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Variation in hypoglycemia ascertainment and report in type 2 diabetes observational studies: a meta-epidemiological study

René Rodríguez-Gutiérrez,[1,2,3,4] Alejandro Salcido-Montenegro ,[4,5] José Gerardo González-González,[3,4] Rozalina G McCoy [1,6,7]

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RR-G and AS-M contributed equally.

RR-G and AS-M are joint first authors.

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For numbered affiliations see end of article.

Correspondence to
Dr Rozalina G McCoy;
mccoy.rozalina@mayo.edu

ABSTRACT

Introduction Observational studies constitute an important evidence base for hypoglycemia in diabetes management. This requires consistent and reliable ascertainment and reporting methodology, particularly in studies of type 2 diabetes where hypoglycemia risk is heterogeneous. Therefore, we aimed to examine the definitions of hypoglycemia used by observational studies of patients with type 2 diabetes.

Research design and methods We conducted a meta-epidemiological review of observational studies reporting on hypoglycemia or evaluating glucose-lowering medications in adults with type 2 diabetes. MEDLINE and Google Scholar were searched from January 1970 to May 2018. The definitions of non-severe, severe and nocturnal hypoglycemia were examined.

Results We reviewed 243 studies: 47.7% reported on non-severe hypoglycemia, 77.8% on severe hypoglycemia and 16.9% on nocturnal hypoglycemia; 5.8% did not specify. Among 116 studies reporting non-severe hypoglycemia, 18.1% provided no definition, 23.3% used glucose values, 38.8% relied on patient-reported symptoms, 17.2% accepted either glucose values or patient-reported symptoms and 2.6% relied on International Classification of Disease (ICD) codes. Among 189 studies reporting severe hypoglycemia, 11.1% provided no definition, 53.4% required symptoms needing assistance, 3.7% relied on glucose values, 14.8% relied on ICD codes, 2.6% relied on ICD codes or glucose values and 15.9% required both symptoms needing assistance and glucose values. Overall, 38.2% of non-severe and 67.7% of severe hypoglycemia definitions were consistent with the International Hypoglycemia Study Group.

Conclusions The marked heterogeneity in how hypoglycemia is defined in observational studies may contribute to the inadequate understanding and correction of hypoglycemia risk factors among patients with type 2 diabetes.

Significance of this study

What is already known about this subject?

- Since 2016, the International Hypoglycemia Study Group (IHSG) defined hypoglycemia severity levels and recommended their use for assessment and report in research studies.
- The definitions of hypoglycemia used by randomized clinical trials of diabetes therapies are still diverse and inconsistent.

What are the new findings?

- In the 243 observational studies of type 2 diabetes therapies reviewed, the hypoglycemia definitions reported were heterogeneous.
- More than half of the observational studies published after the IHSG hypoglycemia definition were compliant with their recommendations.
- Almost a fifth of the observational studies reporting hypoglycemia outcomes did not provide a specific definition for the event.

How might these results change the focus of research or clinical practice?

- Heterogeneity in hypoglycemia definitions hinders the comparison of observational studies.
- Using standardized hypoglycemia definition, ascertainment and reporting in observational studies could lead to a better comprehension of these events in a real-world setting, as well as supporting the development of better risk stratification and prevention strategies.

INTRODUCTION

Hypoglycemia is a serious and potentially preventable adverse event in diabetes management, leading to morbidity, impaired quality of life, high costs for patients and society, and death.[1–3] While hypoglycemia is more common among people with type 1 diabetes,[4–6] it also affects people with type 2 diabetes, particularly those with multiple or advanced comorbidities and those treated with insulin (including concentrated insulin) and/or insulin secretagogues.[7–11] Efforts to better understand hypoglycemia risk factors and develop interventions for those at highest risk are predicated on reliably, accurately and consistently identifying events as they occur. In epidemiologic assessments and in

research, such efforts have been hindered by the lack of standardized and universally used reporting parameters for clinically significant hypoglycemia.

The International Hypoglycemia Study Group (IHSG), on behalf of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), has defined level 1 hypoglycemia as any glucose value ≤70 mg/dL (3.9 mmol/L), level 2 hypoglycemia as glucose <54 mg/dL (3.0 mmol/L) and level 3 ('severe') hypoglycemia as any glucose value associated with severe cognitive impairment requiring external assistance for recovery.[12 13] Recognizing the importance of consistent and standardized reporting of hypoglycemia as an adverse event in diabetes management and data demonstrating marked variability in how hypoglycemia is described in clinical (ie, interventional) trials,[14] the IHSG recommended that level 2–3 hypoglycemia, but not level 1 hypoglycemia, be reported in such trials.[12 13] However, real-world data and observational studies also constitute an importance evidence base for clinical decision making.[15 16] This is particularly important for an outcome like hypoglycemia, the incidence of which is likely to be higher in real-world settings than in closely monitored trials that enroll narrowly defined, and often lower risk, populations. Standardization of hypoglycemia reporting is therefore equally, or even more, important in observational studies and those that rely on real-world data.

To contextualize the existing evidence base regarding hypoglycemia, we examined and summarized the definitions of hypoglycemia used in observational studies centered on patients with type 2 diabetes. We focused specifically on type 2 diabetes because the risk of hypoglycemia in this population is more heterogeneous and treatment-dependent and context-dependent than in type 1 diabetes.[7]

RESEARCH DESIGN AND METHODS

Data sources and selection

We conducted a meta-epidemiological review of the literature in MEDLINE and Google Scholar for observational studies published between January 1970 and May 2018. Our search strategy for the bibliographic databases combined terms for hypoglycemia, glucose-lowering drugs and observational studies of type 2 diabetes in adults and was limited to English language studies and full-length articles. The applied search terms were: 'Diabetes mellitus type 2', 'Hypoglycemia', 'Adverse event', 'Insulin', 'Sulfonylurea', 'Thiazolidinedione', 'Dipeptidyl peptidase 4 inhibitor', 'Glucagon-like peptide-1 receptor agonist', 'Sodium glucose cotransporter-2 inhibitor', as well as different combinations and associated Medical Subject Headings. Two researchers working independently screened papers for eligibility, with a third one resolving discrepancies. We selected observational (ie, not interventional) studies that reported hypoglycemic events or evaluated glucose-lowering drugs (any type of insulin, sulfonylurea, thiazolidinedione, dipeptidyl peptidase 4 inhibitor, glucagon-like peptide-1 receptor agonist and sodium glucose cotransporter-2 inhibitor) in adults with type 2 diabetes. We excluded studies that did not report on hypoglycemic events.

Data extraction

From a total of 243 observational studies,[17] two reviewers, working independently and in duplicate, reproducibly (kappa >0.6) extracted the exact definitions used to define non-severe (alternatively named mild/moderate), severe and nocturnal hypoglycemia. Severity of hypoglycemia was assigned on the basis of the definitions used in the reported studies. Unspecified hypoglycemia was defined as any reported hypoglycemic event without a clear definition of being non-severe, severe or nocturnal.

Statistical analysis

Data are presented as frequencies and percentages for categorical variables. Univariate between-group comparisons were performed using χ^2 tests for categorical and binary variables. P values ≤0.05 were considered statistically significant. IBM SPSS V.22.0 (SPSS, Inc, Amonk, New York, USA) was used to perform all analyses.

RESULTS

A total of 4862 research papers were retrieved from the databases search, with 1809 duplicates removed. After the title and abstract screening, 2182 studies did not meet the eligibility criteria and were eliminated. A total of 871 studies underwent full-text review, of which 628 were eliminated for not meeting eligibility criteria, mainly not reporting on hypoglycemia events (figure 1). A total of 243 studies were ultimately reviewed: 53 cross-sectional (21.8%), 99 prospective cohort (40.7%), two case–control (0.8%) and 89 retrospective cohort (36.6%). Overall, 47.7% (n=116) reported on non-severe hypoglycemia, 77.8% (n=189) reported on severe hypoglycemia and 16.9% (n=41) reported on nocturnal hypoglycemia. In 5.8% (n=14) of studies, hypoglycemia type was not specified (table 1). A total of 32 of the analyzed studies were published after November 2016 when IHGS recommendations on standardizing hypoglycemia definitions were published.[12 13] Overall, 38.2% of non-severe and 67.7% of severe hypoglycemia definitions were consistent with the IHSG recommendations. Among studies published before November 2016, 33.3% of studies reporting on non-severe hypoglycemia and 69.6% of studies reporting on severe hypoglycemia were consistent with what would be the IHSG recommendations. After IHSG recommendations were published, 62.5% and 54.1% of non-severe and severe hypoglycemia definitions were consistent with them.

Defining non-severe hypoglycemia

Among the 116 studies reporting non-severe hypoglycemia (table 2), 18.1% (n=21) did not provide a specific definition, stating only that hypoglycemia was 'mild',

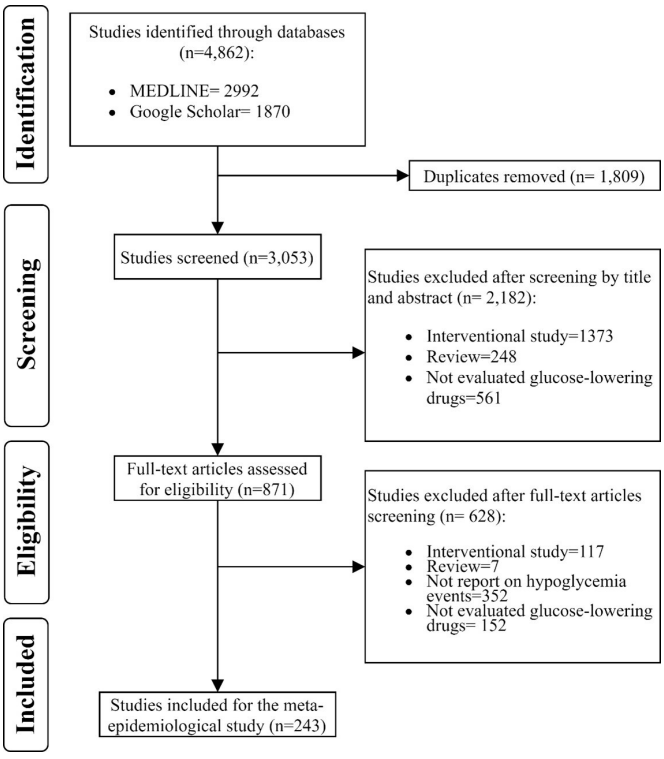

Figure 1 Flow chart of database research, screening and study selection.

'moderate' or 'not severe'; 23.3% (n=27) relied on a range of glucose values; 38.8% (n=45) relied on patient-reported symptoms alone; 17.2% (n=20) accepted either glucose values or patient-reported symptoms; and 2.6% (n=3) relied on International Classification of Disease (ICD) diagnosis codes for hypoglycemia.

Although 47 studies (40.5% of all studies reporting on non-severe hypoglycemia) relied on specific glucose ranges to define non-severe hypoglycemia, only 13.8% (n=16) and 1.7% (n=2) used glucose values consistent with ADA/EASD guidelines and IHSG definitions of level 1 (<3.9 mmol/L) and level 2 hypoglycemia (<3.0 mmol/L), respectively. Remaining studies used thresholds ranging between <50 mg/dL (<2.8 mmol/L) and <70 mg/dL (<3.9 mmol/L) (figure 2A). None of the studies defined hypoglycemia at glucose levels ≥70 mg/dL (3.9 mmol/L).

Severe hypoglycemia

Of the 189 studies reporting severe hypoglycemia (table 2), 11.1% (n=21) did not provide a specific definition for what was considered to be 'severe'; 53.4% (n=101) required symptoms requiring external or medical assistance, including some specifying need for emergency department (ED) care or hospitalization; 3.7% (n=7) relied on a range of glucose values only, without mention of symptoms; 14.8% (n=28) relied on ICD diagnosis codes only; 2.6% (n=2) relied on ICD diagnosis codes and/or glucose values; and 15.9% (n=30) required both symptoms requiring medical assistance and a specific glucose value. In the 30 studies that relied on ICD diagnosis codes, hypoglycemic events were deemed to be 'severe' if the hypoglycemia diagnosis code was present in encounters in the ED only (n=1); hospital only (n=4); ED or hospital (n=3); outpatient clinic only (n=1); or either ED, hospital or outpatient clinic (n=9). Remaining studies did not specify the setting where hypoglycemia diagnoses were ascertained (n=12). Moreover, the diagnosis codes could be in any position of the claim (n=1), primary or secondary position (n=6) or primary position only (n=2); in the vast majority of cases (n=21), the position was not specified. Only 10 of the studies that relied on ICD diagnosis codes used the validated Ginde algorithm for hypoglycemia ascertainment,[18] with the remainder using alternate code sets.

