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Effectiveness and safety of new oral and injectable agents for in-hospital management of type 2 diabetes in general wards: Systematic review and meta-analysis

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ABSTRACT

Background: Current guidelines recommend insulin alone for in-hospital management of diabetes, but growing information suggests that new oral or injectable agents may be as effective and safe.
Methods: Systematic review and meta-analysis with evidence from randomized (RCT) and non-randomized (NRS) studies in PubMed, EMBASE and LILACS databases up to February 10, 2022, for studies including hospitalized type 2 diabetes patients, comparing dipeptidyl peptidase 4 inhibitors (DPP4i), sodium glucose co-transporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP1Ra) with insulin alone for glycemic control and safety outcomes.
Findings: 7 RCT and 3 NRTs were included. There were no differences in mean blood glucose, measurements within range or rate of hypoglycemia between DPP4i and insulin. We found a lower mean glucose for GLP1Ra plus insulin subgroup (−16.36 mg/dL, 95 % CI −27.31, −5.41; $I^2 = 0$ %) with lower incidence of hypoglycemia < 70 mg/dL with GLP1Ra (RR 0.31, CI 95 % 0.14–0.70, $I^2 = 0$ %). SGLT2i data was limited. Adverse events rates were similar between treatments.
Conclusion: Our review suggests that inpatient management in the general ward with DPP4i and GLP1Ra is as effective and safe as management with insulin. More randomized studies are required to support these findings before they could be recommended as usual practice.

1. Introduction

In-hospital, between 22 % and 46 % of patients are diagnosed with diabetes or present hyperglycemia with levels higher than 140 mg/dl [1]. Adequate glycemic control during hospital stay in these patients has shown to reduce infectious complications, prolonged hospitalization and the requirement for readmission [2,3].

In the last decades, insulin-based therapy has been the standard management for achieving adequate in-hospital glycemic control [2]. While regimens such as basal-bolus (one dose of basal insulin and prandial doses of short-acting insulin analogues) have demonstrated good in-hospital glycemic control, they are also associated with high rates of hypoglycemia in medical and surgical patients, ranging from 12 to 32 % [4,5]. Additionally, the administration of multiple injections per day is laborious for the health care staff and uncomfortable for the patient. To overcome these difficulties, different oral antidiabetics of previous generations were evaluated for in-hospital management with unfavorable results such as increased lactic acidosis in some case reports

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with biguanides [6,7], hypoglycemia with sulfonylureas [8,9], and cardiovascular complications with thiazolidinediones [9,10], explaining why they are not currently used in usual practice.

However, new generation of oral or injectable antidiabetics such as dipeptidyl peptidase 4 inhibitors (DPP4i), sodium-glucose co-transporter type 2 inhibitors (SGLT2i), and glucagon-like peptide type 1 agonists (GLP1Ra), have shown similar efficacy to standard therapy for in-hospital management of diabetes in recent small studies, with an acceptable safety profile [3,9]. The aim of the present systematic review and meta-analysis is to evaluate the effectiveness and safety of new oral

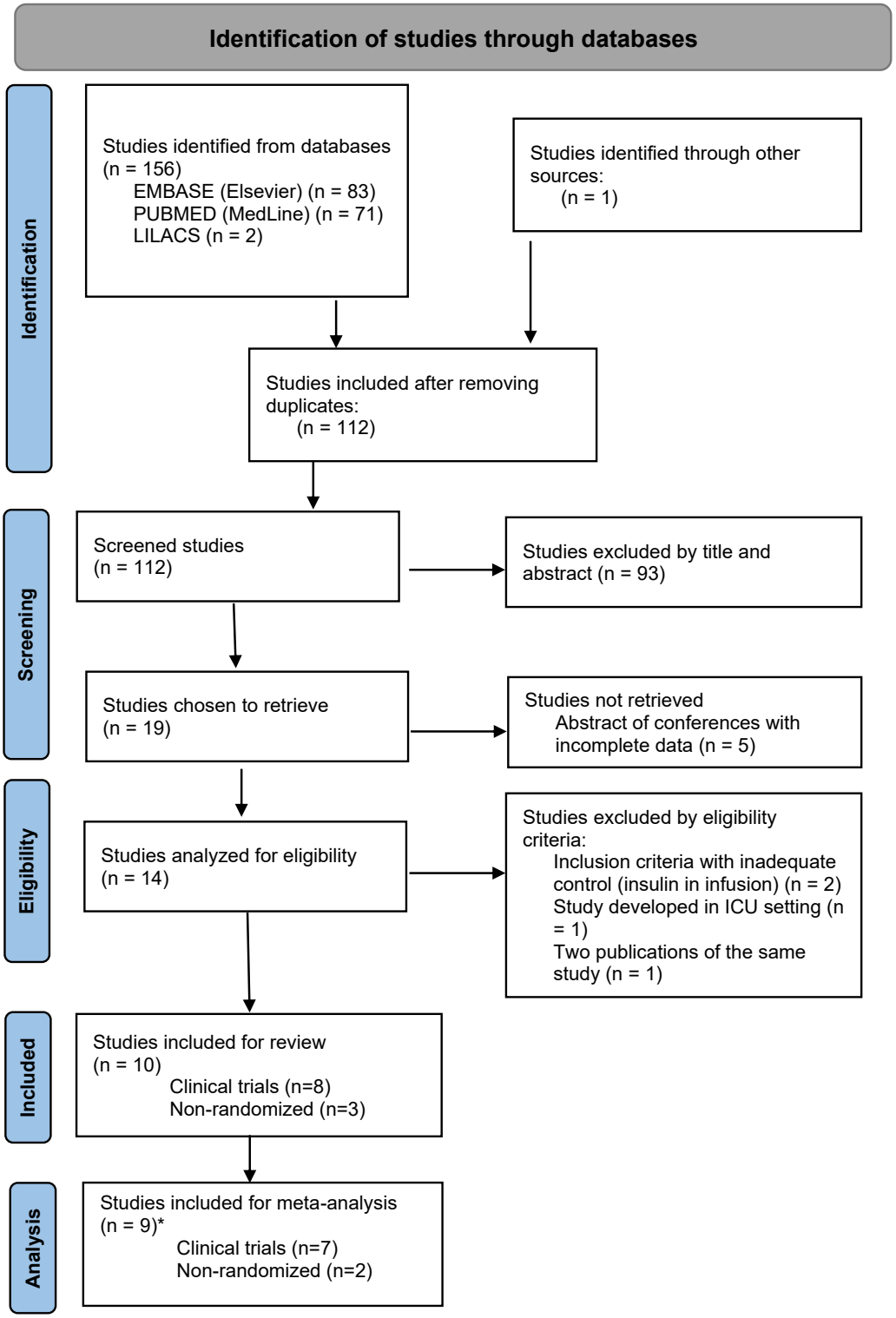


Fig. 1. PRISMA flowchart. *One non-randomized study is analyzed but not included in the meta-analysis as it was the only study analyzing SGLT2i.

