# Reduction of severe hypoglycemic events among outpatients with type 2 diabetes following sodium-glucose cotransporter 2 inhibitor marketing in Japan.

Short running title: Reduction of the number of patients with hypoglycemia was associated with sodium-glucose cotransporter 2 inhibitor.

Koh Yamashita[1)], Shouichi Yoshiike[2)], Taku Yamashita[3)], Jun-ichirou Mori [4)], Toru Aizawa[1)]

1）Diabetes Center, Aizawa Hospital

2）Critical Care Center, Aizawa Hospital

3）School of Pharmacy, Mukogawa Women's University

4）Center for Medical Education, Faculty of Medicine, Shinshu University

*Correspondence should be addressed to,

Dr. Koh Yamashita, Diabetes Center, Aizawa Hospital, 2-5-1 Honjo, Matsumoto, Japan 390-8510

Tel.: +81 263 33 8600, Fax: +81 263 33 8609

ai.67417@ai-hosp.or.jp

**Abstract**

Recently, oral hypoglycemic agents with newer glucose lowering mechanisms have been release. This is mostly to meet the diabetic patient's need to avoid hypoglycemia, which is profoundly important for better long-term outcome of the treatment. In this study, we quantified the annual number of patients with type 2 diabetes who experienced hypoglycemia needed the third-party assistance who had random sample plasma glucose < 59.4 mg/dL (3.3 mmol/L) on one hand and analyzed the prescription trend of hypoglycemic agents all over Japan on the other. The former analysis was performed at Aizawa Hospital, a medical center located in the midst of a city having approximately 250,000 residency and annual ER visitors of approximately 46,000. The study duration was over the 10 years from 2008 to 2019. We found a clear-cut decreasing trend of hypoglycemia over the 10 years, ca. 61/year to 39/year. Immediately after the release of sodium-glucose co-transporter-2 inhibitors, since 2013 to 2017, the decrease was rather sharp as 81/year to 31/year, and the change of the national number of its prescription inversely correlated with the change of the number of the patients with hypoglycemia. This was not the case immediately after the introduction of dipeptidyl peptidase-4 inhibitors in the Japanese market since 2008 to 2012. These was no significant correlation between its prescription and the number of patients with

hypoglycemia. The data strongly suggested there was a causal relationship exclusively between the introduction of sodium-glucose cotransporter-2 inhibitor, and the reduction of hypoglycemic events among patients with type 2 diabetes.

Key words; Etiology, Complication, Adverse effects

## Introduction

Many types of hypoglycemic agents for treatment of diabetes are currently being prescribed, including insulin and non-insulin injectables. Once newer hypoglycemic agents have been launched, there have been mixed reports on the glycemic control: improved, not changed, or sometimes worsened [1,2]. On the other hand, the adverse effects of severe hypoglycemia on cardiovascular event and mortality are firmly established [3] so that obtaining strict glycemic control without serious hypoglycemia in patients with diabetes is strongly awaited. In Japan, an incretin-related drug, dipeptidyl peptidase-4 inhibitors (DPP4i) were launched in 2009, which was followed by sodium-glucose cotransporter-2 inhibitor (SGLT2i) in 2014, and the market share of hypoglycemic agents has drastically changed following the marketing of each of the two classes of oral hypoglycemic agents (Figure 1(a)). On overseas, there here have been reports that the frequency of hypoglycemia has remained unchanged or decreased in association with the appearance of these two drugs, and that the frequency of hypoglycemia has increased [1,4]. But the detailed analysis on the impact of marketing of the number oral hypoglycemic agents (OHAs) on the incidence of hypoglycemia has been lacking.

## Materials and Methods

*Patient recruitment*

Out of 553,201 patients visited our emergency room (ER) for 12 years (from January 1, 2008 to December 31, 2019), 648 adult patients (≥20 years of age) with hypoglycemia were identified by the computer chart screening.

The triggering of various counter-regulatory hormones by hypoglycemia reportedly occur in the order of glucagon (68 ± 2 mg/dL), epinephrine (69 ± 2 mg/dL), growth hormone (66 ± 2 mg/dL), and cortisol (58 ± 2 mg / dL) [5]. Accordingly, we defined the blood glucose levels lower than 3.3 mmol/L (less than 59.4 mg/dL) as took it as the diagnosis of definite hypoglycemia. Blood glucose levels were measured by the glucose oxidase method or point of care testing (POCT; see below). Out of the 648 patients who experienced hypoglycemia thus defined, 437 patients (437/648, 67.4%) had been judged to be with type 2 diabetes mellitus (T2D) as confirmed by the background of the patient and the medication. Between hypoglycemic patients with type 1 and type 2 diabetes, there was a significant difference regarding age and eGFR, but there was no significant difference in sex ratio and plasma glucose concentration (Table 1).

*Medication list and the market share information*

The type and doses of their OHAs and the current use of insulin were surveyed from the interview at the time of the ER visit or later, the referral letter, or the prescription records.

Information on the market share of diabetes mellitus drugs in Japan was provided by JMDC Co., Ltd.

*Chemistry*

*Glucose*

Plasma glucose concentration was measured by glucose oxidase method using Arkray ADAMS GA-1171® (Tokyo, Japan) and Hitachi's Labospect 008 alpha® (Hitachi, Japan). POCT glucose measurement was performed by using Nova Biomedical Statstrip® (Tokyo, Japan).