The 39 studies (20.6% of the 189 reporting on severe hypoglycemia) that included glucose values in their definition of severe hypoglycemia (figure 2B) did not have a consistent threshold for what glucose level constituted severe hypoglycemia. The most prevalent threshold was <50 mg/dL (2.8 mmol/L; n=15, 38.5%), followed by <55.8 mg/dL (3.1 mmol/L; 33.3%, n=13) but ranged between <72 mg/dL (4.0 mmol/L) and <36 mg/dL (2.0 mmol/L).

Nocturnal hypoglycemia

While 41 studies reported on nocturnal hypoglycemia, 41.5% (n=17) did not provide any definition for how these events were defined. In 53.7% (n=22) of the studies, nocturnal hypoglycemia was defined based on temporality without specification of symptom severity, for example: 'A nocturnal hypoglycemic event was defined as an individualized symptomatic event consistent with hypoglycemia that occurred while the patient was asleep, between bedtime (±after the evening insulin injection) and before getting up in the morning (±before morning determination of fasting plasma glucose and morning injection)'.[19 20] Blood glucose levels were required to confirm hypoglycemia in only 4.9% (n=2) of the studies.

CONCLUSIONS

Hypoglycemia is a common, serious, yet potentially preventable, adverse health outcome in the management of type 2 diabetes.[7–9] Hypoglycemia prevention is predicted on the ability to capture, track and evaluate events as they occur in real-world practice. In this meta-epidemiological review of observational studies of patients with type 2 diabetes, we found substantial heterogeneity in the definition, ascertainment and report of hypoglycemia, particularly for non-severe events.

Recognizing the importance of a uniform definition for hypoglycemia, on 21 November 2016, the IHSG proposed a taxonomy for non-severe (further subdivided into level 1 and level 2) and severe (level 3) hypoglycemia.[12 13] The IHSG further advised that all clinical trials of diabetes management report on level 2 and level 3 hypoglycemia, with an option to also report level 1 hypoglycemia.[12 13] However, observational (ie, non-randomized) studies are

Table 1 Study design, type of data source and treatment*

Type of hypoglycemia	Not defined (n=14)	Non-severe (n=40)	Severe (n=113)	Both (n=76)	Nocturnal† (n=41)	Total (n=243)
Study design						
Cross-sectional	0 (0)	15 (37.5)	18 (15.9)	20 (26.3)	8 (19.5)	53 (21.8)
Prospective cohort	5 (35.7)	14 (35.0)	38 (33.6)	42 (55.3)	31 (75.6)	99 (40.7)
Retrospective case–control	0 (0)	0 (0)	1 (0.9)	1 (1.3)	0 (0)	2 (0.8)
Retrospective cohort	9 (64.3)	11 (27.5)	56 (49.6)	13 (17.1)	2 (4.9)	89 (36.6)
Type of data source						
Administrative data	5 (35.7)	3 (7.5)	33 (29.2)	4 (5.3)	0 (0)	45 (18.5)
EHR	3 (21.4)	3 (7.5)	12 (10.6)	9 (11.8)	0 (0)	27 (11.1)
Interview	0 (0)	1 (2.5)	2 (1.8)	3 (3.9)	1 (2.4)	6 (2.5)
Registry	2 (14.3)	5 (12.5)	19 (16.8)	2 (2.6)	0 (0)	28 (11.5)
Study cohort	4 (28.6)	15 (37.5)	34 (30.1)	42 (55.3)	33 (80.5)	95 (39.1)
Survey	0 (0)	13 (32.5)	13 (11.5)	16 (21.1)	7 (17.1)	42 (17.3)
Type of treatment						
Not specified	7 (50)	10 (25.0)	42 (37.2)	17 (22.4)	3 (17.6)	76 (31.3)
Insulin	4 (28.6)	17 (42.5)	41 (36.3)	33 (43.4)	36 (87.8)	95 (39.1)
Sulfonylurea	0 (0)	1 (2.5)	7 (6.2)	9 (11.8)	0 (0)	17 (7)
Insulin+SU	1 (7.1)	2 (5.0)	10 (8.8)	3 (3.9)	0 (0)	16 (6.6)
Other (TZD, DPP-4, GLP1 and SGLT-2)	1 (7.1)	6 (15.0)	8 (7.1)	7 (9.2)	0 (0)	22 (9.1)
Insulin+other (TZD, DPP-4, GLP1 and SGLT-2)	1 (7.1)	2 (5.0)	3 (2.7)	3 (3.9)	2 (4.9)	9 (3.7)
SU+others (TZD, DPP-4, GLP1 and SGLT-2)	0 (0)	2 (5.0)	2 (1.8)	4 (5.3)	0 (0)	8 (3.3)

*Data are presented as number (percentage) unless specified otherwise.
†Studies that reported nocturnal hypoglycemia were the same studies that evaluated severe and/or non-severe episodes and therefore were not included in the statistical analysis.
DPP-4, dipeptidyl peptidase 4 inhibitor; EHR, electronic health record; GLP1, glucagon-like peptide 1 receptor agonist; SGLT-2, sodium glucose cotransporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.

an invaluable source of information on adverse events in real-world settings and as such it was critical to examine how hypoglycemia was defined in such studies. This is especially important for retrospective studies that rely on secondary analyses of existing data collected for other reasons, whether for clinical care or billing/administrative purposes. To our knowledge, this is the first study to systematically examine the definitions of non-severe and severe hypoglycemia used by observational studies that form the evidence base for hypoglycemia prevention

Table 2 Hypoglycemia definitions*

	Not defined (n=14)	Non-severe (n=116)	Severe (n=189)	Total (n=319)†
Hypoglycemia definition				
Not specific definition	14 (100)	21 (18.1)	21 (11.1)	56 (17.6)
Glucose only	–	27 (23.3)	7 (3.7)	34 (10.7)
Symptoms only	–	45 (38.8)	0 (0)	45 (14.1)
Symptoms requiring ED or health provider assistance	–	0 (0)	101 (53.4)	101 (31.7)
ICD codes only	–	3 (2.6)	28 (14.8)	31 (9.7)
Glucose and/or symptoms	–	20 (17.2)	30 (15.9)	41 (12.9)
Glucose and/or ICD codes	–	0 (0)	2 (1.1)	5 (1.6)

*Data are presented as number (percentage) unless specified otherwise.
†This denominator represents all the hypoglycemia definitions for non-severe or severe events across all the analyzed studies.
ED, emergency department; ICD, International Classification of Disease.

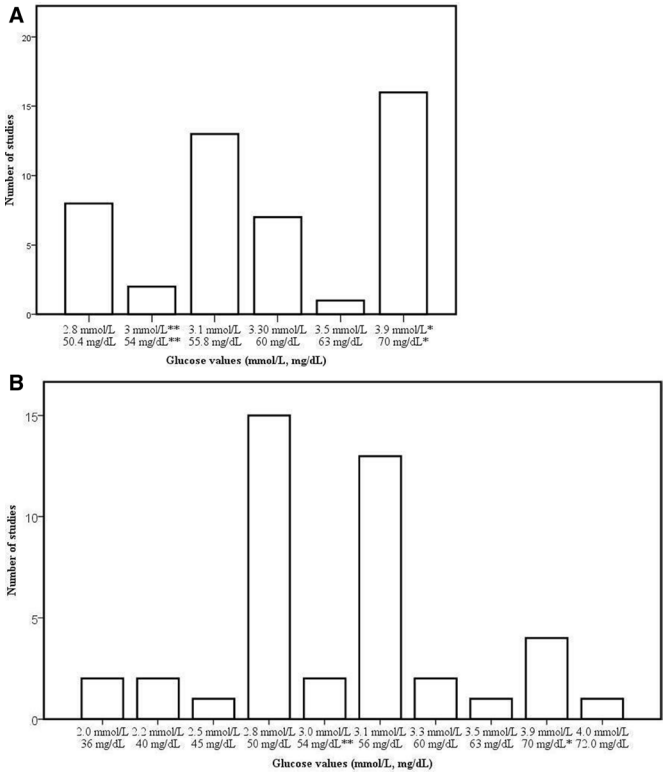

Figure 2 (A) Blood glucose cut-off values for non-severe hypoglycemia (mmol/L, mg/dL). (B) Blood glucose cut-off values for severe hypoglycemia (mmol/L, mg/dL). *The International Hypoglycemia Study Group (IHSG) level 1 of hypoglycemia definition. **IHSG level 2 of hypoglycemia definition. Figure part A shows the glucose values used by the analyzed studies to define non-severe hypoglycemia episodes. Figure part B shows the glucose values used by the analyzed studies to define severe hypoglycemia episodes.

among adults with type 2 diabetes. Although most of the recent studies tend to adhere to the IHSG recommendations, the hypoglycemia definitions remained inconsistent. Overall, almost a fifth of the studies provided no definition of hypoglycemia at all. An additional 17% were loosely adherent, as they relied on ICD diagnosis codes from clinical encounters and may be construed to indirectly imply need for medication attention. Such heterogeneity in hypoglycemia reporting hinders comparisons across studies and precludes generalizable inferences about the safety of diabetes management across populations and settings.

Our study builds on earlier work demonstrating heterogeneity in hypoglycemia definitions in randomized controlled trials (RCTs) of diabetes therapies.[14] Despite the IHSG recommendation, Balijepalli *et al*[14] found that 40% of RCTs included in the Canadian Agency for Drugs and Technologies in Health report for second-line and third-line therapies for type 2 diabetes either did not report on hypoglycemia or did not specify the definition of reported events. Of the 60% that reported and defined hypoglycemia, only 14% used the IHSG definition for level 1 hypoglycemia and 20.8% for level 2 hypoglycemia.[14] In contrast, our analyses that were restricted to the post-IHSG recommendation period found that hypoglycemia reporting in observational studies of type 2 diabetes was better, with 62.5% of studies on non-severe hypoglycemia and 54.1% of studies on severe hypoglycemia consistent with IHSG definitions. Nevertheless, substantial opportunity for improvement remains.

An important consideration for studies that leverage real-world data is how to optimally use administrative claims and electronic health records (EHRs) for large-scale hypoglycemia ascertainment and reporting. Doing so requires accurate and reliable identification of events, which in turn is predicated on patient's reliably reporting events, healthcare providers consistently and uniformly documenting them and such documentation to be available in a format amenable to large scale ascertainment. Our analysis included both prospective and retrospective observational studies, and both study designs demonstrated heterogeneity in how hypoglycemia is defined. However, while prospective studies can homogenize their approach to hypoglycemia ascertainment by adopting IHSG definitions, retrospective studies that rely on secondary analysis of data collected for other reasons (eg, billing or routine care) require that hypoglycemia be uniformly defined and documented across all settings and not just research.

In our analysis, 3 of 116 (2.6%) studies that reported on non-severe hypoglycemia and 30 of 189 (15.9%) studies that reported on severe hypoglycemia used ICD codes to identify events. Because the IHSG definition of non-severe hypoglycemia is predicated solely on glucose levels, diagnosis codes and claims data cannot be used to establish a corresponding definition. Severe hypoglycemia is characterized by the need for third party or medical assistance. It can be inferred that ED or hospital encounters for hypoglycemia represent acute severe events. However, ambulatory documentation of hypoglycemia may reflect prior events being discussed in the office, both severe and non-severe, and not convey the frequency or timing of those events relative to the encounter. Diagnosis codes from ED-based or hospital-based encounters are less likely to be misclassified, particularly if the hypoglycemia code is listed as the primary or principle diagnosis for the acute event. This is the approach used by the Centers for Disease Control and Prevention to quantify severe hypoglycemic events.[21] In contrast, many of the studies examined here did not specify the position of the hypoglycemia code in the encounter, what date range of claims was considered (ie, only from the date of hospital admission, only on the date of discharge or any day throughout the hospitalization) or even the setting(s) eligible for inclusion (ie, office evaluation and management visit, any ambulatory visit, ED visit, observation or inpatient hospital stay). Finally, there is heterogeneity in the specific ICD codes used to define hypoglycemia and whether studies relied on the Ginde algorithm,[18]

a modified version of the Ginde algorithm, or other codes entirely. Each of these parameters has the potential to alter event rates and study inferences. Nevertheless, it is important to note that up to 95% of severe hypoglycemic events do not culminate in an ED visit or hospitalization,[7 22 23] and as such, studies that rely solely on claims data greatly underestimate their frequency.

