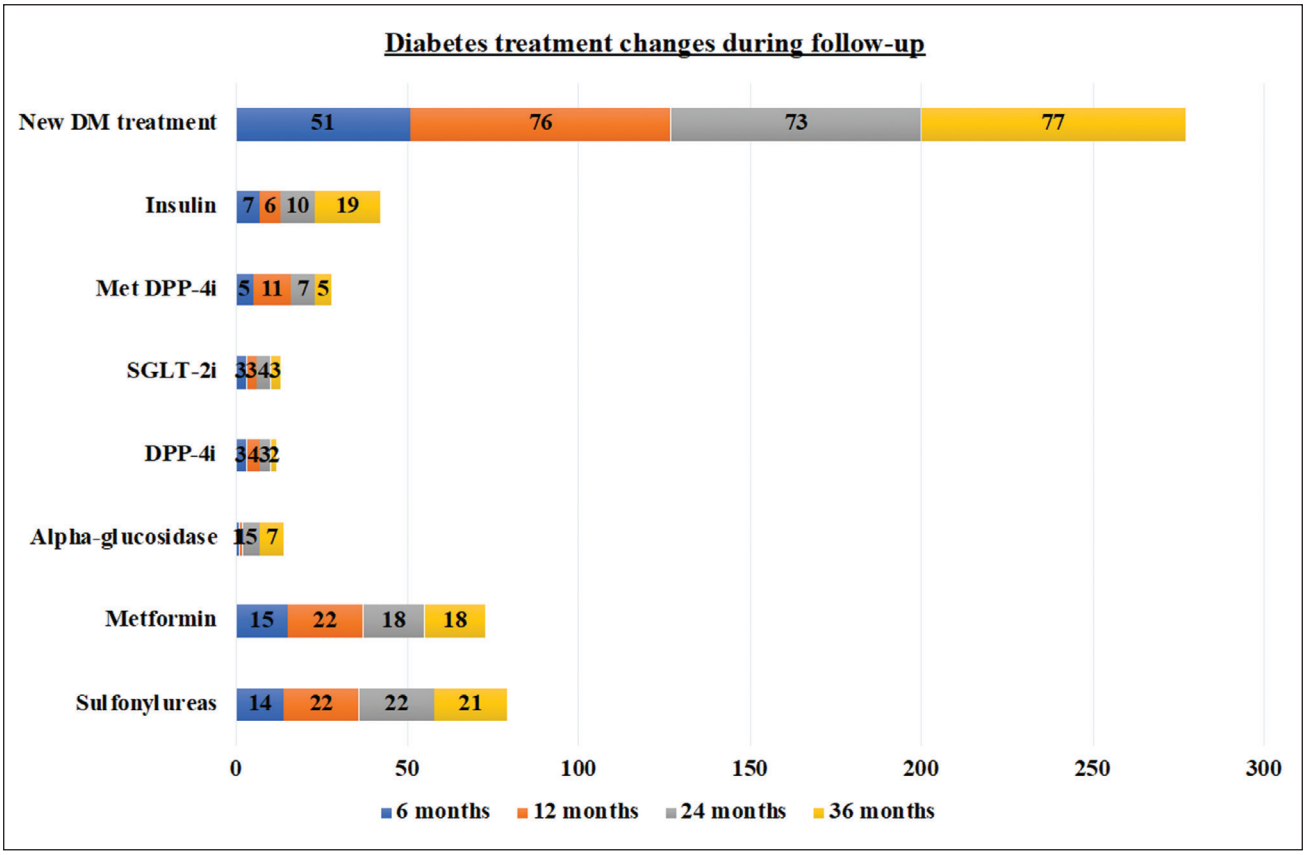

Figure 2. Changes in diabetes treatment during a follow-up period of 36 months. Side bar-graph depicts the frequencies of participants who were prescribed new medication for diabetes during a follow-up period of 36 months.