*Creatinine*

Serum creatinine was measured by the enzyme method using Labospect 008 alpha® (Hitachi, Japan), with the measurement reagent provided by FujiFilm Wako. The estimated glomerular filtration rate (eGFR) was determined by the following formula [6].

Male: $eGFR=194 * \text{serum creatinine (mg/dL)}^{-1.094} * \text{Age}^{-0.287}$

Female: eGFR=194 * serum creatinine (mg/dL)$^{-1.094}$ * Age$^{-0.287}$ * 0.739

*Statistical analysis*

Data were collected both cross-sectionally and longitudinally.

The trend analysis was carried out by Jonkheere-Terpstra test, as described below. To determine the transient effect of the introduction of a new OHA to the market on the number of T2D patients with hypoglycemia, the new share of the medicines in the first 5 years of the marketing was obtained. Namely the share of the year 1was compared to that of year 2, 3, 4 and 5, and the relationship between the numbers of T2D patients with hypoglycemia, in the same period, was analyzed. Thus, for DPP4i, which was released in 2009, the five years corresponds to “2008 to 2012”, and for SGLT2i released in 2014, the five years corresponded to “2013 to 2017”.

Statistical analysis was performed using JMP ver.15 and SPSS ver.21.

**Results**

The baseline characteristics of the patients experienced hypoglycemia are shown in Table 1.

Compared to the non-diabetic patients of hypoglycemia, the patients of hypoglycemia with T2D were elder and with lower eGFR.

Trend of the number of patients with hypoglycemia per year and the fraction, type 1 diabetes, type 2 diabetes or others, of it during 2008 and 2019 are shown in Figure 3(a). The number of patients with hypoglycemia per year increased from 2008 until 2010, and then, there was not a clear-cut change toward 2013. Since 2014, it has clearly started to decline. A significant decrease in the number of hypoglycemic patients was observed during 2014 and 2017.

The patients with hypoglycemia had T2D (N=437), type 1 diabetes (T1D, N=60), chronic malnutrition from alcoholic abuse (N=25), non-specific anorexia (N=29), end stage cancer (N=2) and others (N=95).

Among them, the number of the patients of hypoglycemia with T2D has decreased markedly since 2014 (Figure 3(a)). Regarding hypoglycemic agents prescribed to the hypoglycemic T2D patients, insulin was the most common medication, followed by sulfonylurea (SU) and DPP4i (Figure 1(b)). While the prescription of insulin and SU

drugs decreased over time, that of DPP4i was gradually increased from 2012 until 2016 (Figure 1(a)).

In the yearly share of oral hypoglycemic agents, DPP4i have launched in 2009, strikingly increased from 2010, and has been the most commonly used OHA in Japan thereafter. SGLT2i and Glinide have also increased from 2014 but the rate of increase was less compared to DPP4i (Figure 1(a)).

The annual trend of the number of patients with hypoglycemia taking a single agent was shown in Figure 3(b). Most patients who had hypoglycemia with a single drug were caused by SU or insulin, but some were caused by DPP4i. None of the patients taking biguanide (BG), thiazolidinedione (TZD), alpha glucosidase inhibitor (aGI), fast-acting insulin secretagogue (Glinide), SGLT2i, or glucagon like peptide-1 receptor agonist (GLP-1-RA), TZD, aGI, Glinide, SGLT2i, or GLP-1RA as a single class of hypoglycemic agent developed hypoglycemia severe enough to bring them to the hospital.

Considering the bias of the fluctuation by the T2D patient with hypoglycemia who had consulted another medical institution, we analyzed the ratio of the hypoglycemia patient to the total ER patient. The change of the number of T2D patients with hypoglycemia by the number of all patients who visited to our hospital ER was similar to the change of the absolute number of T2D patients with hypoglycemia. The value of T2D

hypoglycemia patients by all ER patients was no significant change from 2008 until 2013, on and after 2014, it declined from 2014 and has remained generally flat since 2017.

Considering the bias of the fluctuation by the T2D patient with hypoglycemia who had consulted another medical institution, we analyzed the ratio of the hypoglycemia patient to the total ER patient. For the deeper understanding of the relationship between the variation of prevalence of hypoglycemia and marketing of DPP4i and SGLT2i, following analyses was performed. Figure 4(a) showed the trend of the number of T2D patients with hypoglycemia and the share of each drug from 2008 to 2012. As can be seen, the number of T2D patients with hypoglycemia did not show a significant change from 2008 to 2012 despite a rapid increase in the share of DPP4i. As for this, the number of T2D patients with hypoglycemia per the number of all the patients who visited to ER of our hospital was stable and not correlated with the share of DPP4i (Figure 4(b)). A statistical analysis was performed on the transition of the number of T2D patients with hypoglycemia from 2008 to 2012 and the proportion of hypoglycemia patients in ER. The results were 1.000 and 0.624, respectively. So, there was no significant downward trend. In addition, the relationship between each change and the annual transition of the share of DPP4i revealed that the p-values were 0.7474 and 0.4330, respectively, and there was no significant correlation. That is, there was no correlation between the increase in the

share of DPP4i and the change in the number of hypoglycemia patients and the proportion of hypoglycemia patients in ER. However, as for SGLT2i, after its release, a decrease in the number of T2D patients with hypoglycemia occurred in association of an increase in the share of SGLT2i (Figure 4(c)). The trend was statistically significant also in the percent of T2D patients with hypoglycemia in the number of all the patients who visited to ER of our hospital has not changed. The situation was different from DPP4i (Figure 4(d)). As with DPP4i, the Jonkheere-Terpstra test was performed in the study of the change in the number of hypoglycemia patients and the proportion of hypoglycemia patients in ER. The results are both 0.014, so there were significant downward trends. In addition, regarding the relationship between the number of hypoglycemia patients and the ratio of hypoglycemia patients to ER and the annual transition of drug share of SGLT2i, each p-value was statistically significant as 0.0055 and 0.0082.