and injectable antidiabetic drugs, compared with the usual management with insulin, for the management of patients hospitalized in general ward with type 2 diabetes mellitus, synthesizing and critically evaluating the evidence available in randomized and nonrandomized studies.

2. Methods

This review is reported according to the preferred reporting items for systematic review and meta-analysis (PRISMA) [11]. The protocol of this review was registered in PROSPERO 2022 (ID: CRD42022309823).

2.1. Search strategy and selection criteria:

We included randomized (RCT) and non-randomized (NRS) clinical studies that included adults with a diagnosis of type 2 diabetes mellitus prior to hospitalization, comparing treatment with DPP4i, SGLT2i and GLP1Ra in monotherapy or combined with insulin in sliding scale, with standard insulin therapy in a basal-bolus (BB) or basal-plus (BP) scheme.

To be included, the study had to evaluate outcomes of glycemic control and patient safety, including average glucose, percentage of glucose measurements at target, percentage of time in range (for those who had continuous glucose monitoring), percentage of measurements in range of hyperglycemia (>240 mg/dl), percentage of measurements in range of hypoglycemia < 70 mg/dl, incidence of hypoglycemia < 70 mg/dl and < 54 mg/dl (at least 1 episode during hospitalization), incidence rate of hypoglycemia < 70 mg/dl (events/patient-day), and adverse events (gastrointestinal or genitourinary infections). Studies in which the type of diabetes was not clear, and those that evaluated pregnant patients, patients in intensive care unit management or hospitalized for acute decompensation of diabetes (diabetic ketoacidosis, hyperosmolar hyperglycemic state, or mixed state) were excluded.

A search was conducted in PubMed (MedLine), EMBASE (Elsevier) and LILACS databases, using the search terms: “diabetes mellitus”, “diabetes”, “inpatient”, “hospitalised”, “hospitalized”, “hospital setting”, “in-hospital”, “hospital medicine”, “hospital patient”, “general ward”, “sitagliptin”, “vildagliptin”, “saxagliptin”, “linagliptin”, “alogliptin”, “canagliflozin”, “empagliflozin”, “sotagliflozin”, “dapagliflozin”, “ertugliflozin”, “liraglutide”, “lixisenatide”, “exenatide”, “albiglutide”, “dulaglutide”, “semaglutide”, “insulin”. There was no limitation by language. Search was updated to February 10, 2022. Search strategies for each database can be found in Appendix 1.

Two authors (MJS, JPA or CEL) independently reviewed the title and abstract of each retrieved record and evaluated the full texts of all potentially eligible articles. Any discrepancies were resolved by consensus or through a third reviewer (OMM). Fig. 1 shows the PRISMA flowchart describing the selection process.

Outcome data were independently extracted by two authors (MJS, JPA, or CEL) in a standardized method, and differences were resolved by consensus. Contact with authors was attempted to obtain missing information in cases with incomplete data.

Risk of bias assessment in RCT was performed independently by two authors (MJS, JPA, or CEL) using the Cochrane Collaboration’s tool for assessing risk of bias version 2 (RoB2) [12]. The NRS were assessed using the ROBINS-I tool [13]. Differences were resolved by consensus or by a third reviewer (OMM). The assessment of the certainty of evidence for each outcome was performed using the GRADE methodology [14].

2.2. Data analysis

Evaluation of each glycemic control outcome including average glucose in mg/dl, percentage of episodes at targets 70 to 180 mg/dl, percentage of time in range by continuous glucose monitoring, hyperglycemia as percentage of hyperglycemia episodes > 200 mg/dl, and hypoglycemia as percentage of hypoglycemia episodes < 70 mg/dl, incidence of hypoglycemia < 70 mg/dl during stay, incidence of hypoglycemia < 54 mg/dl and rate incidence of hypoglycemia < 70 mg/dl (events/patient-day) was synthesized. Outcomes reported in the RCT were included in the meta-analysis, and those reported in the NRS were presented descriptively, clarifying whether they supported the findings of the RCT, and describing possible causes if heterogeneity was evident [15]. The meta-analysis of NRS was considered only for the outcome of hypoglycemia < 54 mg/dL, since there was no adequate evidence from RCT.

Meta-analyses were performed using a random-effects model, pooling studies that included medications from the same group (DPP4i, SGLT2i, or GLP1Ra). Subgroup analyses were performed when the drug was administered as monotherapy or combined with insulin as sliding scale. Dichotomous outcomes are presented as relative risks (RR) and continuous outcomes as mean difference (MD). Summary measures are presented as a Forest Plot or as part of the narrative synthesis of the review. Heterogeneity was assessed using the I^2 statistic, allowing to know the proportion of the variation in the results of the studies due to heterogeneity between studies and not due to sampling error [14]. For the synthesis and analysis of the results, the Review Manager tool (RevMan version 5.4®) of the Cochrane collaboration was employed. Tables of synthesis and evaluation of the evidence obtained were generated, including the certainty of the body of evidence for each outcome, using the GRADE pro tool [14].