The majority of patients in the Indonesia DISCOVER study were initiated on metformin alone (36.7%), sulfonylurea alone (19.9%), or combination of these medications (10.9%). This was based on the HbA1c result or clinician's decision based on PERKINI guidelines.[14] As second-line therapy, metformin and sulfonylurea (26.7%) and metformin, sulfonylurea and DPP-4i (11.3%) were the most frequently prescribed combinations. The switch to second-line therapy was also consistent with some clinical guidelines.[3,5,9] After 3 years of follow-up, it was observed that metformin, sulfonylureas and basal insulin were used as diabetes treatments. Innovative oral anti-diabetic medications such as SGLT-2i and DPP-4i were used in only 1.2% and 1.1% of patients, respectively. A local study showed that 61.9% of patients received only oral anti-diabetic drugs (OAD), followed by insulin and OAD (19.4%), insulin monotherapy (17.3%), no pharmacologic treatment (1.1%) and herbal treatment (0.3%).[12] T2DM medications such as inhibitors of sodium-glucose cotransporter-2 (SGLT-2i) significantly reduce the risk of cardiovascular complications in high-risk patients, implying that treatment patterns may be beneficial to prevent further complications.[7,15-19] These newer and safer agents appear to be underutilized, maybe because they were more costly and unavailable in some provinces, despite their high efficacy and additional benefits for blood pressure, lipid and weight reduction, and cardio-renal outcomes.[16,17,19]

In Indonesia, 28% of patients with T2DM develop microvascular complications such as nephropathy (7.7%), neuropathy (17.6%) and retinopathy (2.7%). Whereas, 16.8% of patients develop macrovascular complications e.g., CAD (5.4%), heart failure (5%) and cerebrovascular disease (5.4%).[1] It is estimated that the relative risk of patients with T2DM for microvascular complications is at least 10–20 times greater compared to people without T2DM. Moreover, the risk for macrovascular disorders is about 2–4 times greater and accounts for approximately 65 percent of deaths.[5,20] Our study revealed that microvascular and macrovascular complications occurred at rates of 32% and 52%, respectively. Due to a lot of missing data on microvascular complications, these may be underestimated but enough to demonstrate the critical importance of early disease diagnosis, as recommended by guidelines.

The rate of complications in T2DM patients is concerning and warrants further investigation in Indonesia. T2DM and its complications have reached epidemic proportions, especially in developing countries.[1,21] The significant increase in the prevalence of diagnosed and undiagnosed T2DM, combined with advancements in diabetes treatment, has resulted in increased financial burden of diabetic complications; for example, 53% of the disease's lifetime medical costs have been attributed to treating complications. The critical importance of aggressive efforts to raise awareness, compliance to treatment, early diagnosis, and optimal monitoring to achieve treatment

goals are necessary to slow the progression of cardio-renal complications associated with T2DM.[22]

This study had major limitations. The recruited sample size was smaller than the calculated sample size (221 vs. 285 patients) due to a number of reasons. The study was multi-center and involved a number of physicians, hence, it was difficult to manage and follow-up all patients at 13 sites for a period of 36 months. The mortality rate was approximately 6% and lost to follow-up rate was 9%. Practical constraints such as lack of infrastructure, high proportions of missing data at centers, or unwillingness of centers to participate in observational research might have caused potential selection bias. Furthermore, the different sites had different standards of health facilities for the diagnosis and treatment of patients. Due to the differences in the modalities, the opinions and clinical judgement of the physician plays a vital role in the determination and classification of diabetes complications. Patients were randomly recruited during the index period of 2015-2016 only, such that their follow up ended in 2019. Thus, considering all these factors, the current scenario of T2DM in Indonesia may be slightly different than the findings reported in the present study but likely to reflect the routine clinical care in the country.

CONCLUSION

The DISCOVER study is a large global initiative that provides critical information about the real-world management of patients with T2DM. This is the first study in Indonesia that gives a picture of T2DM management over 3 years follow-up. Majority of patients had suboptimal glycemic and metabolic control. The characteristics of T2DM patients in Indonesia were elevated BMI, hypertension and hyperlipidemia, which were the most common comorbidities, and it showed the wide use of metformin and sulfonylurea for treatment. After 3 years of follow-up, HbA1c levels, vascular complications and other risk factors remained high. Increased awareness, early detection and intervention, as well as optimal initiation of available glucose-lowering medications and treatment of other risk factors are important to improve T2DM management and outcome in Indonesia.

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Statement of Authorship
The authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
DWS, RR, MRS, RPS, WOT: Conceptualization, Methodology, Validation, Formal analysis, Writing – original draft preparation and Writing – review and editing.

Author Disclosure
Dr. Made Ratna Saraswati is the JAFES Associate Editor of Indonesia. Dr. Widya Oktaviana Tarigan is the Medical Scientific Liaison of AstraZeneca Indonesia. Drs. Soeatmadji, Rosandi and Sibarani declared no conflicts of interest.

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