## Discussion

During the 12 years from 2008 to 2019, the number of patients per year coming to ER of our hospital due to hypoglycemia has been significantly declined. This was clearly associated with reduction of the number of type 2 diabetes mellitus patients with hypoglycemia who had visited the ER. Therefore, the percent of patients with type 2 diabetes having hypoglycemia among the entire number of ER patients also decreased. During this period, we have experienced a dramatic change of the pharmacological treatment for type 2 diabetes mellitus. That is, DPP4i, which is the most frequently prescribed for type 2 diabetes patients in Japan (Figure 1(a)), has launched in 2009. Five years later in 2014, SGLT2i, which is now attracting worldwide attention for its seemingly multi-organ benefit in diabetes [7,8,9], has been introduced to the market.

We would call the action of the two classes of OHA as “novel” because the glucose-lowering mechanism of DPP4i and SGLT2i were totally new in the clinical diabetology [10,11].

In this study, we carefully analyzed relationship between the market share of DPP4i and SGLT2i and the number of hypoglycemic patients treated at ER of our hospital. Despite rapid and substantial increase in the market share of DPP4i between 2009~2013, there was no significant decline in the number of patients with hypoglycemia and their

proportions. It was considered due to the main mechanism of glucose-lowering action of DPP4i was inhibition of DPP4, an enzyme that inactivates endogenous incretin, thereby enhancing the incretin action augmenting insulin secretion [10]. Therefore, the risk of hypoglycemia (in contrast to the initial expectation) was not necessarily low especially when used with SU [12]. The situation was clearly different in the case of SGLT2i. The number of patients with hypoglycemia visited to our ER has dramatically declined between 2014~2017, during which time, the market share of SGLT2i has increased as much as five times (5.8% to 29.4%) in Japan (Figure 1). The drug is considered to impede glucose reabsorption in the renal tubules only when plasma glucose is over the threshold of the renal tubules, which is approximately 10 mmol/L (180 mg/dL) of the plasma glucose level. Thus, SGLT2i's glucose lowering action is independent of insulin action, and the drug would not cause hypoglycemia by itself [11]. The difference of glucose lowering mechanism between DPP4i and SGLT2i was considered reflecting into the difference in the number of patients with hypoglycemia.

There are several limitations in this study. First, this study was a retrospective, observational study. So that the causality cannot be directly discussed. Secondly, this study is a single center research. We used patient data of only in our hospital, and there might be the bias that it is the phenomena peculiar to our hospital although such

possibility is quite low. In addition, the tendency of the number of patients with hypoglycemia who visited to our hospital ER was compared with the that of the medication share all over Japan. Therefore, the possible influence such as the regional difference in the market share was ignored.

## Conclusion

In this study, it was found that the number of emergency outpatients due to hypoglycemia decreased sharply during 2014 and 2018. During the same period, the market share of SGLT2i have risen from 5.8% to 29.4%. We considered it is likely that increased prescription of SGLT2i favorably affected for the reduction of the number of patients with hypoglycemia, which could be detected at Aizawa Hospital ER is related to increase in the market share of SGLT2i. A prospective study with a larger number of participants is necessary to prove our hypothesis.

**References**


1 Yan Zhi Tan, Hua Heng Cheen, Su-Yen Goh et al. Trends in medication utilization, glycemic control and outcomes among type 2 diabetes patients in a tertiary referral center in Singapore from 2007 to 2017. J Diabetes, 2019; 11:573-581.

2 John M Dennis, E Henley, Andrew P McGovern et al. Time trends in prescribing of type 2 diabetes drugs, glycaemic response and risk factors: A retrospective analysis of primary care data, 2010-2017. Diabetes Obes Metab, 2019; 21:1576-1584.

3 Sophia Zoungas, Anushka Patel, John Chalmers, et al. Severe Hypoglycemia and Risks of Vascular Events and Death. N Engl J Med, 2010; 363:1410-1418.

4 Wajd Alkabbani, GambleJohn-Michael. Profile of Ipragliflozin, an Oral SGLT-2 Inhibitor for the Treatment of Type 2 Diabetes: The Evidence to Date. Drug Des Devel Ther, 2021; 15:3057-3069.

5 P E Cryer, J N Fisher, H Shamoon. Hypoglycemia. Diabetes Care, 1994; 17:734-55.

6 Seiichi MatsuoImai, Masaru Horio, Yoshinari Yasuda et al. Revised Equations for Estimated GFR From Serum Creatinine in Japan. Am J Kidney Dis, 2009;

53:982-92.

7 Bernard Zinman , Christoph Wanner, John M Lachin et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015; 373:2117-28.

8 A J Scheen. Beneficial effects of SGLT2 inhibitors on fatty liver on type 2 diabetes: A common comorbidity associated with severe complications. Diabetes Metab. 2019; 45:213-223.

9 Hiddo J L Heerspink, Bergur V Stefánsson, Ricardo Correa-Rotter et al. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med. 2020; 383:1436-1446.

10 Chee W Chia, Josephine M Egan. Incretin-based therapies in type 2 diabetes mellitus. J Clin Endocrinol Metab. 2008; 93:3703-16.