2.3. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

3. Results

Ten studies were included for review, seven RCT [16–22] and three retrospective real-life NRS [23–25] (Fig. 1). Table 1 presents the population characteristics of each study. Three of the RCT employed GLP1Ra with and without insulin in sliding scale as intervention [20–22,26], and four evaluated DPP4i with and without insulin in sliding scale [16–19]. Two RCT used DPP4i with insulin in sliding scale as an intervention [23,25], and only one study used SGLT2i with insulin in sliding scale [24].

The most frequently used drug was linagliptin (3 of 10 studies) [17,23,25], and the most frequently insulin regimen was BB (8 of 10). Mean ages ranged from 55.7 to 72.4 years. The mean HbA1c ranged from 6.6 % to 8.6 %. Only four studies reported comorbidities, the most prevalent being heart failure and coronary artery disease. Five studies specified the type of patients included (medical vs surgical), with two of them including surgical patients only.

Although all the randomized studies were open-label due to the characteristics of the compared agents, only the study by Kaneko [22] had high risk of bias. The nonrandomized studies with DPP4i showed low risk [23,25] and the study of SGLT2i had serious risk of bias [24]. Tables 2 and 3 present the risk of bias assessments for each study.

3.1. Outcomes

3.1.1. Glycemic control

No differences were observed in mean blood glucose in the global analysis of patients managed with GLP1Ra or DPP4i compared to insulin (Fig. 2). However, when independently evaluating mean blood glucose in the GLP1Ra subgroup with sliding scale insulin compared to insulin, a significant difference was found (−16.36 mg/dL, 95 % CI, −27.31, −5.41; $I^2 = 0$ %), which was not evidenced in patients managed with GLP1Ra as monotherapy compared to insulin (Fig. 2.1). The findings were consistent between low and high-risk of bias studies. Similar findings were presented in the NRS, with no significant difference in mean glucose between the groups with DPP4i or SGLT2i versus insulin (Table 4) [23–25].

Two RCT showed no difference in percentage of measurements in

Table 1
Characteristics of included studies.

Author, year	Intervention (Agent, dose)	Control (insulin scheme)	N. subjects (I, C)	Age (Years) (mean, SD)	Female sex	BMI (kg/m2) (mean, SD)	Comorbidities	HbA1c (%) (mean, SD)	Length of stay (days) (Median, IQR)	Type of patient (medical, surgical)
Randomized studies (GLP1Ra)										
Fushimi 2020 (21)	Dulaglutide 0.75 mg SD + BP	BP	N = 54 (Du + BP, n = 27) (BP, n = 27)	70.5 (13.5)	38,5%	24.9 (6.2)	NR	8.1 % (1.8)	NR	NE
Fayfman 2019 (20)	Exenatide 5 ug BID Exenatide 5 ug BID + BI	BB	N = 150 (Ex, n = 47) (Ex + BB, n = 51) (BB, n = 52)	55.7 (12)	49,3%	33.7 (6)	CAD 7,3% HF 6 % HTN 41,3% CKD 28 %	8.6 % (2)	NR	Medical 70,6% Surgical 29,4%
Kaneko 2018 (22)	Liraglutide (initial dose NE)	BP	N = 90 (Lir, n = 49) (BP, n = 41)	68.8 (9.4)	57.8 %	25.1 (6)	NR	7.4 % (1.1)	NR	Surgical 100 %
Randomized studies (DPP4i)										
Vellanki 2019 (17)	Linagliptin 5 mg QD + SS	BB	N = 250 (Lina + SS, n = 128) (BB, n = 122)	58 (11)	50 %	34.0 (8)	NR	7.8 % (4)	Lina + SS = 4 (3–5) BB=3 (3–6)	Surgical 100 %
Garg 2017 (18)	Saxagliptin 5 mg QD Saxagliptin 2.5 mg QD (eGFR > 50 mL/min or inhibitors CYP3A4/5)	BB	N = 66 (Saxa, n = 33) (BB, n = 33)	68 (10)	54 %	33.5 (9.4)	NR	6.6 % (0.5)	NR	Medical 25,5% Surgical 74,5%
Pasquel 2017 (16)	Sitagliptin 100 mg QD (eGFR > 50 mL/min) + BI Sitagliptin 50 mg QD (eGFR 30–50 mL/min) + BI Sitagliptin 25 mg QD (eGFR < 30 mL/min) + BI	BB	N = 277 (Sit + BI, n = 138) (BB, n = 139)	57 (11)	40 %	35.2 (10)	NR	8.6 % (2)	4 (3–8)	Medical 84 % Surgical 16 %
Umpierrez 2013 (19)	Sitagliptin 100 mg QD (eGFR > 50 mL/min) Sitagliptin 50 mg QD (eGFR 30–50 mL/min) Sitagliptin 100 mg QD (eGFR > 50 mL/min) + BI Sitagliptin 50 mg QD (eGFR 30–50 mL/min) + BI	BB	N = 82 (Sit, n = 27) (Sit + BI, n = 29) (BB, n = 26)	57.8 (11)	46,3%	33.5 (10)	NR	8.2 % (2)	6,5 (mean) (SD 3)	Medical 61 % Surgical 39 %
Nonrandomized studies										
Perez-Belmonte 2022 (23)	Linagliptin 5 mg QD + BI	BB	N = 292 (Lina + BI, n = 146) (BB, n = 146)	72.7 (5.4)	52.1 %	28.8 (2)	HF 100 % CAD 48.3 %	7.3 % (0.6)	6.8 (1.7)	NE
Pérez-Belmonte 2018 (25)	Linagliptin 5 mg QD + BI	BB	N = 454 (Lina + BI, n = 227) (BB, n = 227)	72.2 (8.2)	52.6 %	29.2 (1.9)	HTN 63.7 % CKD 19.9 % CAD 36.4 % HF 69.6 %	7.2 % (0.6)	6.8 (1.8)	NE
Perez-Belmonte 2021(24)	Empagliflozin 10/25 mg + BI	BB	N = 182 (Emp + BI, n = 91) (BB, n = 91)	72.4 (5.7)	51.6 %	29.2 (2.1)	HF 100 % CAD 51 %	7.2 % (0.6)	8.0 (2.4)	NE

GLP1Ra: glucagon-like peptide type 1 receptor agonists; DPP4i: dipeptidyl peptidase 4 inhibitors; I: intervention; C: control; QD: once daily; BID: twice daily; BB: basal insulin-bolus scheme; BI: basal insulin; SS: sliding scale insulin; BP: basal-plus insulin; SD: single dose; Ex: exenatide; Du: dulaglutide; Lir: liraglutide; Sit: sitagliptin; Lina: linagliptin; Saxa: saxagliptin; Emp: empagliflozin; CAD: coronary artery disease; HF: heart failure; HTN: arterial hypertension; CKD: chronic kidney disease; NE: not specified.***

Table 2
Assessment of risk of bias (RoB2): randomized studies.