Many observational studies rely on events documented as part of routine care (eg, registries, EHR and claims), yet collecting data about hypoglycemia in the real-world is challenging. Patients rarely volunteer information about hypoglycemia to their clinicians,[24–28] and clinicians do not routinely screen their patients for hypoglycemia even when they are at risk for these events.[7 29] As a result, patient-reported hypoglycemia is not easily captured in clinical practice, despite its association with increased all-cause mortality and impaired quality of life.[30 31] Data from glucometers and continuous glucose monitors (CGMs), while valuable, is also not commonly available in the EHR, whether due to patients not using these devices (particularly in developing countries) or the inability of many practices, particularly in primary care, to consistently download device information into the EHR. Additionally, CGM use among patients with type 2 diabetes remains uncommon particularly when not treated with intensive insulin therapy.[32] Reliance on events that do come to medical attention, whether in the ambulatory setting, ED or hospital, will miss most events and patients who experience them. Thus, it is critical to raise awareness among clinicians, patients and policy makers about the importance of routine and standardized hypoglycemia ascertainment and documentation, in accordance with ADA guidelines.[33]

This study should be considered in the context of its limitations. We focused on observational studies conducted among patients with type 2 diabetes. A large number of studies were excluded from analysis because they did not specify diabetes type and thus included patients with both type 1 and type 2 diabetes, as reliable classification of diabetes is often challenging in real-world data sources (references 214–243 of the online supplemental material).[17] This contributed to the relatively small number of observational research studies analyzed. Our analyses included studies through May 2018, and hypoglycemia reporting may have improved over the past 2 years with greater attention and awareness paid to hypoglycemia by clinicians, professional societies and regulatory agencies. Nevertheless, our data point to the substantial gap in the quality of hypoglycemia ascertainment and reporting in research. This is confounded by persistent gaps in clinical hypoglycemia ascertainment[7] and ultimately may contribute to inadequate understanding and correction of hypoglycemia risk factors among patients with diabetes.

Observational studies and real-world data are an invaluable evidence base for comparative effectiveness and safety research that complement knowledge gleaned from interventional trials. They are particularly useful when studying adverse drug events such as hypoglycemia. The marked heterogeneity in how hypoglycemia is defined, documented and reported is a major barrier to assessing its prevalence, identifying highest risk subpopulations, promoting screening for and disclosure of events and developing prevention strategies. As such, this work reinforces the urgent need to promote, facilitate and use standardized ascertainment, documentation and reporting of hypoglycemia in observational studies and in the data sources that feed them. Using tools such as the IHSG hypoglycemia definitions in research studies could homogenize hypoglycemia reporting and evaluation. Furthermore, patients' education to recognize, report and manage hypoglycemia is a very important tool we can use right now to decrease mortality and morbidity. Ultimately, the ability to reliably study hypoglycemic events in real-world settings will support better risk stratification and prevention strategies aimed to stopping these common, harmful yet potentially preventable adverse events.

Author affiliations
[1]Knowledge and Evaluation Research Unit in Endocrinology, Mayo Clinic, Rochester, Minnesota, USA
[2]Division of Endocrinology, Diabetes, Metabolism and Nutrition, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA
[3]Endocrinology Division, Department of Internal Medicine, University Hospital "Dr. José E. González", Universidad Autonoma de Nuevo León, Monterrey, Nuevo León, México
[4]Plataforma INVEST Medicina UANL – KER Unit (KER Unit México), Subdirección de Investigación, Universidad Autónoma de Nuevo León, Monterrey, Nuevo León, México
[5]Department of Internal Medicine, University Hospital "Dr. José E. González", Universidad Autonoma de Nuevo Leon, Monterrey, Nuevo León, México
[6]Division of Community Internal Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA
[7]Division of Health Care Policy & Research, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA

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ORCID iDs
Alejandro Salcido-Montenegro http://orcid.org/0000-0002-2487-0241
Rozalina G McCoy http://orcid.org/0000-0002-2289-3183

REFERENCES

1 Zoungas S, Patel A, Chalmers J, *et al*. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410–8.
2 Bonds DE, Miller ME, Bergenstal RM, *et al*. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the Accord study. *BMJ* 2010;340:b4909.
3 Khunti K, Davies M, Majeed A, *et al*. Hypoglycemia and risk of cardiovascular disease and all-cause mortality in insulin-treated people with type 1 and type 2 diabetes: a cohort study. *Diabetes Care* 2015;38:316–22.
4 Zhong VW, Juhaeri J, Cole SR, *et al*. Incidence and trends in hypoglycemia hospitalization in adults with type 1 and type 2 diabetes in England, 1998-2013: a retrospective cohort study. *Diabetes Care* 2017;40:1651–60.
5 Donnelly LA, Morris AD, Frier BM, *et al*. Frequency and predictors of hypoglycaemia in type 1 and insulin-treated type 2 diabetes: a population-based study. *Diabet Med* 2005;22:749–55.
6 Ratzki-Leewing A, Harris SB, Mequanint S, *et al*. Real-world crude incidence of hypoglycemia in adults with diabetes: results of the InHypo-DM study, Canada. *BMJ Open Diabetes Res Care* 2018;6:e000503.
7 Silbert R, Salcido-Montenegro A, Rodriguez-Gutierrez R, *et al*. Hypoglycemia among patients with type 2 diabetes: epidemiology, risk factors, and prevention strategies. *Curr Diab Rep* 2018;18:53.
8 Karter AJ, Warton EM, Lipska KJ, *et al*. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. *JAMA Intern Med* 2017;177:1461–70.
9 Schroeder EB, Xu S, Goodrich GK, *et al*. Predicting the 6-month risk of severe hypoglycemia among adults with diabetes: development and external validation of a prediction model. *J Diabetes Complications* 2017;31:1158–63.
10 McCoy RG, Lipska KJ, Van Houten HK, *et al*. Association of cumulative multimorbidity, glycemic control, and medication use with Hypoglycemia-Related emergency department visits and hospitalizations among adults with diabetes. *JAMA Netw Open* 2020;3:e1919099.
11 Chatterjee S, Khunti K, Davies MJ. Achieving glycaemic control with concentrated insulin in patients with type 2 diabetes. *Drugs* 2019;79:173–86.
12 International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American diabetes association and the European association for the study of diabetes. *Diabetes Care* 2017;40:155–7.
13 International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/l (54 mg/dl) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 2017;60:3–6.
14 Balijepalli C, Druyts E, Siliman G, *et al*. Hypoglycemia: a review of definitions used in clinical trials evaluating antihyperglycemic drugs for diabetes. *Clin Epidemiol* 2017;9:291–6.
15 Kesselheim AS, Avorn J. New "21st Century Cures" Legislation: Speed and Ease vs Science. *JAMA* 2017;317:581–2.
16 21St century cures act. may 19, 2015. Available: https://docs.house.gov/meetings/IF/IF00/20150519/103516/BILLS-1146ih.pdf [Accessed 15 Dec 2019].
17 Rodriguez-Gutierrez R, Salcido-Montenegro A, González-González JG, *et al*. Data from variation in hypoglycemia ascertainment and report in type 2 diabetes observational studies: a meta-epidemiological study. Available: https://figshare.com/articles/online_resource/Hypoglycemia_definition_Supplementary_1_docx/12971921
18 Ginde AA, Blanc PG, Lieberman RM, *et al*. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord* 2008;8:86–92.
19 El Shiekh AR, Farrag HA, Ashour T, *et al*. Clinical safety of insulin detemir in patients with type 2 diabetes in the Gulf countries: the multicenter, noninterventional, open-label LevSafe study. *Indian J Endocrinol Metab* 2016;20:443–50.
20 Lüddeke H-J, Sreenan S, Aczel S, *et al*. PREDICTIVE- a global, prospective observational study to evaluate insulin detemir treatment in types 1 and 2 diabetes: baseline characteristics and predictors of hypoglycaemia from the European cohort. *Diabetes Obes Metab* 2007;9:428–34.
21 Centers of Disease Control and Prevention. United States diabetes surveillance system, division of diabetes translation, CDC. Available: https://gis.cdc.gov/grasp/diabetes/DiabetesAtlas.html [Accessed 15 Dec 2019].
22 Lipska KJ, Warton EM, Huang ES, *et al*. HbA1c and risk of severe hypoglycemia in type 2 diabetes: the diabetes and aging study. *Diabetes Care* 2013;36:3535–42.
23 Karter AJ, Moffet HH, Liu JY, *et al*. Surveillance of hypoglycemia-limitations of emergency department and hospital utilization data. *JAMA Intern Med* 2018;178:987–8.
24 Brož J, Brabec M, Janíčková Žďárská D, *et al*. Fear of driving license withdrawal in patients with insulin-treated diabetes mellitus negatively influences their decision to report severe hypoglycemic events to physicians. *Patient Prefer Adherence* 2015;9:1367–70.
25 Ohashi Y, Wolden ML, Hyllested-Winge J, *et al*. Diabetes management and daily functioning burden of non-severe hypoglycemia in Japanese people treated with insulin. *J Diabetes Investig* 2017;8:776–82.
26 Brod M, Rana A, Barnett AH. Impact of self-treated hypoglycaemia in type 2 diabetes: a multinational survey in patients and physicians. *Curr Med Res Opin* 2012;28:1947–58.
27 Emral R, Pathan F, Cortés CAY, *et al*. Self-reported hypoglycemia in insulin-treated patients with diabetes: results from an international survey on 7289 patients from nine countries. *Diabetes Res Clin Pract* 2017;134:17–28.
28 Levy JC, Davies MJ, Holman RR, *et al*. Continuous glucose monitoring detected hypoglycaemia in the treating to target in type 2 diabetes trial (4-T). *Diabetes Res Clin Pract* 2017;131:161–8.
29 Rodriguez-Gutierrez R, Salcido-Montenegro A, Singh-Ospina NM, *et al*. Documentation of hypoglycemia assessment among adults with diabetes during clinical encounters in primary care and endocrinology practices. *Endocrine* 2020;67:552–60.
30 McCoy RG, Van Houten HK, Ziegenfuss JY, *et al*. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care* 2012;35:1897–901.
31 McCoy RG, Van Houten HK, Ziegenfuss JY, *et al*. Self-report of hypoglycemia and health-related quality of life in patients with type 1 and type 2 diabetes. *Endocr Pract* 2013;19:792–9.
32 Petrie JR, Peters AL, Bergenstal RM, *et al*. Improving the clinical value and utility of CGM systems: issues and recommendations: a joint statement of the European association for the study of diabetes and the American diabetes association diabetes technology Working group. *Diabetes Care* 2017;40:1614–21.
33 American Diabetes Association. 2. Classification and Diagnosis of Diabetes: *Standards of Medical Care in Diabetes-2020*. *Diabetes Care* 2020;43:S61–70.

1. Nassar DT, Habib OS, Mansour AA. Predictors of hypoglycemia in insulin-treated patients with type 2 diabetes mellitus in Basrah. World J Diabetes. 2016;7(18):470.

2. Seufert J, Pegelow K, Bramlage P. Efficacy and safety of insulin glargine added to a fixed-dose combination of metformin and a dipeptidyl peptidase-4 inhibitor: Results of the GOLD observational study. Vasc Health Risk Manag. 2013;9(1):711–7.

3. Shin S, Kim H. The effect of sitagliptin on cardiovascular risk profile in Korean patients with type 2 diabetes mellitus: A retrospective cohort study. Ther Clin Risk Manag. 2016;12:435–44.

4. Birkeland KI, Jørgensen ME, Carstensen B, Persson F, Gulseth HL, Thuresson M, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. Lancet Diabetes Endocrinol. 2017;5(9):709–17.

5. Quah HMJ, Teo SHS, Yap HBG, Lim HB, Chow MH. Clinical audit on hypoglycaemic symptoms in type 2 diabetic patients in SingHealth Polyclinics. Proc Singapore Healthc. 2011;20(2):89–96.

6. Aloumanis K, Benroubi M, Sourmeli S, Drossinos V. Clinical outcomes and costs for patients with type 2 diabetes mellitus initiating insulin therapy in Greece: Two-year experience from the INSTIGATE study. Prim Care Diabetes. 2013;7(3):235–42.

7. Berntorp K, Haglund M, Larsen S, Petruckevitch A, Landin-Olsson M. Initiation of biphasic insulin aspart 30/70 in subjects with type 2 diabetes mellitus in a largely primary care-based setting in Sweden. Prim Care Diabetes. 2011;5(2):89–94.

8. Chen YJ, Yang CC, Huang LC, Chen L, Hwu CM. Increasing trend in emergency department visits for hypoglycemia from patients with type 2 diabetes mellitus in Taiwan. Prim Care Diabetes . 2015;9(6):490–6.

9. Cigrovski Berković M, Herman Mahečić D, Gradišer M, Bilić-Ćurčić I. Impact of health policy and practice on finding the best fit for patients with type 2 diabetes after metformin failure: Croatian pilot study. Prim Care Diabetes. 2017;11(3):265–72.