11 M A Abdul-Ghani, R A DeFronzo. Lowering plasma glucose concentration by inhibiting renal sodium-glucose cotransport. J Intern Med. 2014; 276:352-63.

12 R Arechavaleta, T Seck, Y Chen et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab. 2011; 13 160-168.

**Figure legends**

Figure 1

(a)Annual trends in the yearly share of anti-diabetic agents based on the market survey results by JMDC.

(b) Annual trends in the number of T2D patients with hypoglycemia taking each drug

Over time, the number of patients with insulin and SU decreased in parallel with the transition of the number of hypoglycemia patients. On the other hand, the number of patients with DPP4i increased and decreased repeatedly until 2016, and it gradually decreased there after that. The number of patients taking SGLT2 inhibitors did not increase significantly after the release.

blue; biguanide, orange; sulfonyl urea, red; insulin, sky-blue; glinide, yellow; alpha glucosidase inhibitor, gray; thiazolidinedione, black; glucagon like peptide-1 receptor agonist, green; dipeptidyl peptidase-4 inhibitor, navy blue; sodium-glucose cotransporter-2 inhibitor

purple bar; the number of T2D patients with hypoglycemia, light green bar; the value of the number of T2D patients with hypoglycemia by the number of all patients who visited ER in our hospital each year

Figure 2

The partients extraction protocol

Figure 3

(a) Annual trend in the number of patients with hypoglycemia

The number of hypoglycemic patients increased toward 2010 and remained almost unchanged until 2013. Since 2014, it has started to decline. The number of patients with type 1 diabetes did not have a clear trend, but the number of patients with type 2 diabetes has markedly dropped since 2014.

blue; patients with Type 1 diabetes, red; patients with Type 2 diabetes, dark yellow; patients without diabetes

(b) Annual trends in the number of T2D patients with hypoglycemia in single agents.

Most patients who had hypoglycemia with a single drug were caused by SU or insulin, but some were caused by DPP4i.

All of BG, TZD, alpha-GI, glinide, SGLT2i, GLP-1 RA were not found in patients with hypoglycemia by single drug administration.

dark red; sulfonyl urea, orange; insulin, green; dipeptidyl peptidase-4 inhibitor

Figure 4

(a)Yearly trends in the number of hypoglycemia patients with type 2 diabetes and the share of each drug for a total of 5 years from the previous year to 4 years after the launch of DPP4i

Since the release of the DPP4i, it has been increasing and decreasing repeatedly. There was no apparent decrease in the number of hypoglycemia patients.

(b) Yearly trends in the value of the number of hypoglycemia patients with type 2 diabetes by the number of all patients who visited ER in our hospital each year and the share of each drug for a total of 5 years from the previous year to 4 years after the launch of DPP4i

Since the release of the DPP4i, it has been increasing and decreasing repeatedly. There was no apparent decrease in the number of hypoglycemia patients.

(c) Yearly trends in the number of hypoglycemia patients with type 2 diabetes and the share of each drug for a total of 5 years from the previous year to 4 years after the launch of SGLT2i

Since the release of the SGLT2i, the number of hypoglycemia patients were rapidly decreased.

(d) Yearly trends in the value of the number of hypoglycemia patients with type 2 diabetes by the number of all patients who visited ER in our hospital each year and the share of

each drug for a total of 5 years from the previous year to 4 years after the launch of SGLT2i

Since the release of the SGLT2i, it has been rapidly decreasing

blue; biguanide, orange; sulfonyl urea, gray; thiazolidinedione, yellow; alpha glucosidase inhibitor, sky-blue; glinide, green; dipeptidyl peptidase-4 inhibitor, navy blue; sodium-glucose cotransporter-2 inhibitor, red; insulin, black; glucagon like peptide-1 receptor agonist

purple bar; number of hypoglycemic patients with type 2 diabetes, light-green bar; value of the number of hypoglycemic patients with type 2 diabetes by the number of all patients who visited ER in our hospital each year

**Table legends**

Table 1

The baseline characteristics of participants.

Table 2

Medications in all patients with hypoglycemia from 2008 to 2019

BG; biguanide, SU; sulfonyl urea, TZD; thiazolidinedione, aGI; alpha glucosidase inhibitor, Glinide; fast-acting insulin secretagogue, DPP4i; dipeptidyl peptidase-4 inhibitor, SGLT2i; sodium-glucose cotransporter-2 inhibitor; GLP-1-RA; glucagon like peptide-1 receptor agonist

| | Total | Non-DM | T2D | T1D | Non-T2D |
|---|---|---|---|---|---|
| Number | 648 | 151 | 437 | 60 | 211 |
| Age | 72.9 ± 14.6 | 73.2 ± 17.1 | 75.7 ± 10.5 | 51.6 ± 15.6 | 67.1 ± 19.4 |
| Sex(M/F) | 392/256 | 109/42 | 253/184 | 30/30 | 139/72 |
| Plasma glucose concentration (mg/dL) | 34.1 ± 12.7 | 32.2 ± 16.4 | 34.6 ± 11.3 | 35.5 ± 11.5 | 33.1 ± 15.2 |
| eGFR (ml/min/1.73m$^2$) | 59.8 ± 34.6 | 66.8 ± 39.0 | 53.8 ± 30.2 | 77.4 ± 31.5 | 69.4 ± 37.5 |
| Glycated hemoglobin (mmol/mol) | | | 52.2 ± 14.1 | | |
| The number of hypoglycemic agents | | | 1.7 ± 0.8 | | |