Author, year	R	D	Mi	Me	S	O
GLP1Ra						
Kaneko, 2018 (22)						
Fushimi, 2020 (21)						
Fayfman, 2019 (20)						
DPP4i						
Vellanki, 2019 (17)						
Pasquel, 2017 (16)						
Garg, 2017 (18)						
Umpierrez, 2013 (19)						

R: Bias arising from the randomization process.
D: Bias due to deviations from intended interventions.
Mi: Bias due to missing outcome data.
Me: Bias in measurement of the outcome.
S: Bias in selection of the reported result.
O: Overall risk of bias.
Result:
Low Some concerns High.

Table 3
Risk of bias assessment (ROBINS-I): non-randomized.

Author, year	C	S	I	D	MD	MO	R	O
Pérez-Belmonte 2018 (25)								
Pérez-Belmonte 2021 (24)								
Pérez-Belmonte 2022 (23)								

C: bias due to confounding.
S: bias in selection of participants into the study.
I: bias in classification of interventions.
D: bias due to deviations from intended interventions.
MD: bias due to missing data.
MO: bias due to measurement of outcomes.
R: bias in selection of the reported result.
O: Overall risk of bias.
Result:
Low Moderate Serious Critical No information.

target reported as 70–140 mg/dl [16,17] when comparing DPP4i with sliding scale insulin vs insulin alone (Mean difference −0.60; 95 % CI −5.39, 4.20, $I^2 = 0$ %). A study with the same agent evaluated the percentage of measurements in range between 140 and 180 mg/dl, with similar findings (sitagliptin 30 % ± 21 vs sitagliptin plus basal insulin 35 % ± 25 vs insulin 23 % ± 17, p = 0.14) [19]. Only one study with GLP1Ra reported the percentage of on-target measurements in a post-hoc analysis, being significantly higher in the GLP1Ra plus insulin group when compared to insulin (Exenatide plus insulin 77.7 % ± 31 vs Exenatide alone 62.3 % ± 39 vs BB 63.3 % ± 31, p = 0.02) [20]. No NRS reported this outcome. None of the RCT or NRS evaluated percent of time in range with continuous glucose monitoring (CGM).

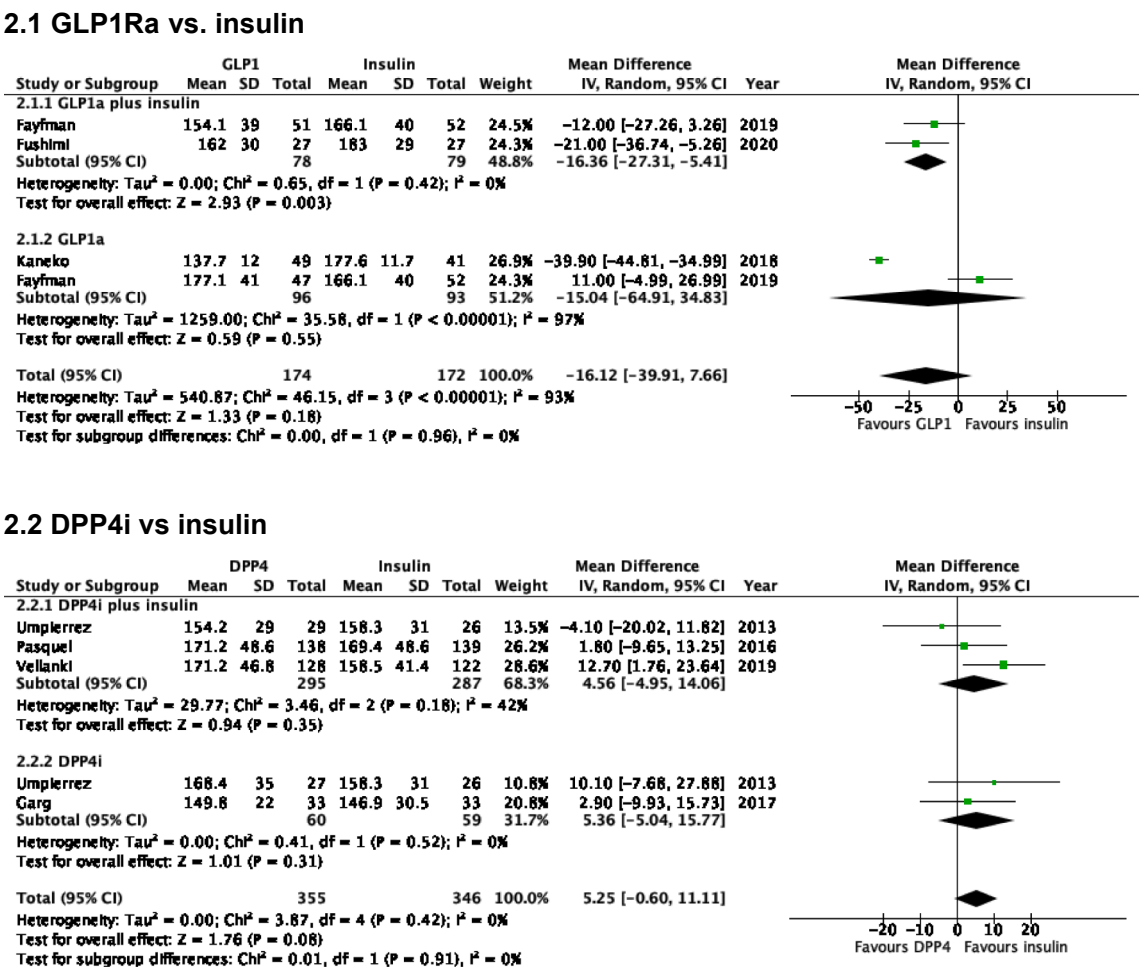


Fig. 2. Oral or injectable antidiabetics vs insulin: mean blood glucose (mg/dl). 2.1 GLP1Ra vs insulin. 2.2 DPP4i vs insulin.