10. Bron M, Marynchenko M, Yang H, Yu AP, Wu EQ. Hypoglycemia, treatment discontinuation, and costs in patients with type 2 diabetes mellitus on oral antidiabetic drugs. Postgrad Med. 2012;124(1):124–32.

11. Digenio A, Karve S, Candrilli SD, Dalal M. Prandial insulin versus glucagon-like peptide-1 added to basal insulin: Comparative effectiveness in the community practice setting. Postgrad Med. 2014;126(6):49–59.

12. Lopez JMS, Bailey RA, Rupnow MFT. Demographic Disparities among Medicare Beneficiaries with Type 2 Diabetes Mellitus in 2011: Diabetes Prevalence, Comorbidities, and Hypoglycemia Events. Popul Health Manag. 2015;18(4):283–9.

13. Cobden D, Lee WC, Balu S, Joshi A V, Pashos CL. Health outcomes and economic impact of therapy conversion to a biphasic insulin analog pen among privately insured patients with type 2 diabetes mellitus. Pharmacotherapy [Internet]. 2007;27(7):948–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17594200

14. Besen DB, Surucu HA, Koşar C. Self-reported frequency, severity of, and awareness of hypoglycemia in type 2 diabetes patients in Turkey. PeerJ. 2016;2016(12):1–14.

15. Walz L, Pettersson B, Rosenqvist U, Deleskog A, Journath G, Wändell P. Impact of symptomatic hypoglycemia on medication adherence, patient satisfaction with treatment, and glycemic control in patients with type 2 diabetes. Patient Prefer Adherence. 2014;8:593–601.

16. Lopez JMS, Annunziata K, Bailey RA, Rupnow MFT, Morisky DE. Impact of hypoglycemia on patients with type 2 diabetes mellitus and their quality of life, work productivity, and medication adherence. Patient Prefer Adherence. 2014;8:683–92.

17. Miao R, Wei W, Baser O, Xie L. Real world outcomes of adding rapid-acting insulin versus switching to analog premix insulin among US patients with type 2 diabetes treated with insulin glargine. Patient Prefer Adherence. 2013;7:951–60.

18. Montilla S, Marchesini G, Sammarco A, Trotta MP, Siviero PD, Tomino C, et al. Drug utilization, safety, and effectiveness of exenatide, sitagliptin, and vildagliptin for type 2 diabetes in the real world: Data from the Italian AIFA Anti-diabetics Monitoring Registry. Nutr Metab Cardiovasc Dis. 2014;24(12):1346–53.

19. Luk AOY, Ho TST, Lau ESH, Ko GTC, Ozaki R, Tsang CC, et al. Association of self-reported recurrent mild hypoglycemia with incident cardiovascular disease and all-cause mortality in patients with type 2 diabetes Prospective analysis of the Joint Asia Diabetes Evaluation Registry. Med (United States). 2016;95(45):1–7.

20. Kim HM, Seong J-M, Kim J. Risk of hospitalization for hypoglycemia among older Korean people with diabetes mellitus. Medicine (Baltimore). 2016;95(42):e5016.

21. Mondal SK, Dasgupta S, Mondal S, Das N. Incidence of and risk factors for severe hypoglycaemia in treated type 2 diabetes mellitus patients in. Kathmandu Univ Med J. 2014;5(3):18–23.

22. Mehta HB, Mehta V, Goodwin JS. Association of Hypoglycemia with Subsequent Dementia in Older Patients with Type 2 Diabetes Mellitus. Journals Gerontol - Ser A Biol Sci Med Sci. 2017;72(8):1110–6.

23. Mahar SA, Hasan MI, Khan MIH, Fawwad A, Hussain S, Maheshwary N, et al. Comparison of hypoglycaemia episodes in people with type-2 diabetes fasting in Ramazan, Treated with vildaglipton or sulphonylurea: Results of the Pakistani cohort of the VIRTUE study. J Pak Med Assoc. 2014;64(11):1297–302.

24. Abbatecola AM, Bo M, Barbagallo M, Incalzi RA, Pilotto A, Bellelli G, et al. Severe Hypoglycemia Is Associated With Antidiabetic Oral Treatment Compared With Insulin Analogs in Nursing Home Patients With Type 2 Diabetes and Dementia: Results From the DIMORA Study. J Am Med Dir Assoc. 2015;16(4):349.e7-349.e12.

25. Pandya N, Wei W, Meyers JL, Kilpatrick BS, Davis KL. Burden of sliding scale insulin use in elderly long-term care residents with type 2 diabetes mellitus. J Am Geriatr Soc. 2013;61(12):2103–10.

26. Curkendall SM, Zhang B, Oh KS, Williams SA, Pollack MF, Graham J. States : Analysis of a Health Insurance Database. J Med Chem. 2011;18(10):455–62.

27. Raju A, Shetty S, Cai B, D'Souza AO. Hypoglycemia incidence rates and associated health care costs in patients with type 2 diabetes mellitus treated with second-line linagliptin or sulfonylurea after metformin monotherapy. J Manag Care Spec Pharm. 2016;22(5):483–92.

28. Lin CH, Sheu WHH. Hypoglycaemic episodes and risk of dementia in diabetes mellitus: 7-year follow-up study. J Intern Med. 2013;273(1):102–10.

29. Min JY, Griffin MR, Hung AM, Grijalva CG, Greevy RA, Liu X, et al. Comparative Effectiveness of Insulin versus Combination Sulfonylurea and Insulin: a Cohort Study of Veterans with Type 2 Diabetes. J Gen Intern Med. 2016;31(6):638–46.

30. Sarkar U, Karter AJ, Liu JY, Moffet HH, Adler NE, Schillinger D. Hypoglycemia is more common among type 2 diabetes patients with limited health literacy: The diabetes study of northern California (distance). J Gen Intern Med. 2010;25(9):962–8.

31. Qiao Q, Johnsson K, Grandy S, Kostev K. Treatment Outcomes and Tolerability Following Initiation of GLP-1 Receptor Agonists among Type 2 Diabetes Patients in Primary Care Practices in Germany. J Diabetes Sci Technol. 2017;11(2):272–7.

32. Gehlaut RR, Dogbey GY, Schwartz FL, Marling CR, Shubrook JH. Hypoglycemia in type 2 diabetes - More common than you think: A continuous glucose monitoring study. J Diabetes Sci Technol. 2015;9(5):999–1005.

33. Bo M, Gallo S, Zanocchi M, Maina P, Balcet L, Bonetto M, et al. Prevalence , Clinical Correlates , and Use of Glucose-Lowering Drugs among Older Patients with Type 2 Diabetes Living in Long-Term Care Facilities. J Diabetes Res. 2015;2015:2–7.

34. Sakane N, Kotani K, Tsuzaki K, Nishi M, Takahashi K, Murata T, et al. Fear of hypoglycemia and its determinants in insulin-treated patients with type 2 diabetes mellitus. J Diabetes Investig. 2015;6(5):567–70.

35. Kobuke K, Yoneda M, Nakanishi S, Ohno H, Maeda S, Egusa G. Efficacy and safety of insulin degludec in Japanese patients with type 1 and type 2 diabetes: 24-week results from the observational study in routine clinical practice. J Diabetes Investig. 2016;7(1):94–9.

36. Candrilli SD, Meyers JL, Boye K, Bae JP. Health care resource utilization and costs during episodes of care for type 2 diabetes mellitus-related comorbidities. J Diabetes Complications. 2015;29(4):529–33.

37. Murata GH, Duckworth WC, Shah JH, Wendel CS, Mohler MJ, Hoffman RM. Hypoglycemia in stable, insulin-treated veterans with type 2 diabetes: A prospective study of 1662 episodes. J Diabetes Complications. 2005;19(1):10–7.

38. Alemayehu B, Liu J, Rajpathak S, Engel SS. Healthcare resource use and associated costs of hypoglycemia in patients with type 2 diabetes prescribed sulfonylureas. J Diabetes Complications. 2017;31(11):1620–3.

39. Ross S, Dzida G, Ji Q, Kaiser M, Ligthelm R, Meneghini L, et al. Safety of once-daily insulin detemir in patients with type 2 diabetes treated with oral hypoglycemic agents in routine clinical practice. J Diabetes. 2014;6(3):243–50.

40. Fukuda M, Doi K, Sugawara M, Naka Y, Mochizuki K. Survey of Hypoglycemia in Elderly People With Type 2 Diabetes Mellitus in Japan. J Clin Med Res. 2015;7(12):967–78.

41. Davis TME, Brown SGA, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: The Fremantle diabetes study. J Clin Endocrinol Metab. 2010;95(5):2240–7.

42. Kumar S, Pathak AK, Saikia D, Kumar A. Efficacy, safety and treatment satisfaction of glimepiride vs sitagliptin in combination with metformin in type 2 diabetes mellitus. J Clin Diagnostic Res. 2015;9(12):FC07-FC10.

43. Rao P V., Bhattacharyya A, Sahay RK. Initiation of insulin aspart to Indian subjects on OADs show significant improvement in glycaemic outcomes: The A1chieve® observational study. J Assoc Physicians India. 2013;61(SPL. 1):21–3.

44. Sharma SK, Joshi SR, Kumar A, Unnikrishnan AG, Hoskote SS, Moharana AK, et al. Efficacy, safety and acceptability of biphasic insulin aspart 30 in Indian patients with type 2 diabetes: Results from the PRESENT study. J Assoc Physicians India. 2008;56(NOV.):859–63.

45. Prinz N, Ebner S, Grünerbel A, Henkelüdecke U, Hermanns N, Hummel M, et al. Female sex, young age, northern German residence, hypoglycemia and disabling diabetes complications are associated with depressed mood in the WHO-5 questionnaire – A multicenter DPV study among 17,563 adult patients with type 2 diabetes. J Affect Disord . 2017;208(October 2016):384–91.

46. McCoy RG, Lipska KJ, Yao X, Ross JS, Montori VM, Shah ND. Intensive treatment and severe hypoglycemia among adults with type 2 diabetes. JAMA Intern Med. 2016;176(7):969–78.

47. Karter AJ, Warton EM, Lipska KJ, Ralston JD, Moffet HH, Jackson GG, et al. Development and validation of a tool to identify patients with type 2 diabetes at high risk of hypoglycemia-related emergency department or hospital use. JAMA Intern Med. 2017;177(10):1461–70.

48. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus : the diabetes and aging study. JAMA Intern Med. 2014;174(2):251–8.

49. Whitmer RA, Karter AJ, Yaffe K, Quesenberry CPJ, Selby J V. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. JAMA. 2009;301(15):1565–72.

50. Landgraf R, Frank M, Bauer C, Leyck Dieken M. Prandial glucose regulation with repaglinide: its clinical and lifestyle impact in a large cohort of patients with Type 2 diabetes. Int J Obes. 2000;24:S38–44.

51. Gallwitz B, Kusterer K, Hildemann S, Fresenius K. Type II diabetes and its therapy in clinical practice - Results from the standardised non-interventional registry SIRTA. Int J Clin Pract. 2014;68(12):1442–53.

52. Almansari A, Khader S, Kharawagh A, Abdelfattah W, Badawy T. Safety and efficacy of biphasic insulin aspart 30 in type 2 diabetes patients switched from either biphasic or basal human insulin: Results from the Gulf cohort of the A1chieve study. Int J Clin Pract. 2014;68(7):850–6.

53. Valensi P, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al. Initiating insulin therapy with, or switching existing insulin therapy to, biphasic insulin aspart 30/70 (NovoMix® 30) in routine care: Safety and effectiveness in patients with type 2 diabetes in the IMPROVE™ observational study. Int J Clin Pract. 2009;63(3):522–31.

54. El-Naggar N, Almansari A, Khudada K, Salman S, Mariswamy N, Abdelfattah W, et al. The A1chieve study - An observational non-interventional study of patients with type 2 diabetes mellitus initiating or switched to insulin analogue therapy: Subgroup analysis of the Gulf population. Int J Clin Pract. 2013;67(2):128–38.

55. Al-Arouj M, Hassoun AAK, Medlej R, Pathan MF, Shaltout I, Chawla MS, et al. The effect of vildagliptin relative to sulphonylureas in Muslim patients with type 2 diabetes fasting during Ramadan: The VIRTUE study. Int J Clin Pract. 2013;67(10):957–63.

56. Shah S, Benroubi M, Borzi V, Gumprecht J, Kawamori R, Shaban J, et al. Safety and effectiveness of biphasic insulin aspart 30/70 (NovoMix ® 30) when switching from human premix insulin in patients with type 2 diabetes: Subgroup analysis from the 6-month IMPROVE™ observational study. Int J Clin Pract. 2009;63(4):574–82.