Table 1

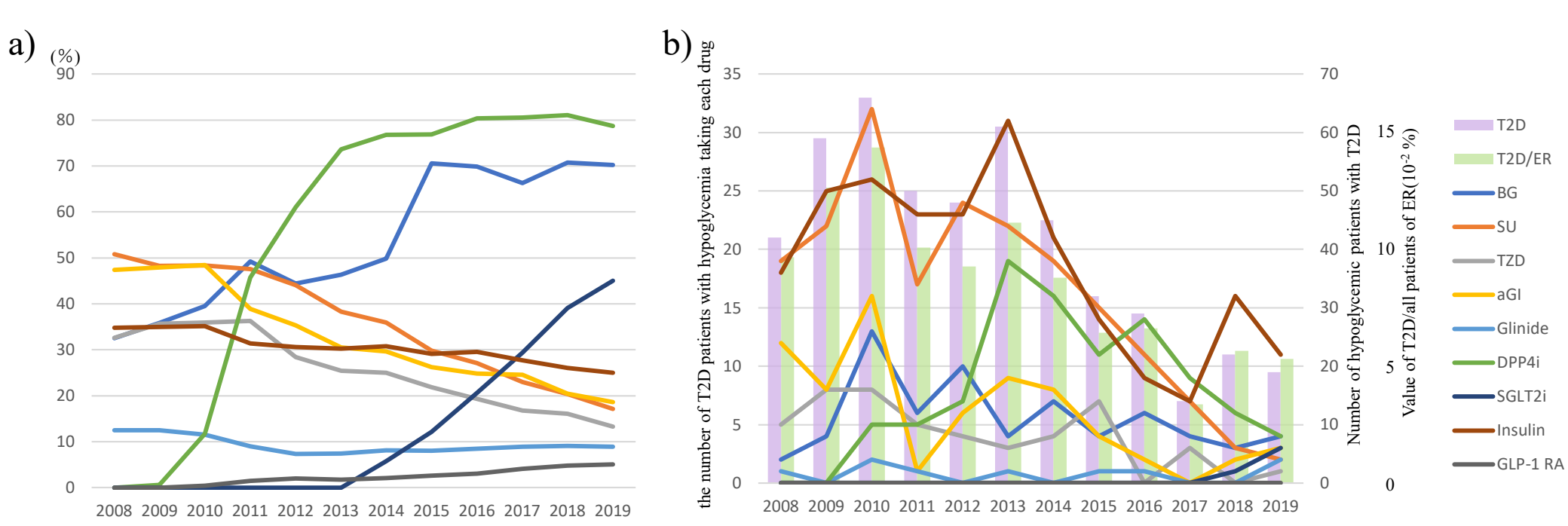
The baseline characteristics of participants.

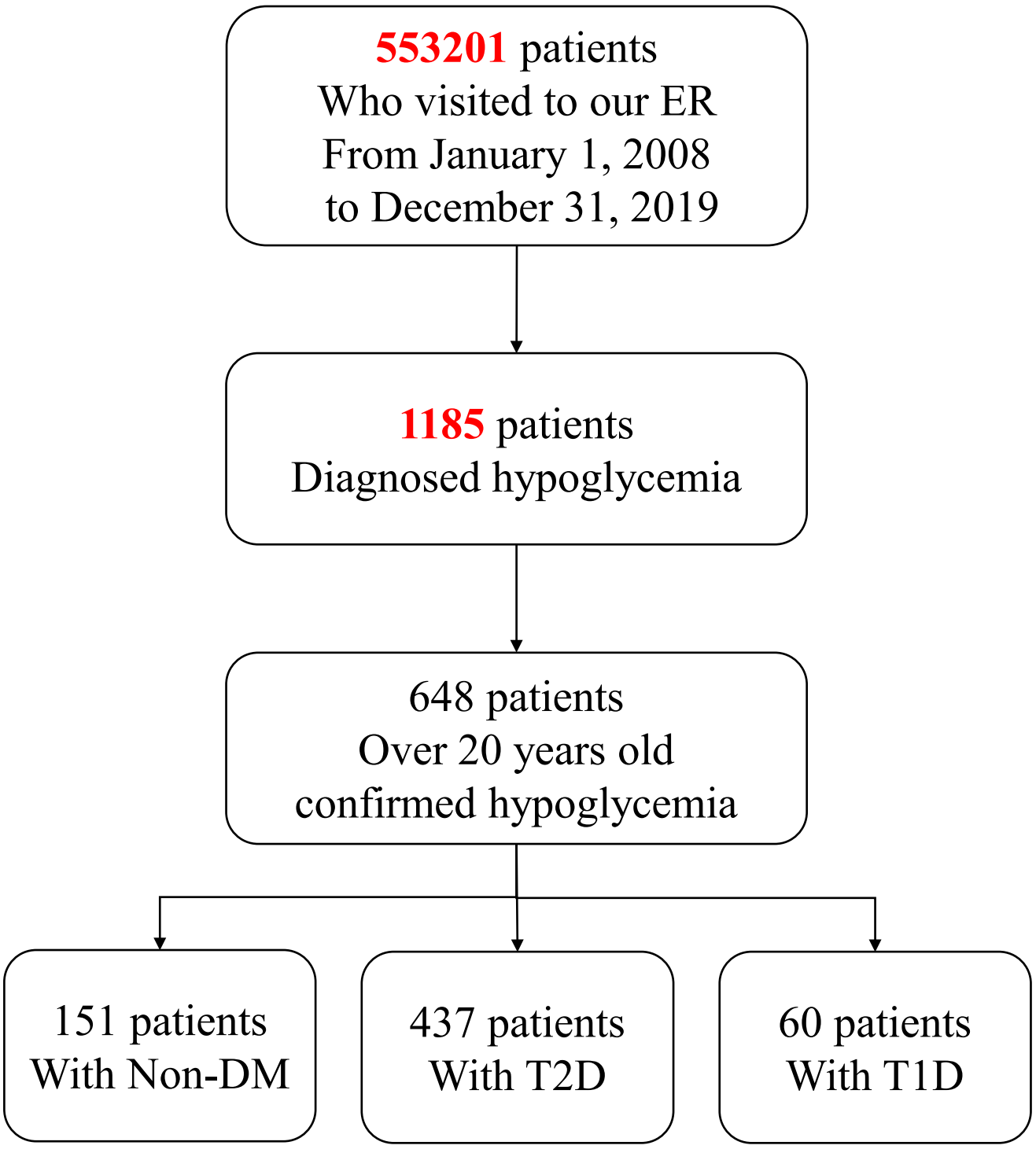
| | | Combination of medications | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Number | BG | SU | TZD | aGI | Glinide | DPP-4i | SGLT2i | Insulin | GLP-1RA |
| BG | 67 | - | 52 | 8 | 12 | 2 | 23 | 3 | 16 | 0 |
| SU | 194 | 52 | - | 37 | 55 | 2 | 56 | 0 | 14 | 1 |
| TZD | 48 | 8 | 37 | - | 10 | 1 | 5 | 0 | 13 | 0 |
| aGI | 71 | 12 | 55 | 10 | - | 4 | 8 | 0 | 17 | 0 |
| Glinide | 9 | 2 | 2 | 1 | 4 | - | 3 | 0 | 4 | 0 |
| DPP-4i | 97 | 23 | 56 | 5 | 8 | 3 | - | 1 | 41 | 1 |
| SGLT2i | 4 | 3 | 0 | 0 | 0 | 0 | 1 | - | 4 | 0 |
| Insulin | 225 | 16 | 14 | 13 | 17 | 4 | 41 | 4 | - | 1 |
| GLP-1RA | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | - |

Table 2

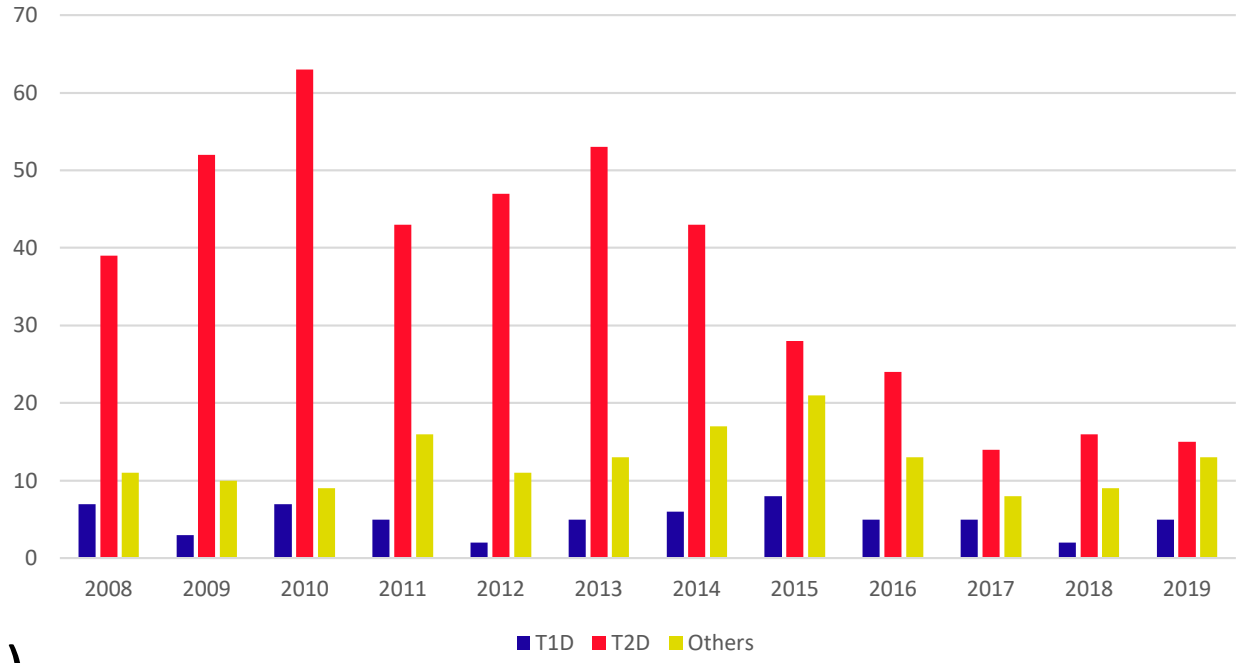
Medications in all patients with hypoglycemia from 2008 to 2019

BG; biguanide, SU; sulfonyl urea, TZD; thiazolidinedione, aGI; alpha glucosidase inhibitor, Glinide; fast-acting insulin secretagogue, DPP4i; dipeptidyl peptidase-4 inhibitor, SGLT2i; sodium-glucose cotransporter-2 inhibitor; GLP-1-RA; glucagon like peptide-1 receptor agonist


a)
(%)
90
80
70
60
50
40
30
20
10
0
2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019
b)
the number of T2D patients with hypoglycemia taking each drug
35
30
25
20
15
10
5
0
Number of hypoglycemic patients with T2D
70
60
50
40
30
20
10
0
Value of T2D/all patients of ER($10^{-2}$ %)
15
10
5
0
2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019
T2D
T2D/ER
BG
SU
TZD
aGI
Glinide
DPP4i
SGLT2i
Insulin
GLP-1 RA