3.1.2. Hypoglycemia

All studies evaluated incidence of hypoglycemia < 70 mg/dL. The meta-analysis showed lower incidence in the GLP1Ra group (RR 0.31, 95 % CI, 0.14–0.70, $I^2 = 0$ %) compared to insulin, and similar incidence in the DPP4i group compared to insulin (RR 0.54, 95 % CI, 0.26–1.14; $I^2 = 21$ %) as shown in Fig. 3. The NRS showed similar findings, with lower incidence of hypoglycemia when comparing SGLT2i and DPP4i sliding scale insulin-associated versus BB insulin ($p < 0.05$) [23,24], as shown in Table 4. Results were consistent across studies with low and high risk of bias.

Incidence of hypoglycemia < 54 mg/dL was evaluated in all studies. The meta-analysis showed no differences between the new antidiabetic agents and insulin schemes (Appendix 2). The results were similar for GLP1Ra vs insulin (RR 0.26, 95 % CI, 0.07–1.02; $I^2 = 0$ %) and DPP4i vs insulin (RR 0.86, 95 % CI, 0.05–15.06; $I^2 = 59$ %), but are very imprecise given the low number of events (3 vs 4), as shown in Appendix 2. Similarly, meta-analysis of NRS comparing DPP4i plus insulin versus insulin showed no significant differences (RR 0.59, 95 % CI, 0.23–1.5: $I^2 = 0$ %) (Appendix 2). These studies presented low risk of bias.

Only two RCT reported the percentage of measurements in hypoglycemia range < 70 mg/dl; one compared GLP1Ra (exenatide 0 % ± 0 vs exenatide plus insulin 0.4 % ± 1.5 vs insulin BB 1.1 % ± 4.1)[20] and another DPP4i (sitagliptin 0.1 % ± 0.6 vs sitagliptin plus insulin 0.7 % ± 2.9 vs insulin BB 0.9 % ± 3.9) [19] with insulin, without showing significant differences. These studies had low risk of bias. No NRS reported this outcome.

One RCT reported the incidence rate of hypoglycemia (events/patient-day), presenting the same number of events when comparing DPP4i with BB insulin (1 vs 1) [18]. Two of the NRS evaluated this outcome, with fewer events in groups treated with SGLT2i (8.4 vs 16 events/patient-year, $p = 0.002$) and DPP4i (7.4 vs 17 events/patient-year, $p < 0.001$) when compared with insulin [23,24].

3.1.3. Hyperglycemia

There were no significant differences between percentage of measurements in hyperglycemia range (>240 mg/dl) when comparing DPP4i plus sliding scale insulin with insulin in usual schemes (mean difference −2.35, 95 % CI −6.53, 1.82; $I^2 = 0$ %) [16,19]. One of the studies reported the outcome with DPP4i without insulin, with no significant differences with regard to insulin (sitagliptin 12 % ±16 vs sitagliptin plus insulin 5 % ±10 vs BB 8 % ±14, $p = 0.17$) [19]. Similarly, when comparing GLP1Ra with insulin, one study showed no significant differences (exenatide 10.4 % ± 24 vs exenatide plus insulin 5.1 % ± 16 vs BB 11.2 % ± 23, $p = 0.08$) [20]. All studies evaluating this outcome showed low risk of bias. No NRS reported this endpoint.

3.1.4. Adverse events

No significant differences in the occurrence of gastrointestinal adverse events in GLP1Ra compared with insulin were reported, as shown in Table 5. One study reported significant association of GLP1Ra adverse effects with the discontinuation of the drug (exenatide 6 % vs exenatide plus insulin 0 % vs insulin BB 0 %). Only Vellanki [17] evaluated gastrointestinal adverse events with DPP4i, reporting no significant differences (1 vs 2 events). The retrospective study with SGLT2i documented no differences in renal and urinary adverse events vs insulin use ($p = 0.293$) [24].

Table 4
Results of non-randomized studies.

Author, year	Total patients (I/C)	Intervention			Control			P value	Comments
		Agent	Mean	SD†	Insulin scheme	Mean	SD		
Mean Blood glucose (mg/dL)									
Perez-Belmonte 2018	454 (227/227)	Linagliptin 5 mg QD + BI	151.2	14.3	BB	149.8	13.5	0.177	Results post-propensity matching
Perez-Belmonte 2022	292 (146/146)	Linagliptin 5 mg QD + BI	163.6	21.2	BB	159.6	19.2	0.210	Results post-propensity matching
Perez-Belmonte 2021	182 (91/91)	Empagliflozin 10/25 mg + BI	155.2	19.7	BB	152.1	17.8	0.289	Results post-propensity matching
Incidence of hypoglycemia < 70 mg/dL at follow-up time (# patients with at least 1 event, %).									
Perez-Belmonte 2018	454 (227/227)	Linagliptin 5 mg QD + BI	16	7	BB	21	9.3	0.247	Results post-propensity matching
Perez-Belmonte 2022	292 (146/146)	Linagliptin 5 mg QD + BI	11	7.5	BB	16	11	0.020*	Results post-propensity matching
Perez-Belmonte 2021	182 (91/91)	Empagliflozin 10/25 mg + BI	6	6.6	BB	10	11	0.021*	Results post-propensity matching
Incidence of hypoglycemia < 54 mg/dL at follow-up time (# patients with at least 1 event, %).									
Perez-Belmonte 2018	454 (227/227)	Linagliptin 5 mg QD + BI	5	2.2	BB	7	3.1	0.199	Results post-propensity matching
Perez-Belmonte 2022	292 (146/146)	Linagliptin 5 mg QD + BI	2	1.3	BB	5	3.4	0.043*	Results post-propensity matching
Perez-Belmonte 2021	182 (91/91)	Empagliflozin 10/25 mg + BI	2	2.2	BB	3	3.3	0.109	Results post-propensity matching
Incidence rate of hypoglycemia < 70 mg/dL (patient-days)									
Perez-Belmonte 2018	454 (227/227)	Linagliptin 5 mg QD + BI	NR		BB	NR		–	
Perez-Belmonte 2022	292 (146/146)	Linagliptin 5 mg QD + BI	7.4		BB	17		<0.001*	100 patient-years, post-propensity matching results
Perez-Belmonte 2021	182 (91/91)	Empagliflozin 10/25 mg + BI	8.4		BB	16		0.002*	100 patient-years, post-propensity matching results