57. Delgado E. Outcomes with insulin glargine in patients with type 2 diabetes previously on NPH insulin: Evidence from clinical practice in Spain. Int J Clin Pract. 2012;66(3):281–8.

58. Munro N, Barnett AH. Incidence, worry and discussion about dosing irregularities and self-treated hypoglycaemia amongst HCPs and patients with type 2 diabetes: Results from the UK cohort of the Global Attitudes of Patient and Physicians (GAPP2) survey. Int J Clin Pract. 2014;68(6):692–9.

59. Gumprecht J, Benroubi M, Borzi V, Kawamori R, Shaban J, Shah S, et al. Intensification to biphasic insulin aspart 30/70 (BIAsp 30, NovoMix ® 30) can improve glycaemic control in patients treated with basal insulins: A subgroup analysis of the IMPROVE™ observational study. Int J Clin Pract. 2009;63(6):966–72.

60. Pĩrãgs V, El Damassy H, Dąbrowski M, Gönen MS, Račická E, Martinka E, et al. Low risk of severe hypoglycaemia in patients with type 2 diabetes mellitus starting insulin therapy with premixed insulin analogues BID in outpatient settings. Int J Clin Pract. 2012;66(11):1033–41.

61. Tada Y, Kanazawa I, Notsu M, Tanaka KI, Kiyohara N, Sasaki M, et al. Long-term efficacy and safety of sitagliptin in elderly patients with type 2 diabetes mellitus. Intern Med. 2016;55(10):1275–8.

62. Shriraam V, Mahadevan S, Anitharani M, Jagadeesh N, Kurup S, Vidya T, et al. Reported hypoglycemia in Type 2 diabetes mellitus patients: Prevalence and practices-a hospital-based study. Indian J Endocrinol Metab. 2017;21(1):148–53.

63. El Shiekh A, Farrag H, Ashour T, Alshali K, Abdelfattah W. Clinical safety of insulin detemir in patients with Type 2 diabetes in the Gulf countries: The multicenter, noninterventional, open-label LevSafe study. Indian J Endocrinol Metab. 2016;20(4):443–50.

64. Das AK, Kalra S, Akhtar S, Shetty R, Kumar A. Clinical experience of switching from biphasic human insulin to biphasic insulin aspart 30 in Indian patients with type 2 diabetes in the A 1 chieve study. Indian J Endocrinol Metab. 2015;19(1):110–5.

65. Rombopoulos G, Hatzikou M, Latsou D, Yfantopoulos J. The prevalence of hypoglycemia and its impact on the quality of life (QoL) of type 2 diabetes mellitus patients (The HYPO Study). Hormones. 2013;12(4):550–8.

66. Jermendy G, Erdesz D, Nagy L, Yin D, Phatak H, Karve S, et al. Outcomes of adding second hypoglycemic drug after metformin monotherapy failure among type 2 diabetes in Hungary. Health Qual Life Outcomes. 2008;6:1–8.

67. Stargardt T, Gonder-Frederick L, Krobot KJ, Alexander CM. Fear of hypoglycaemia: Defining a minimum clinically important difference in patients with type 2 diabetes. Health Qual Life Outcomes. 2009;7:1–8.

68. Tago M, Oyama JI, Sakamoto Y, Shiraki A, Uchida F, Chihara A, et al. Efficacy and safety of sitagliptin in elderly patients with type 2 diabetes mellitus. Geriatr Gerontol Int. 2018;18(4):631–9.

69. Doucet JA, Bauduceau B, Le Floch JP, Verny C. Medical treatments of elderly, French patients with type 2 diabetes: Results at inclusion in the GERODIAB Cohort. Fundam Clin Pharmacol. 2016;30(1):76–81.

70. Perriello G, Caputo S, De Pergola G, Di Carlo A, Grassi G, Lapolla A, et al. Improved glycemic control with weight loss and a low risk of hypoglycemia with insulin detemir: Insights from the Italian cohort of the PREDICTIVE study after 6-month observation in type 2 diabetic subjects. Expert Opin Pharmacother. 2011;12(16):2449–55.

71. Siegmund T, Weber S, Blankenfeld H, Oeffner A, Schumm-Draeger PM. Comparison of Insulin Glargine Versus NPH Insulin in People with Type 2 Diabetes Mellitus Under Outpatient-Clinic Conditions for 18 Months Using a Basal-Bolus Regimen with a Rapid-Acting Insuliun Analogue as Mealtime Insulin. Exp Clin Endocrinol Diabetes. 2007;115:349–53.

72. Echtay A, Andari E, Atallah P, Moufarrege R, Nemr R. I nsulin D etemir in C ombination with O ral A ntidiabetic D rugs I mproves G lycemic C ontrol in P ersons with T ype 2 D iabetes in N ear E ast C ountries : R esults from the L ebanese S ubgroup. Ethn Dis. 2017;27(1):45–55.

73. Ampudia-Blasco FJ, Galán M, Brod M. A cross-sectional survey among patients and prescribers on insulin dosing irregularities and impact of mild (self-treated) hypoglycemia episodes in Spanish patients with type 2 diabetes as compared to other European patients. Endocrinol y Nutr (English Ed. 2014;61(8):426–33.

74. DePablos-Velasco P, Salguero-Chaves E, Mata-Poyo J, DeRivas-Otero B, García-Sánchez R, Viguera-Ester P. Quality of life and satisfaction with treatment in subjects with type 2 diabetes: Results in Spain of the PANORAMA study. Endocrinol y Nutr (English Ed. 2014;61(1):18–26.

75. Sicras-Mainar A, Navarro-Artieda R, Morano R, Ruíz L. Use of healthcare resources and costs associated to the start of treatment with injectable drugs in patients with type 2 diabetes mellitus. Endocrinol y Nutr (English Ed. 2016;63(10):527–35.

76. Bell DSH, Yumuk V. Frequency of severe hypoglycemia in patients with non-insulin-dependent diabetes mellitus treated with sulfonylureas or insulin. Endocr Pract. 1997;3(5):281.

77. Delal MR, Xie L, Baser O, DiGenio A. Adding rapid-acting insulin or GLP-1 receptor agonist to basal insulin: outcomes in a community setting. Endocr Pract. 2015;21(1):68–76.

78. Mitchell BD, He X, Sturdy IM, Cagle AP, Settles JA. Glucagon prescription patterns in patients with eiter type 1 or 2 dibetes with newly prescribed insulin. Endocr Pract. 2016;22(2):123–35.

79. Davis SN, Wei W, Garg S. Clinical impact of initiating insulin glargine therapy with disposable pen versus vial in patients with type 2 diabetes mellitus in a managed care setting. Endocr Pract. 2011;17(6):845–52.

80. Patell R, Nigmatoulline D, Bena J, Kim DG, Messinger-Rapport B, Lansang MC. Hypeglycemia and Hypoglycemia in Patients with Diabetes in Skilled Nursing Facilities. Endocr Pract. 2017;23(4):458–65.

81. Sicras-Mainar A, Navarro-Artieda R. Use of metformin and vildagliptin fo treatment of type 2 diabetes in the elderly. Drug Des Devel Ther. 2014;8:811–7.

82. Odawara M, Kadowaki T, Naito Y. Incidence and predictors of hypoglycemia in Japanese patients with type 2 diabetes treated by insulin glargine and oral antidiabetic drugs in real-life: ALOHA post-marketing surveillance study sub-analysis. Diabetol Metab Syndr. 2014;6(1):6–7.

83. Tentolouris N, Kyriazopoulou V, Makrigiannis D, Baroutsou B. Intensification of insulin therapy in patients with type 2 diabetes: A retrospective non-interventional cohort study of patients treated with insulin glargine or biphasic human insulin in daily clinical practice. Diabetol Metab Syndr. 2013;5(1):1–8.

84. Heller SR, Choudhary P, Davies C, Emery C, Campbell MJ, Freeman J, et al. Risk of hypoglycaemia in types 1 and 2 diabetes: Effects of treatment modalities and their duration. Diabetologia. 2007;50(6):1140–7.

85. Mogensen UM, Andersson C, Fosbøl EL, Schramm TK, Vaag A, Scheller NM, et al. Sulfonylurea in combination with insulin is associated with increased mortality compared with a combination of insulin and metformin in a retrospective Danish nationwide study. Diabetologia. 2015;58(1):50–8.

86. Bonke FC, Donnachie E, Schneider A, Mehring M. Association of the average rate of change in HbA1c with severe adverse events: a longitudinal evaluation of audit data from the Bavarian Disease Management Program for patients with type 2 diabetes mellitus. Diabetologia. 2016;59(2):286–93.

87. Henderson JN, Allen K V, Dearyt IJ, Frier BM. Hypoglycaemia in insulin-treated Type 2 diabetes: frequency, symptoms and impaired awareness. Diabet Med. 2004;21(2):103–13.

88. Akram K, Pedersen-Bjergaard U, Carstensen B, Borch-Johnsen K, Thorsteinsson B. Frequency and risk factors of severe hypoglycaemia in insulin-treated Type 2 diabetes: a cross-sectional survey. Diabet Med. 2006;23(7):750–6.

89. Hajos TRS, Pouwer F, de Grooth R, Holleman F, Twisk JWR, Diamant M, et al. Initiation of insulin glargine in patients with Type2 diabetes in suboptimal glycaemic control positively impacts health-related quality of life. A prospective cohort study in primary care. Diabet Med. 2011;28(9):1096–102.

90. Quilliam BJ, Ozbay AB, Sill BE, Kogut SJ. The association between adherence to oral anti-diabetic drugs and hypoglycaemia in persons with Type 2 diabetes. Diabet Med. 2013;30(11):1305–13.

91. Jaap AJ, Jones GC, McCrimmon RJ, Deary IJ, Frier BM. Perceived symptoms of hypoglycaemia in elderly Type 2 diabetic patients treated with insulin. Diabet Med. 1998;15(5):398–401.

92. Wendel CS, Fotieo GG, Shah JH, Felicetta J, Curtis BH, Murata GH. Incidence of non-severe hypoglycaemia and intensity of treatment among veterans with Type 2 diabetes in the USA: A prospective observational study. Diabet Med. 2014;31(12):1524–31.

93. Aung PP, Strachan MWJ, Frier BM, Butcher I, Deary IJ, Price JF. Severe hypoglycaemia and late-life cognitive ability in older people with Type2 diabetes: The Edinburgh Type2 Diabetes Study. Diabet Med. 2012;29(3):328–36.

94. Luk AO, Li X, Zhang Y, Guo X, Jia W, Li W, et al. Quality of care in patients with diabetic kidney disease in Asia: The Joint Asia Diabetes Evaluation (JADE) Registry. Diabet Med. 2016;33(9):1230–9.

95. Müller N, Lehmann T, Gerste B, Adler JB, Kloos C, Hartmann M, et al. Increase in the incidence of severe hypoglycaemia in people with Type 2 diabetes in spite of new drugs: analysis based on health insurance data from Germany. Diabet Med. 2017;34(9):1212–8.

96. Holstein A, Plaschke A, Egberts EH. Lower incidence of severe hypoglycaemia in patients with type 2 diabetes treated with glimepiride versus glibenclamide. Diabetes Metab Res Rev. 2001;17(6):467–73.

97. Schloot NC, Haupt A, Schütt M, Nicolay C, Reaney M, Fink K, et al. Risk of severe hypoglycemia in sulfonylurea-treated patients from diabetes centers in Germany/Austria: How big is the problem? Which patients are at risk? Diabetes Metab Res Rev. 2016;32:316–24.

98. Verges B, Brun JM, Tawil C, Alexandre B, Kerlan V. Strategies for insulin initiation: insights from the French LIGHT observational study. Diabetes Metab Res Rev. 2012;28:97–105.

99. Meneghini LF, Rosenberg KH, Koenen C, Merilainen MJ, Lüddeke HJ. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: Clinical practice experience from a German subgroup of the PREDICTIVE st. Diabetes, Obes Metab. 2007;9(3):418–27.

100. Persson F, Nyström T, Jørgensen ME, Carstensen B, Gulseth HL, Thuresson M, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl

peptidase-4 inhibitor therapy: A multinational observational study. Diabetes, Obes Metab. 2018;20(2):344–51.

101. Rhoads GG, Dain MP, Zhang Q, Kennedy L. Two-year glycaemic control and healthcare expenditures following initiation of insulin glargine versus neutral protamine Hagedorn insulin in type 2 diabetes. Diabetes, Obes Metab. 2011;13:711–7.

102. Vexiau P, Mavros P, Krishnarajah G, Lyu R, Yin D. Hypoglycaemia in patients with type 2 diabetes treated with a combination of metformin and sulphonylurea therapy in France. Diabetes, Obes Metab. 2008;10(SUPPL.1):16–24.