553201 patients
Who visited to our ER
From January 1, 2008
to December 31, 2019
1185 patients
Diagnosed hypoglycemia
648 patients
Over 20 years old
confirmed hypoglycemia
151 patients
With Non-DM
437 patients
With T2D
60 patients
With T1D

a)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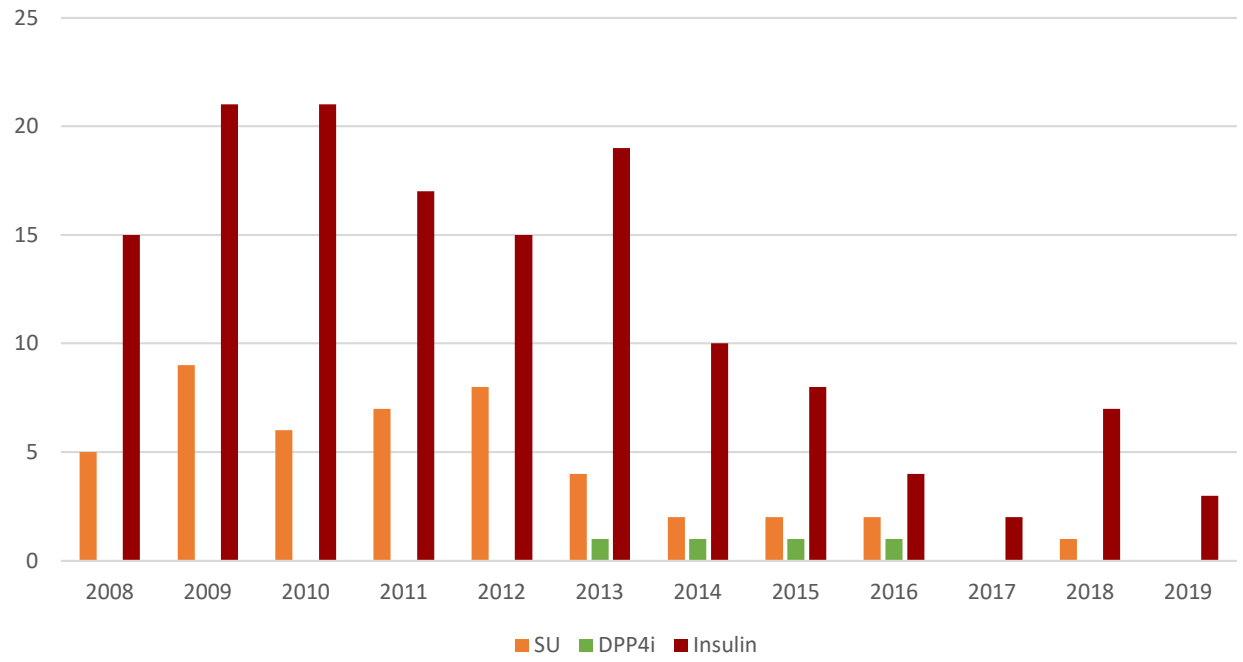
T1D
T2D
Others

b)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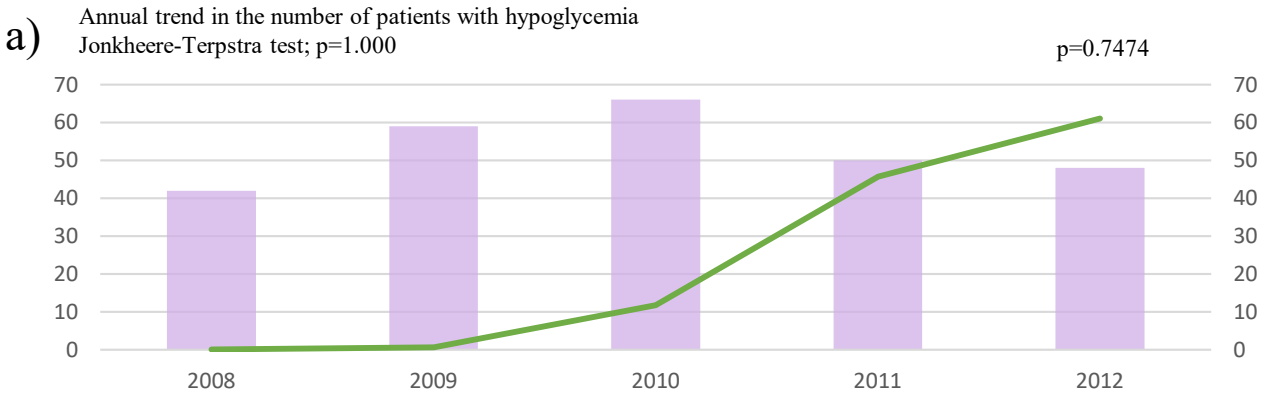
SU
DPP4i
Insulin

a)