*Statistically significant difference; NR: not registered; I: intervention; C: control; SD: standard deviation; BI: basal insulin; BB: basal-bolus insulin.
† Number (%) for incidence of hypoglycemia < 70 mg/dL at follow-up time (# patients with at least 1 event) and for Incidence of hypoglycemia < 54 mg/dL at follow-up time (# patients with at least 1 event); and number of event per patient-day for Incidence rate of hypoglycemia < 70 mg/dL.

3.2. GRADE profile and summary of findings

Synthesis of findings and assessment of the certainty of the body of evidence is presented in Table 6. We assessed the quality of evidence for each outcome by group agent (DPP4i, GLP1Ra), finding high quality of evidence for average glucose (DPP4i), percentage of measurements at target (DPP4i) and incidence of hypoglycemia < 70 mg/dL. Moderate quality for percentage of measurements > 240 mg/dL (DPP4i), percentage of measurements in hypoglycemia < 70 mg/dL (DPP4i) and incidence of hypoglycemia < 70 mg/dl (GLP1Ra).

Low quality of evidence was documented for the outcomes of average blood glucose (GLP1Ra), percentage of measurements at target (GLP1Ra), percentage of measurements > 240 mg/dl (GLP1Ra), percentage of measurements in hypoglycemia < 70 mg/dl (GLP1Ra), hypoglycemia incidence < 54 mg/dl (GLP1Ra), and hypoglycemia incidence rate < 70 mg/dl (events/patient-day)(DPP4i). The outcome of hypoglycemia incidence < 54 mg/dl in DPP4i presented very low quality of evidence in both RCT and NRS.

4. Discussion

In this systematic review and meta-analysis, we evaluated the effectiveness and safety of new oral and injectable antidiabetic agents compared with usual insulin management for the management of hospitalized patients with type 2 diabetes mellitus in the general ward, including randomized and non-randomized studies. No differences were found between the use of new antidiabetics and the usual insulin regimens in glycemic control, hypoglycemia, hyperglycemia, or adverse events; even showing a discrete benefit in mean blood glucose with GLP1Ra with sliding scale insulin compared to insulin in usual schemes, and in incidence of hypoglycemia with GLP1Ra globally.

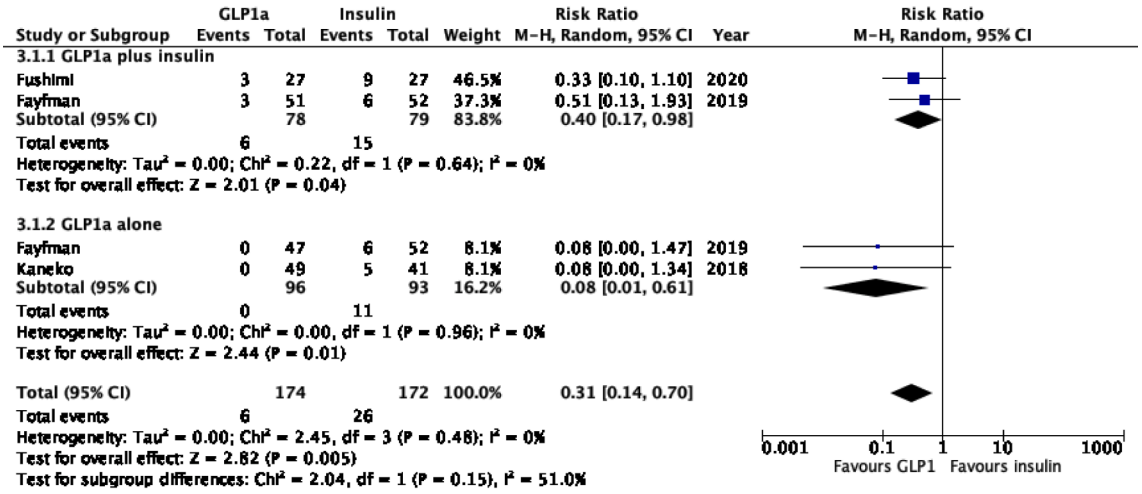
Average age of the patients was between 55 and 75 years, reflecting the ages with the highest prevalence of diabetes worldwide [27]. Mean BMI showed some differences between populations, however, most patients were overweight or obese. Mean HbA1c values were slightly off target according to ADA recommendations [2], with higher values in the GLP1Ra group, although with similar values among subgroup studies. Two studies included only surgical patients, which may impact outcomes such as hypoglycemia in relation to changes in perioperative intake [28], however, outcomes were similar in medical and surgical patients.

We evaluated glycemic control through different outcomes. Results show no difference in mean glucose between using DPP4i or GLP1Ra in monotherapy or DPP4i with sliding scale insulin when compared to usual management, with high certainty of evidence. Similar findings were found in NRS evaluating DPP4i and SGLT2i. Insulin-associated GLP1Ra even showed a discrete benefit in mean blood glucose with a decrease between 5.41 and 27.31 mg/dl of mean blood glucose against the usual regime, which is clinically relevant. However, the limited number of patients and the quality of the studies limit the certainty of this evidence, so new, larger RCT will be required to confirm this finding.

Similarly, the percentage of on-target measurements were similar with DPP4i and GLP1Ra versus insulin, with high certainty for DPP4i, although unfortunately no study evaluated the percentage of time in range measured by continuous glucose monitoring (CGM). These findings suggest that in-hospital glycemic control with the new drugs is at least similar to that achieved with conventional insulin therapy. However, these findings should be confirmed in RCT that evaluate in detail 24-hour glycemic control with CGM [29].