103. Jang HC, Lee SR, Vaz JA. Biphasic insulin aspart 30 in the treatment of elderly patients with type 2 diabetes: A subgroup analysis of the PRESENT Korea NovoMix® study. Diabetes, Obes Metab. 2009;11(1):20–6.

104. Mauricio D, Meneghini L, Seufert J, Liao L, Wang H, Tong L, et al. Glycaemic control and hypoglycaemia burden in patients with type 2 diabetes initiating basal insulin in Europe and the USA. Diabetes, Obes Metab. 2017;19(8):1155–64.

105. Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. Diabetes, Obes Metab. 2012;14(7):634–43.

106. Marrett E, Stargardt T, Mavros P, Alexander CM. Patient-reported outcomes in a survey of patients treated with oral antihyperglycaemic medications: Associations with hypoglycaemia and weight gain. Diabetes, Obes Metab. 2009;11(12):1138–44.

107. Nyström T, Bodegard J, Nathanson D, Thuresson M, Norhammar A, Eriksson JW. Novel oral glucose-lowering drugs are associated with lower risk of all-cause mortality, cardiovascular events and severe hypoglycaemia compared with insulin in patients with type 2 diabetes. Diabetes, Obes Metab. 2017;19(6):831–41.

108. Conceição J, Dores J, Araújo F, Laires PA, Carr RD, Brodovicz K, et al. Severe hypoglycaemia among patients with type 2 diabetes requiring emergency hospital admission: The Hypoglycaemia In Portugal Observational Study–Emergency Room (HIPOS–ER). Diabetes, Obes Metab. 2018;20(1):50–9.

109. Khunti K, Caputo S, Damci T, Dzida GJ, Ji Q, Kaiser M, et al. The safety and efficacy of adding once-daily insulin detemir to oral hypoglycaemic agents in patients with type 2 diabetes in a clinical practice setting in 10 countries. Diabetes Obes Metab. 2011;14:1129–36.

110. Yee M, Siaw L, Ek D, Chew K, Dalan R, Abdul S, et al. Investigators from Tan Tock Seng Hospital Release New Data on Hypoglycemia (Evaluating the Effect of Ramadan Fasting on Muslim Patients with Diabetes in relation to Use of Medication and Lifestyle Patterns: A Prospective Study). Diabetes Week. 2014;2014:171.

111. Khattab M, Mahmoud K, Shaltout I. Effect of Vildagliptin Versus Sulfonylurea in Muslim Patients with Type 2 Diabetes Fasting During Ramadan in Egypt: Results from VIRTUE Study. Diabetes Ther. 2016;7(3):551–60.

112. Khamseh ME, Haddad J, Yang W, Zilov A, Bech OM, Hasan MI. Safety and effectiveness of biphasic insulin aspart 30 in different age-groups: A1chieve sub-analysis. Diabetes Ther. 2013;4(2):347–61.

113. Chen Y, Liu L, Gu L, Babineaux S, Colclough H, Curtis B. Glycemic Control in Chinese Patients with Type 2 Diabetes Mellitus Receiving Oral Antihyperglycemic Medication-Only or Insulin-Only Treatment: A Cross-Sectional Survey. Diabetes Ther. 2015;6(2):197–211.

114. Mulligan CM, Harper R, Harding J, Mcilwaine W, Petruckevitch A, McLaughlin DM. A retrospective audit of type 2 diabetes patients prescribed liraglutide in real-life clinical practice. Diabetes Ther. 2013;4(1):147–51.

115. Majanovic SK, Janez A, Lefterov I, Tasic S, Cikac T. The Real-Life Effectiveness and Care Patterns of Diabetes Management Study for Balkan Region (Slovenia, Croatia, Serbia, Bulgaria): A Multicenter, Observational, Cross-Sectional Study. Diabetes Ther. 2017;8(4):929–40.

116. Brod M, Galstyan G, Unnikrishnan AG, Harman-Boehm I, Prusty V, Lavalle F, et al. Self-Treated Hypoglycemia in Type 2 Diabetes Mellitus: Results from the Second Wave of an International Cross-Sectional Survey. Diabetes Ther. 2016;7(2):279–93.

117. Simon D, Detournay B, Eschwege E, Bouée S, Bringer J, Attali C, et al. Use of Vildagliptin in Management of Type 2 Diabetes: Effectiveness, Treatment Persistence and Safety from the 2-Year Real-Life VILDA Study. Diabetes Ther. 2014;5(1):207–24.

118. Balkau B, Charbonnel B, Penfornis A, Chraibi N, Lahouegue A, Faure C, et al. The Use of Saxagliptin in People with Type 2 Diabetes in France: The Diapazon Epidemiological Study. Diabetes Ther. 2017;8(5):1147–62.

119. Echtay A, Tsur A, Hasan MI, Abu-Hijleh MO, Khatib N Al, Andari E, et al. Clinical experience with insulin detemir in patients with type 2 diabetes from the near East Countries. Diabetes Ther. 2013;4(2):399–408.

120. Matsuba I, Sawa T, Kawata T, Kanamori A, Jiang D, Machimura H, et al. Cross-National Variation in Glycemic Control and Diabetes-Related Distress Among East Asian Patients Using Insulin: Results from the MOSAIc Study. Diabetes Ther. 2016;7(2):349–60.

121. Halimi S, Levy M, Huet D, Quéré S, Dejager S. Experience with vildagliptin in type 2 diabetic patients fasting during Ramadan in France: Insights from the VERDI study. Diabetes Ther. 2013;4(2):385–98.

122. Sicras-Mainar A, Navarro-Artieda R. Healthcare costs of the combination of metformin/dipeptidyl peptidase-4 inhibitors compared with metformin/other oral antidiabetes agents in patients with type 2 diabetes and metabolic syndrome. Diabetes Technol Ther. 2014;16(11):722–7.

123. Xie L, Zhou S, Pinsky BW, Buysman EK, Baser O. Impact of initiating insulin glargine disposable pen versus vial/syringe on real-world glycemic outcomes and persistence among patients with type 2 diabetes mellitus in a large managed care plan: A claims database analysis. Diabetes Technol Ther. 2014;16(9):567–75.

124. Guan X, Mu Y, Zhou X, Chen S, Dong J, Liao L. Efficacy and Safety of Insulin Therapy in Patients with Type 2 Diabetes Treated at Different Grades of Hospitals in China: Subgroup Analysis of the Real-World SEAS Study. Diabetes Technol Ther. 2017;19(1):34–40.

125. Ji L, Zhang P, Weng J, Lu J, Guo X, Jia W, et al. Observational Registry of Basal Insulin Treatment (ORBIT) in Patients with Type 2 Diabetes Uncontrolled by Oral Hypoglycemic Agents in China - Study Design and Baseline Characteristics. Diabetes Technol Ther. 2015;17(10):735–44.

126. Kesavadev J, Shankar A, Pillai PBS, Krishnan G, Jothydev S. Cost-effective use of telemedicine and self-monitoring of blood glucose via Diabetes Tele Management System (DTMS) to achieve target glycosylated hemoglobin values without serious symptomatic hypoglycemia in 1,000 subjects with type 2 diabetes mellitus - . Diabetes Technol Ther. 2012;14(9):772–6.

127. Pettersson B, Rosenqvist U, Deleskog A, Journath G, Wändell P. Self-reported experience of hypoglycemia among adults with type 2 diabetes mellitus (Exhype). Diabetes Res Clin Pract. 2011;92(1):19–25.

128. Murata GH, Duckworth WC, Shah JH, Wendel CS, Hoffman RM. Factors affecting hypoglycemia awareness in insulin-treated type 2 diabetes: The Diabetes Outcomes in Veterans Study (DOVES). Diabetes Res Clin Pract. 2004;65(1):61–7.

129. Nunes AP, Yang J, Radican L, Engel SS, Kurtyka K, Tunceli K, et al. Assessing occurrence of hypoglycemia and its severity from electronic health records of patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2016;121:192–203.

130. Bebakar WMW, Lim-Abrahan MA, Jain AB, Seah D, Soewondo P. Safety and effectiveness of insulin aspart in type 2 diabetic patients: Results from the ASEAN cohort of the A1chieve study. Diabetes Res Clin Pract. 2013;100(SUPPL.1):17–23.

131. Lim-Abrahan MA, Jain AB, Bebakar WMW, Seah D, Soewondo P. Safety and effectiveness of biphasic insulin aspart 30 in type 2 diabetes: Results from the ASEAN cohort of the A1chieve study. Diabetes Res Clin Pract. 2013;100(SUPPL.1):S3–9.

132. Chraibi A, Ajdi F, Belkhadir J, El Ansari N, Marouan F, Farouqi A. Safety and effectiveness of insulin analogues in Moroccan patients with type 2 diabetes: A sub-analysis of the A1chieve study. Diabetes Res Clin Pract. 2013;101(SUPPL.1):S27–36.

133. Prinz N, Stingl J, Dapp A, Denkinger MD, Fasching P, Jehle PM, et al. High rate of hypoglycemia in 6770 type 2 diabetes patients with comorbid dementia: A multicenter cohort study on 215,932 patients from the German/Austrian diabetes registry. Diabetes Res Clin Pract. 2016;112:73–81.

134 Almustafa M, Yeo JP, Khutsoane D. Glycaemic control and hypoglycaemia in the PRESENT study. Diabetes Res Clin Pract. 2008;81(SUPPL.1).

135. Reaney M, Cypryk K, Tentolouris N, Jecht M, Cleall S, Petzinger U, et al. Resource utilisation and clinical data before and after switching between short-acting human insulin and rapid-acting insulin analogues in patients with type 2 diabetes: The SWING study. Diabetes Res Clin Pract. 2012;97(2):231–41.

136. Soewondo P, Mohamed M, Jain AB, Sy RAG, Khoo CM. Safety and effectiveness of insulin detemir in type 2 diabetes: Results from the ASEAN cohort of the A1chieve study. Diabetes Res Clin Pract. 2013;100(SUPPL.1):S10–6.

137. Malek R, Arbouche Z, Dahaoui A, Bachaoui M. Safety and effectiveness of insulin analogues in type 2 diabetic patients from Algeria: A sub-analysis of the A1chieve study. Diabetes Res Clin Pract [Internet]. 2013;101(SUPPL.1):S15–26.

138. Shestakova M, Bech OM, Momani MS. Study design and baseline characteristics of patients in the PRESENT study. Diabetes Res Clin Pract. 2008;81(SUPPL.1):3–9.

139. Belhadj M, Dahaoui A, Jamoussi H, Farouqi A. Exploring insulin analogue safety and effectiveness in a Maghrebian cohort with type 2 diabetes: Results from the A1chieve study. Diabetes Res Clin Pract. 2013;101(SUPPL.1):S4–14.

140. Bourdel-Marchasson I, Druet C, Helmer C, Eschwege E, Lecomte P, Le-Goff M, et al. Correlates of health-related quality of life in French people with type 2 diabetes. Diabetes Res Clin Pract [Internet]. 2013;101(2):226–35.

141. Eriksson JW, Bodegard J, Nathanson D, Thuresson M, Nyström T, Norhammar A. Sulphonylurea compared to DPP-4 inhibitors in combination with metformin carries increased risk of severe hypoglycemia, cardiovascular events, and all-cause mortality. Diabetes Res Clin Pract. 2016;117:39–47.

142. Soewondo P, Kshanti IA, Pramono RB, Langi YA, Dalem-Pemayun TG. Clinical experience with insulin detemir: Results from the Indonesian cohort of the international A1chieve study. Diabetes Res Clin Pract. 2013;100(SUPPL.1):S47–53.

143. Schopman JE, Geddes J, Frier BM. Prevalence of impaired awareness of hypoglycaemia and frequency of hypoglycaemia in insulin-treated Type 2 diabetes. Diabetes Res Clin Pract. 2010;87(1):64–8.

144. Pilemann-Lyberg S, Thorsteinsson B, Snorgaard O, Zander M, Vestergaard H, Røder ME. Severe hypoglycaemia during treatment with sulphonylureas in patients with type 2 diabetes in the Capital Region of Denmark. Diabetes Res Clin Pract. 2015;110(2):202–7.

145. Solomon MD, Vijan S, Forma FM, Conrad RM, Summers NT, Lakdawalla DN. The impact of insulin type on severe hypoglycaemia events requiring inpatient and emergency department care in patients with type 2 diabetes. Diabetes Res Clin Pract. 2013;102(3):175–82.

146. Chin SO, Rhee SY, Chon S, Baik SH, Park Y, Nam MS, et al. Hypoglycemia is associated with dementia in elderly patients with type 2 diabetes mellitus: An analysis based on the Korea National Diabetes Program Cohort. Diabetes Res Clin Pract. 2016;122:54–61.