Annual trend in the number of patients with hypoglycemia
Jonkheere-Terpstra test; p=1.000
p=0.7474
70
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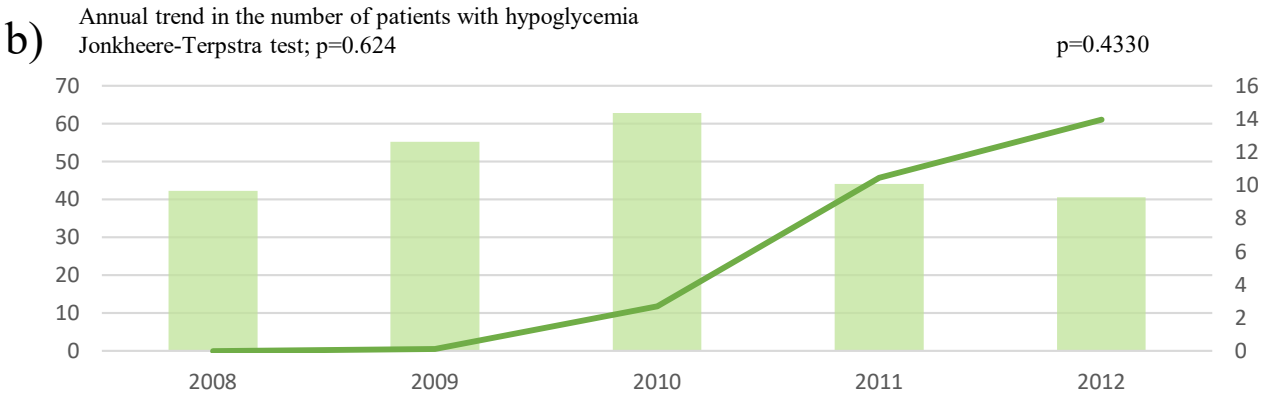
2012

b)


Annual trend in the number of patients with hypoglycemia
Jonkheere-Terpstra test; p=0.624
p=0.4330
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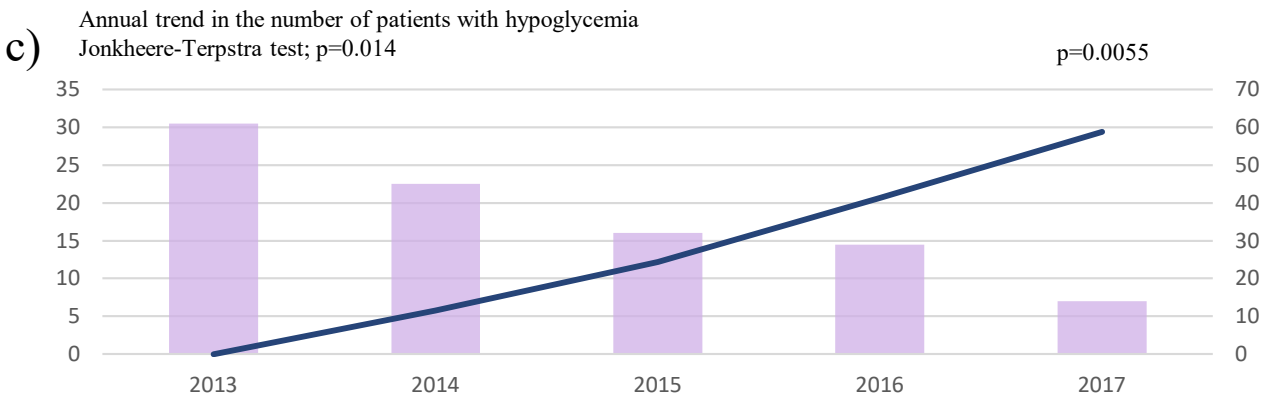
c)


Annual trend in the number of patients with hypoglycemia
Jonkheere-Terpstra test; p=0.014
p=0.0055
35
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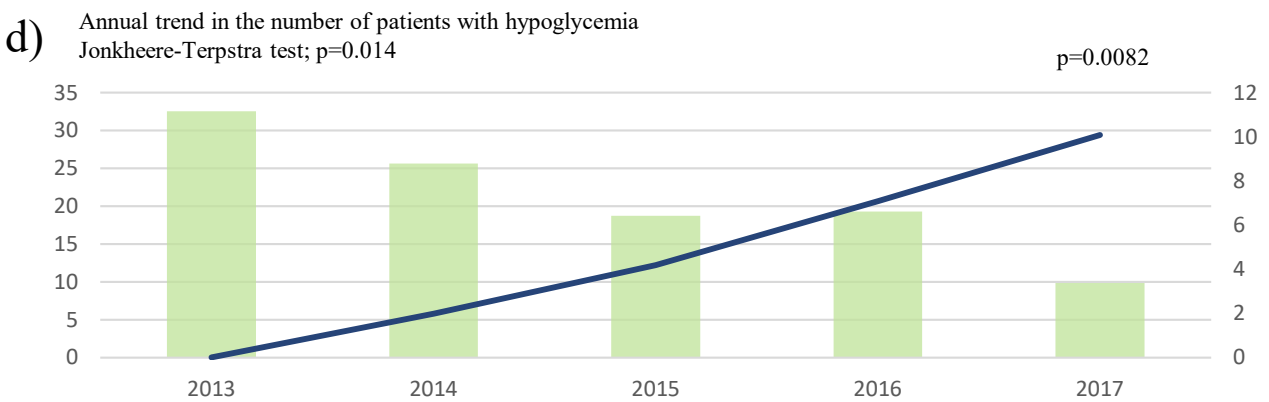
d)


Annual trend in the number of patients with hypoglycemia
Jonkheere-Terpstra test; p=0.014
p=0.0082
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