We found a similar incidence of hypoglycemia < 70 mg/dl when comparing DPP4i with insulin and, interestingly, a significantly lower incidence in the group treated with GLP1Ra, with moderate quality evidence in this group. These findings suggest benefits in both effectiveness and safety with new antidiabetics versus the usual management with insulin, as reported in multicentric studies in the outpatient setting

3.1 GLP1Ra vs. insulin



3.2 DPP4i vs insulin

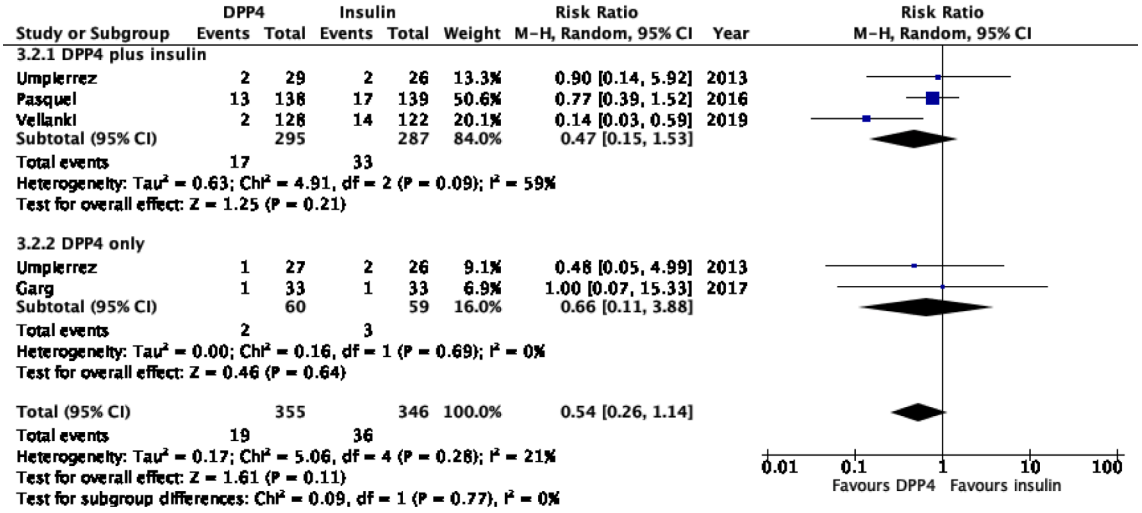


Fig. 3. Oral or injectable antidiabetics vs insulin: incidence of hypoglycemia < 70 mg/dL. 3.1 GLP1Ra vs insulin. 3.2 DPP4i vs insulin.

Table 5
Adverse events.

Author, year	Total patients included	Intervention	Adverse events n (%)	Insulin (control)	Adverse events n (%)	P-value	Definition
GLP1Ra (Gastrointestinal)							
Kaneko 2018	90	Liraglutide starting dose EN	3 (6.1)	BP	0 (0)	NR	Nausea
Fayfmann 2019	150	Exenatide 5ug BID	5 (11)	BB	1 (2)	0.17	Nausea or vomiting
Fushimi 2020	54	Dulaglutide 0.75 mg DU + BP	11 (41)	BP	6 (22)	0.24	Gastrointestinal symptoms
DPP4i (Gastrointestinal)							
Vellanki 2019	250	Linagliptin 5 mg QD + IC	1	BB	2	NR	Nausea or vomiting
SGLT2i (Renal/Urinary)							
Perez-Belmonte 2021	182 (91/91)	Empagliflozin 10/25 mg + BI	2 (2.2 %)	BB	2 (2.2 %)	0.293	–

[29–31]. The NRS support these findings, with a higher number of patients assessed than in RCT, but with a limited number of events, so further larger RCT will be required to improve the precision of the estimation, although the data suggest a potentially clinically important benefit.

When evaluating the incidence of hypoglycemia events < 54 mg/dl, we found a notable imprecision of the results, which conditioned very low certainty of the evidence in both RCT and NRS for all the evaluated drugs, so more information is required to explore this outcome. Similarly, we evaluated the incidence of hyperglycemia events. Although the