147. El Naggar NK, Soewondo P, Khamseh ME, Chen JW, Haddad J. Switching from biphasic human insulin 30 to biphasic insulin aspart 30 in type 2 diabetes is associated with improved glycaemic control and a positive safety profile: Results from the A1chieve study. Diabetes Res Clin Pract. 2012;98(3):408–13.

148. Sugarman JR. Hypoglycemia associated hospitalizations in a population with a high prevalence of non-insulin-dependent diabetes mellitus. Diabetes Re. 1991;14:139–48.

149. Nunes A, Iglay K, Radican L, Engel SS, Yang J, Doherty MC, et al. Hypoglycaemia seriousness and weight gain as determinants of cardiovascular disease outcomes among sulfonylurea ussers. Diabetes Obes Metab. 2017;19:1425–35.

150. Zhao Y, Campbell CR, Fonseca V, Shi L. Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. Diabetes Care. 2012;35(5):1126–32.

151. Feinkohl I, Aung PP, Keller M, Robertson CM, Morling JR, McLachlan S, et al. Severe hypoglycemia and cognitive decline in older people with type 2 diabetes: The edinburgh type 2 diabetes study. Diabetes Care. 2014;37(2):507–15.

152. Punthakee Z, Miller ME, Launer LJ, Williamson JD, Lazar RM, Cukierman-Yaffee T, et al. Poor cognitive function and risk of severe hypoglycemia in type 2 diabetes: Post hoc epidemiologic analysis of the ACCORD trial. Diabetes Care. 2012;35(4):787–93.

153. Lipska KJ, Yao X, Herrin J, McCoy RG, Ross JS, Steinman MA, et al. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006-2013. Diabetes Care. 2017;40(4):468–75.

154. Bedenis R, Price AH, Robertson CM, Morling JR, Frier BM, Strachan MWJ, et al. Association between severe hypoglycemia, adverse macrovascular events, and inflammation in the Edinburgh type 2 diabetes study. Diabetes Care. 2014;37(12):3301–8.

155. Yun JS, Kim JH, Song KH, Ahn YB, Yoon KH, Yoo KD, et al. Cardiovascular autonomic dysfunction predicts severe hypoglycemia in patients with type 2 diabetes: A 10-year follow-up study. Diabetes Care. 2014;37(1):235–41.

156. Douros A, Yin H, Yu OHY, Filion KB, Azoulay L, Suissa S. Pharmacologic differences of sulfonylureas and the risk of adverse cardiovascular and hypoglycemic events. Diabetes Care. 2017;40(11):1506–13.

157. Davis WA, Bruce DG, Davis TM. Is self-monitoring of blood glucose appropriate for all type 2 diabetic patients? The Fremantle Diabetes Study. Diabetes Care. 2006;29(8):1764–70.

158. Lipska KJ, Warton EM, Huang ES, Moffet HH, Inzucchi SE, Krumholz HM, et al. HbA1c and risk of severe hypoglycemia in type 2 diabetes : the diabetes and aging study. Diabetes Care. 2013;36(11):3535–42.

159. Salti I, Bénard E, Detournay B, Bianchi-Biscay M, Le Brigand C, Voinet C, et al. A population-based study of diabetes and its characteristics during the fasting month of ramadan in 13 countries: Results of the epidemiology of diabetes and ramadan 1422/2001 (EPIDIAR) study. Diabetes Care. 2004;27(10):2306–11.

160. Hsu PF, Sung SH, Cheng HM, Yeh JS, Liu WL, Chan WL, et al. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: A nationwide population-based study. Diabetes Care. 2013;36(4):894–900.

161. Johnston SS, Conner C, Aagren M, Smith DM, Bouchard J, Brett J. Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with type 2 diabetes. Diabetes Care. 2011;34(5):1164–70.

162. Bajaj HS, Venn K, Ye C, Patrick A, Kalra S, Khandwala H, et al. Lowest glucose variability and hypoglycemia are observed with the combination of a GLP-1 receptor agonist and basal insulin (VARIATION Study). Diabetes Care. 2017;40(2):194–200.

163. Bodmer, M., Meier, C., Jick, S., Meier, C.R., Krahenbuhl S. Antidiabetes Drugs and the Risk of Lactic Acidosis or Hypoglycemia. Diabetes Care [Internet]. 2008;31(11):p2086-91.

164. Tschöpe D, Bramlage P, Schneider S, Gitt AK. Incidence, characteristics and impact of hypoglycaemia in patients receiving intensified treatment for inadequately controlled type 2 diabetes mellitus. Diabetes Vasc Dis Res. 2016;13(1):2–12.

165. Penfornis A, Bourdel-Marchasson I, Quere S, Dejager S. Real-life comparison of DPP4-inhibitors with conventional oral antidiabetics as add-on therapy to metformin in elderly patients with type 2 diabetes: The HYPOCRAS study. Diabetes Metab. 2012;38(6):550–7.

166. Valensi P, de Pouvourville G, Benard N, Chanut-Vogel C, Kempf C, Eymard E, et al. Treatment maintenance duration of dual therapy with metformin and sitagliptin in type 2 diabetes: The ODYSSEE observational study. Diabetes Metab. 2015;41(3):231–8.

167. Tanaka S, Kawasaki R, Tanaka-Mizuno S, Iimuro S, Matsunaga S, Moriya T, et al. Severe hypoglycaemia is a major predictor of incident diabetic retinopathy in Japanese patients with type 2 diabetes. Diabetes Metab. 2017;43(5):424–9.

168. Maggi S, Noale M, Pilotto A, Tiengo A, Cavallo Perin P, Crepaldi G. The METABOLIC Study: Multidimensional assessment of health and functional status in older patients with type 2 diabetes taking oral antidiabetic treatment. Diabetes Metab. 2013;39(3):236–

169. Pornet C, Bourdel-Marchasson I, Lecomte P, Eschwège E, Romon I, Fosse S, et al. Évolution de 2001 à 2007 de la qualité des soins reçue par les personnes âgées atteintes de diabète de type 2 (études Entred) renforcer sécurité et qualité. Diabetes Metab. 2011;37(2):152–61.

170. Buysschaert M, Preumont V, Oriot PR, Paris I, Ponchon M, Scarnière D, et al. Évolution Métabolique Après Un an De Patients Diabétiques De Type 2 Traités Par Exénatide Et Suivis En Routine Clinique. Diabetes Metab. 2010;36(5):381–8.

171. Bordier L, Buysschaert M, Bauduceau B, Doucet J, Verny C, Lassmann Vague V, et al. Predicting factors of hypoglycaemia in elderly type 2 diabetes patients: Contributions of the GERODIAB study. Diabetes Metab. 2015;41(4):301–3.

172. Chandrakumar A, Vikas P V., Tharakan PG, Aravind C. Prevalence of hypoglycemia among diabetic old age home residents in South India. Diabetes Metab Syndr Clin Res Rev. 2016;10(1):S144–6.

173. Cha SA, Yun JS, Lim TS, Hwang S, Yim EJ, Song KH, et al. Severe Hypoglycemia and Cardiovascular or All-Cause Mortality in Patients with Type 2 Diabetes. Diabetes Metab J. 2016;6087:202–10.

174. Aravind SR, Tayeb K Al, Ismail SB, Shehadeh N, Kaddaha G, Liu R, et al. Hypoglycaemia in sulphonylurea-treated subjects with type 2 diabetes undergoing Ramadan fasting: A five-country observational study. Curr Med Res Opin. 2011;27(6):1237–42.

175. Nobels F, D'Hooge D, Crenier L. Switching to biphasic insulin aspart 30/50/70 from biphasic human insulin 30/50 in patients with type 2 diabetes in normal clinical practice: Observational study results. Curr Med Res Opin. 2012;28(6):1017–26.

176. Oguz A, Benroubi M, Brismar K, Melo P, Morar C, Cleall SP, et al. Clinical outcomes after 24 months of insulin therapy in patients with type 2 diabetes in five countries: Results from the TREAT study. Curr Med Res Opin. 2013;29(8):911–20.

177. Dalal MR, Kazemi MR, Ye F. Hypoglycemia in patients with type 2 diabetes newly initiated on basal insulin in the US in a community setting: impact on treatment discontinuation and hospitalization. Curr Med Res Opin. 2017;33(2):209–14.

178. Shestakova M, Sharma SK, Almustafa M, Min KW, Ayad N, Azar ST, et al. Transferring type 2 diabetes patients with uncontrolled glycaemia from biphasic human insulin to biphasic insulin aspart 30: Experiences from the PRESENT study. Curr Med Res Opin. 2007;23(12):3209–14.

179. Davis KL, Tangirala M, Meyers JL, Wei W. Real-world comparative outcomes of US type 2 diabetes patients initiating analog basal insulin therapy. Curr Med Res Opin. 2013;29(9):1083–91.

180. Ayvaz G, Keskin L, Akin TF, Dokmetas HS, Tasan E, Ar IB, et al. Real-life safety and efficacy of vildagliptin as add-on to metformin in patients with type 2 diabetes in Turkey - GALATA study. Curr Med Res Opin. 2015;31(4):623–32.

181. Rombopoulos G, Panitti E, Varounis C, Katsinas C, Stefanidis I, Goumenos D. A multicenter, epidemiological study of the treatment patterns, comorbidities and hypoglycemia events of patients with type 2 diabetes and moderate or severe chronic kidney disease - The LEARN study. Curr Med Res Opin. 2016;32(5):939–47.

182. Brod M, Rana A, Barnett AH. Impact of self-treated hypoglycaemia in type 2 diabetes: a multinational survey in patients and physicians. Curr Med Res Opin. 2012;28(12):1947–58.

183. Shelbaya S, Rakha S. Effectiveness and safety of vildagliptin and vildagliptin add-on to metformin in real-world settings in Egypt–results from the GUARD study. Curr Med Res Opin. 2017;33(5):797–801.

184. Nisa L, Giger R. Practice Clinical images - Lingua plicata. Cmaj. 2012;184(3):2012.

185. Baser O, Tangirala K, Wei W, Xie L. Real-world outcomes of initiating insulin glargine-based treatment versus premixed analog insulins among US patients with type 2 diabetes failing oral antidiabetic drugs. Clin Outcomes Res. 2013;5(1):497–505.

186. Lopez JMS, Bailey RA, Rupnow MFT, Annunziata K. Characterization of type 2 diabetes mellitus burden by age and ethnic groups based on a nationwide survey. Clin Ther. 2014;36(4):494–506.

187. Davis KL, Wei W, Meyers JL, Kilpatrick BS, Pandya N. Use of basal insulin and the associated clinical outcomes among elderly nursing home residents with type 2 diabetes mellitus: A retrospective chart review study. Clin Interv Aging. 2014;9:1815–22.

188. De Pablos-Velasco P, Parhofer KG, Bradley C, Eschwège E, Gönder-Frederick L, Maheux P, et al. Current level of glycaemic control and its associated factors in patients with type 2 diabetes across Europe: Data from the PANORAMA study. Clin Endocrinol (Oxf). 2014;80(1):47–56.

189. Svensson A-M, Miftaraj M, Franzén S, Eliasson B. Clinical effects, cardiovascular and renal outcomes associated with rapid-acting insulin analogs among individuals with type 2 diabetes: a nation-wide observational cohort study. Clin Diabetes Endocrinol. 2017;3(1):1–8.

190. Gitt AK, Bramlage P, Schneider S, Tschöpe D. A real world comparison of sulfonylurea and insulin vs. incretin-based treatments in patients not controlled on prior metformin monotherapy. Cardiovasc Diabetol. 2015;14(1):1–8.

191. Rodríguez Á, Reviriego J, Karamanos V, del Cañizo FJ, Vlachogiannis N, Drossinos V. Management of cardiovascular risk factors with pioglitazone combination therapies in type 2 diabetes: An observational cohort study. Cardiovasc Diabetol. 2011;10(1):18.

192. Bramlage P, Gitt AK, Binz C, Krekler M, Deeg E, Tschöpe D. Oral antidiabetic treatment in type-2 diabetes in the elderly: balancing the need for glucose control and the risk of hypoglycemia. Cardiovasc Diabetol [Internet]. 2012;11(1):122.

193. Kawamori R, Node K, Hanafusa T, Atsumi Y, Naito Y, Oka Y. Baseline and 1-year interim follow-up assessment of Japanese patients initiating insulin therapy who were enrolled in the cardiovascular risk evaluation in people with type 2 diabetes on insulin therapy study: An international, multicenter, observational . Cardiovasc Diabetol. 2013;12(1):1. Available from: Cardiovascular Diabetology

194. Eby EL, Curtis BH, Gelwicks SC, Hood RC, Idris I, Peters AL, et al. Initiation of human regular U-500 insulin use is associated with improved glycemic control: a real-world US cohort study. BMJ Open Diabetes Res Care. 2015;3(1):e000074.

195. Wang L, Wei W, Miao R, Xie L, Baser O. Real-world outcomes of US employees with type 2 diabetes mellitus treated with insulin glargine or neutral protamine Hagedorn insulin: A comparative retrospective database study. BMJ Open. 2013;3(4).

196. Rauh SP, Rutters F, Thorsted BL. Self-reported hypoglycaemia in patients with type 2 diabetes treated with insulin in the Hoorn Diabetes Care System Cohort, the Netherlands: a prospective cohort study. BMJ Open. 2016;6(9):e012793.

197. Hippisley-Cox J, Coupland C. Diabetes treatments and risk of amputation, blindness, severe kidney failure, hyperglycaemia, and hypoglycaemia: Open cohort study in primary care. BMJ. 2016;352.

198. Romley JA, Gong C, Jena AB, Goldman DP, Williams B, Peters A. Association between use of warfarin with common sulfonylureas and serious hypoglycemic events: Retrospective cohort analysis. BMJ. 2015;351.

199. Marrett E, Radican L, Davies MJ, Zhang Q. Assessment of severity and frequency of self-reported hypoglycemia on quality of life in patients with type 2 diabetes treated with oral antihyperglycemic agents: A survey study. BMC Res Notes. 2011;4(1):251.

200. Tschöpe D, Bramlage P, Binz C, Krekler M, Deeg E, Gitt AK. Incidence and predictors of hypoglycaemia in type 2 diabetes - an analysis of the prospective DiaRegis registry. BMC Endocr Disord. 2012;12:1–9.

201. Mitchell BD, Vietri J, Zagar A, Curtis B, Reaney M. Hypoglycaemic events in patients with type 2 diabetes in the United Kingdom: Associations with patient-reported outcomes and self-reported HbA1c. BMC Endocr Disord. 2013;13.

202. Medagama AB, Bandara R, Abeysekera RA, Imbulpitiya B, Pushpakumari T. Use of complementary and alternative medicines (CAMs) among type 2 diabetes patients in Sri Lanka: A cross sectional survey. BMC Complement Altern Med. 2014;14(1):1–5.

203. Klen J, Goričar K, Janež A, Dolžan V. The role of genetic factors and kidney and liver function in glycemic control in type 2 diabetes patients on long-term metformin and sulphonylurea cotreatment. Biomed Res Int. 2014;2014.

204. Akkineni S, Mathews AM, Apuroopa G, Neha Sridhar N, Rodrigues PA. A study on patients' awareness, recognition management and prevalence of hypoglycemic episodes in type 2 diabetes mellitus in a tertiary care hospital. Asian J Pharm Clin Res. 2015;8(2):390–4.

205. Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. Arch Intern Med. 2001;161(13):1653–9.

206. Bullano MF, Fisher MD, Grochulski WD, Menditto L, Willey VJ. Hypoglycemic events and glycosylated hemoglobin values in patients with type 2 diabetes mellitus newly initiated on insulin glargine or premixed insulin combination products. Am J Heal Pharm. 2006;63(24):2473–82.

207. Quilliam BJ, Simeone JC, Ozbay B, Kogut S. The Incidence and Costs of Hypoglycemia in Type 2 Diabetes. Am J Manag Care. 2011;17(10):673–80.

208. Gautier JF, Martinez L, Penfornis A, Eschwège E, Charpentier G, Huret B, et al. Effectiveness and Persistence with Liraglutide Among Patients with Type 2 Diabetes in Routine Clinical Practice—EVIDENCE: A Prospective, 2-Year Follow-Up, Observational, Post-Marketing Study. Adv Ther. 2015;32(9):838–53.

209. Xie L, Wei W, Pan C, Du J, Baser O. A real-world study of patients with type 2 diabetes initiating basal insulins via disposable pens. Adv Ther. 2011;28(11):1000–11.

210. Dalal MR, Kazemi M, Ye F, Xie L. Hypoglycemia After Initiation of Basal Insulin in Patients with Type 2 Diabetes in the United States: Implications for Treatment Discontinuation and Healthcare Costs and Utilization. Adv Ther. 2017;34(9):2083–92.

211. Wei W, Zhou S, Miao R, Pan C, Xie L, Baser O, et al. Much ado about nothing? A real-world study of patients with type 2 diabetes switching basal insulin analogs. Adv Ther. 2014;31(5):539–60.

212. Chitnis AS, Ganz ML, Benjamin N, Langer J, Hammer M. Clinical Effectiveness of Liraglutide Across Body Mass Index in Patients with Type 2 Diabetes in the United States: A Retrospective Cohort Study. Adv Ther. 2014;31(9):986–99.

213. Bellia A, Babini AC, Marchetto PE, Arsenio L, Lauro D, Lauro R. Effects of switching from NPH insulin to insulin glargine in patients with type 2 diabetes: The retrospective, observational LAUREL study in Italy. Acta Diabetol. 2014;51(2):269–75.

214. Weitgasser R, Lopes S. Self-reported frequency and impact of hypoglycaemic events in insulin-treated diabetic patients in Austria. Wien Klin Wochenschr. 2015;127(1–2):36–44.

215 Tabaei BP, Shillnovak J, Brandle M, Burke R, Kaplan RM, Herman WH. Glycemia and the quality of well-being in patients with diabetes. Qual Life Res. 2004;13(6):1153–61.

216. Dømgaard M, Bagger M, Rhee NA, Burton CM, Thorsteinsson B. Individual and societal consequences of hypoglycemia: A crosssectional survey. Postgrad Med. 2015;127(5):438–45.

217. Polonsky WH, Peters AL, Hessler D. The Impact of Real-Time Continuous Glucose Monitoring in Patients 65 Years and Older. J Diabetes Sci Technol. 2016;10(4):892–7.

218. Malkani S, Kotwal A. Frequency and Predictors of Self-Reported Hypoglycemia in Insulin-Treated Diabetes. J Diabetes Res. 2017;2017.

219. Ohashi Y, Wolden ML, Hyllested-Winge J, Brod M. Diabetes management and daily functioning burden of non-severe hypoglycemia in Japanese people treated with insulin. J Diabetes Investig. 2017;8(6):776–82.

220. Mantovani A, Grani G, Chioma L, Vancieri G, Giordani I, Rendina R, et al. Severe hypoglycemia in patients with known diabetes requiring emergency department care: A report from an Italian multicenter study. J Clin Transl Endocrinol. 2016;5:46–52.

221. Rawdaree P, Sarinnapakorn V, Pattanaungkul S, Khovidhunkit W, Tannirandorn P, Peerpatdit T. A Prospective, Longitudinal, Multicenter, Observational Study to Assess Insulin Treatment Patterns in Diabetic Patients in Thailand: Results From the TITAN Study. J Med Assoc Thai. 2014;97(11):1140–50.

222. Dornhorst A, Lüddeke HJ, Sreenan S, Kozlovski P, Hansen JB, Looij BJ, et al. Insulin detemir improves glycaemic control without weight gain in insulin-naïve patients with type 2 diabetes: Subgroup analysis from the PREDICTIVE™ study. Int J Clin Pract. 2008;62(4):659–65.

223. Sämanna A, Lehmann T, Heller T, Müller N, Hartmann P, Wolf GB, et al. A retrospective study on the incidence and risk factors of severe hypoglycemia in primary care. Fam Pract. 2013;30(3):290–3.

224. Leese G, Wang J, Broomhall J, Kelly P, Marsden A, Morrison W, et al. Frequency of Severe Hypoglycemia in Patients With Non-Insulin-Dependent Diabetes Mellitus Treated With Sulfonylureas or Insulin. Endocr Pract. 2003;26(4):1176–80.

225. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Self-report of hypoglycemia and health-related quality of life in patients with type 1 and type 2 diabetes. Endocr Pract. 2013;19(5):792–9.

226. Bruce DG, Davis WA, Casey GP, Clarnette RM, Brown SGA, Jacobs IG, et al. Severe hypoglycaemia and cognitive impairment in older patients with diabetes: The Fremantle Diabetes Study. Diabetologia. 2009;52(9):1808–15.

227. Östenson CG, Geelhoed-Duijvestijn P, Lahtela J, Weitgasser R, Markert Jensen M, Pedersen-Bjergaard U. Self-reported non-

severe hypoglycaemic events in Europe. Diabet Med. 2014;31(1):92–101.

228. Frier BM, Jensen MM, Chubb BD. Hypoglycaemia in adults with insulin-treated diabetes in the UK: self-reported frequency and effects. Diabet Med. 2016;33(8):1125–32.

229. Laubner K, Molz K, Kerner W, Karges W, Lang W, Dapp A, et al. Daily insulin doses and injection frequencies of neutral protamine hagedorn (NPH) insulin, insulin detemir and insulin glargine in type 1 and type 2 diabetes: a multicenter analysis of 51 964 patients from the German/Austrian DPV-wiss database K. Diabetes Metab Res Rev. 2014;30:395–404.

230. Lüddeke HJ, Sreenan S, Aczel S, Maxeiner S, Yenigun M, Kozlovski P, et al. PREDICTIVE™ - A global, prospective observational study to evaluate insulin detemir treatment in types 1 and 2 diabetes: Baseline characteristics and predictors of hypoglycaemia from the European cohort. Diabetes, Obes Metab. 2007;9(3):428–34.

231. Sreenan S, Andersen M, Thorsted BL, Wolden ML, Evans M. Increased Risk of Severe Hypoglycemic Events with Increasing Frequency of Non-severe Hypoglycemic Events in Patients with Type 1 and Type 2 Diabetes. Diabetes Ther. 2014;5(2):447–58.

232. Orozco-Beltrán D, Mezquita-Raya P, Ramírez de Arellano A, Galán M. Self-Reported Frequency and Impact of Hypoglycemic Events in Spain. Diabetes Ther. 2014;5(1):155–68.

233. Bohn B, Kerner W, Seufert J, Kempe HP, Jehle PM, Best F, et al. Trend of antihyperglycaemic therapy and glycaemic control in 184,864 adults with type 1 or 2 diabetes between 2002 and 2014: Analysis of real-life data from the DPV registry from Germany and Austria. Diabetes Res Clin Pract. 2016;115(May 2015):31–8.

234. Emral R, Pathan F, Cortés CAY, El-Hefnawy MH, Goh SY, Gómez AM, et al. Self-reported hypoglycemia in insulin-treated patients with diabetes: Results from an international survey on 7289 patients from nine countries. Diabetes Res Clin Pract. 2017;134:17–28.

235. Donnelly L, Morris A, Frier B, Ellis J, Donnan P, Durrant R, et al. Frequency and predictors of hypoglycaemia in Type 1 and insulintreated Type 2 diabetes: a population-based study. Diabetes Med. 2005;22(6):749–55.

236. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes Care. 2012;35(9):1897–901.

237. Cox D, Penberthy J, Zrebiec J, Weinger K, Aikens J, Frier B, et al. Diabetes and driving mishaps. Diabetes Care. 2003;26(8):2329–2329.

238. Khunti K, Davies M, Majeed A, Thorsted BL, Wolden ML, Paul SK. Hypoglycemia and risk of cardiovascular disease and all-Causemortality in insulin-treated people with type 1 and type 2 diabetes: A cohort study. Diabetes Care. 2015;38(2):316–22.

239. Monnier L, Colette C, Wojtusciszyn A, Dejager S, Renard E, Molinari N, et al. Toward defining the threshold between low and high glucose variability in diabetes. Diabetes Care. 2017;40(7):832–8.

240. Marre M, Pinget M, Gin H, Thivolet C, Hanaire H, Robert JJ, et al. Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain: 52-week data from the PREDICTIVE™ study in a cohort of French patients with type 1 or type 2 diabetes. Diabetes Metab. 2009;35(6):469–75.

241. Cariou B, Fontaine P, Eschwege E, Lièvre M, Gouet D, Huet D, et al. Frequency and predictors of confirmed hypoglycaemia in type 1 and insulin-treated type 2 diabetes mellitus patients in a real-life setting: Results from the DIALOG study. Diabetes Metab. 2015;41(2):116–25.

242. Morgan CL, Evans M, Toft AD, Jenkins-Jones S, Poole CD, Currie CJ. Clinical Effectiveness of Biphasic Insulin Aspart 30:70 Versus Biphasic Human Insulin 30 in UK General Clinical Practice: A Retrospective Database Study. Clin Ther. 2011;33(1):27–35.

243. Aronson R, Goldenberg R, Boras D, Skovgaard R, Bajaj H. The Canadian Hypoglycemia Assessment Tool Program: Insights Into Rates and Implications of Hypoglycemia From an Observational Study. Can J Diabetes. 2018;42(1):11–7.