Table 6
GRADE summary of findings (PDF document).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	new oral or injectable antidiabetics	insulin	Relative (95% CI)	Absolute (95% CI)		
Mean blood glucose (mg/dL) (GLP1Ra vs. insulin)												
3	randomised trials	serious[a]	serious[b]	not serious	not serious	none	174	172	-	MD **16.12 lower** (39.91 lower to 7.66 higher)	⨁⨁◯◯ Low	CRITICAL
Mean blood glucose (mg/dL) (DPP4i vs. insulin)												
4	randomised trials	not serious	not serious	not serious	not serious	none	355	345	-	MD **5.26 higher** (0.6 lower to 11.11 higher)	⨁⨁⨁⨁ High	IMPORTANT
Mean percentage of episodes in range (70-180 mg/dl) (GLP1Ra vs. insulin)												
1	randomised trials	not serious	not serious	not serious	very serious[c,d]	none	47	52	-	MD **1 lower** (14.98 lower to 12.98 higher)	⨁⨁◯◯ Low	IMPORTANT
Mean percentage of episodes in range (70-140 mg/dl) (DPP4i vs. insulin)												
2	randomised trials	not serious	not serious	not serious	not serious[e]	none	266	261	-	MD **0.6 lower** (5.39 lower to 4.2 higher)	⨁⨁⨁⨁ High	IMPORTANT
Mean percentage of episodes in hyperglycemia >240 mg/dL (GLP1Ra vs. insulin)												
1	randomised trials	not serious	not serious	not serious	very serious[c,d]	none	47	52	-	MD **0.8 lower** (10.08 lower to 8.48 higher)	⨁⨁◯◯ Low	IMPORTANT
Mean percentage of episodes of hyperglycemia >240 mg/dL (DPP4i vs. insulin)												
1	randomised trials	not serious	not serious	not serious	serious[f]	none	167	164	-	MD **2.35 lower** (6.53 lower to 1.82 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Mean percentage of episodes in hypoglycemia <70 mg/dL (GLP1Ra vs. insulin)												
1	randomised trials	not serious	not serious	not serious	very serious[d,g]	none	47	52	-	MD **0** (0 to 0)	⨁⨁◯◯ Low	IMPORTANT
Mean percentage of episodes in hypoglycemia <70 mg/dl (DPP4i vs. insulin)												
1	randomised trials	not serious	not serious	not serious	serious[d,f]	none	27	26	-	MD **0.8 lower** (2.32 lower to 0.72 higher)	⨁⨁⨁◯ Moderate	IMPORTANT
Incidence of hypoglycemia <70 mg/dL at follow-up (GLP1Ra vs. insulin)												
3	randomised trials	serious[a]	not serious	not serious	serious[h]	strong association[i]	6/174 (3.4%)	26/172 (15.1%)	**RR 0.31** (0.14 to 0.70)	**104 fewer per 1,000** (from 130 fewer to 45 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Incidence of hypoglycemia <70 mg/dL at follow-up (DPP4i vs. insulin)												
4	randomised trials	not serious	not serious	not serious	not serious	none	19/355 (5.4%)	36/346 (10.4%)	**RR 0.54** (0.26 to 1.14)	**48 fewer per 1,000** (from 77 fewer to 15 more)	⨁⨁⨁⨁ High	IMPORTANT
Incidence of hypoglycemia <54 mg/dL at follow-up (GLP1Ra vs. insulin)												
2	randomised trials	serious[a]	not serious	not serious	serious[h]	none	2/125 (1,6%)	10/131 (7,6%)	**RR 0.26** (0,07 to 1.02)	**56 fewer per 1,000** (from 71 fewer to 2 more)	⨁⨁◯◯ Low	NOT IMPORTANT
Incidence of hypoglycemia <54 mg/dl (DPP4i vs. insulin)												
2	randomised trials	not serious	very serious[l]	not serious	very serious[h]	none	3/157 (1.9%)	4/148 (2.7%)	**RR 0.86** (0,05 to 15,06)	**4 fewer per 1,000** (from 26 fewer to 380 more)	⨁◯◯◯ Very low[k]	NOT IMPORTANT
Incidence of hypoglycemia <54 mg/dl (DPP4i vs. insulin, non-randomized)												
2	observational studies	not serious	not serious	not serious	serious[l]	none	7/373 (1.9%)	12/373 (3.2%)	**RR 0.59** (0.23 to 1.50)	**13 fewer per 1,000** (from 25 fewer to 16 more)	⨁⨁⨁◯ Moderate	NOT IMPORTANT
Incidence rate of hypoglycemia patient-day (<70 mg/dl) (DPP4i vs. insulin)												
1	randomised trials	not serious	not serious	not serious	very serious[d,h]	none	1/33 (3.0%)	1/33 (3.0%)	**RR 1.00** (0,07 to 15,33)	**0 fewer per 1,000** (from 28 fewer to 434 more)	⨁⨁◯◯ Low	NOT IMPORTANT

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Two studies with high risk of bias
b. High heterogeneity in total.
c. Wide confidence interval (CI) around the estimate of the effect.
d. Only one study included.
e. Each sample size >200
f. Each sample size <200
g. Few patients.
h. Few events with wide confidence interval (CI) around the estimate of the effect.
i. RR <0.5 based on consistent evidence from 3 studies, with no plausible confounders.
j. Substantial heterogeneity, minimal overlap of confidence intervals.
k. Due to the low certainty, an analysis of nonrandomized studies was performed.
l. Few events.

definition was different between studies, ranging from $>$ 140 to $>$ 300 mg/dl, no significant differences were evident between management with GLP1Ra or DPP4i when compared with insulin, with low to moderate certainty of evidence. This outcome should be examined again in subsequent studies.

Finally, we explored the adverse events frequently reported in the outpatient setting for each group of drugs [32,33], finding no differences in gastrointestinal events in the GLP1Ra and DPP4i group, nor in urinary or renal events in SGLT2i. However, one study did report significant association of GLP1Ra (exenatide) adverse effects with the discontinuation of the drug. These events may be underestimated given the low average hospital stay in the studies evaluated.

In summary, there is growing evidence regarding the effect of new oral or subcutaneous agents for in-hospital management of diabetes in the non-critical setting. The highest quality and quantity of evidence is available to evaluate DPP4i, suggesting that both effectiveness and safety are similar to insulin. Studies with GLP1Ra suggest clinically significant benefits compared to insulin, however, they have greater methodological limitations. The information available regarding SGLT2i is very limited. All the foregoing suggests that these therapies could potentially replace insulin for in-hospital glycemic control, but the quality of the evidence is not yet sufficient to generate a strong recommendation to change routine practice. Nevertheless, the data seems sufficient to motivate larger clinical trials that could confirm the findings presented.

Our review has several strengths. First, we included both RCT and

NRS, which provides a broader view of the available evidence. The fact of including real-life observational studies allowed us to learn about the experience of different institutions where in-hospital management of diabetes with these agents is already being performed, and to evaluate a greater number of patients. The estimation of the certainty of the evidence with the GRADE methodology also allowed us to identify gaps in knowledge.

Nevertheless, there are some limitations that must be acknowledged. We were unable to perform meta-analyses of all outcomes, in some cases due to a lack of information and in others due to insufficient reporting in the primary studies. Similarly, we were not able to explore the risk of publication bias given the limited number of studies found. Moreover, a subgroup analysis to differentiate the results in medical or surgical patients was not possible. This suggests that it is necessary to expand the number of studies and patients included in them to reach more robust conclusions.

5. Conclusion

In-hospital management with incretin-based therapies (DPP4i, GLP1Ra) and SGLT2i with or without sliding scale insulin does not seem to present differences with respect to management with insulin in the usual schemes (BB, BP) in terms of effectiveness and safety, even showing a discrete benefit in mean glucose and incidence of hypoglycemia with GLP1Ra. However, we emphasize that evidence supporting these findings is still scarce. Our study opens the way for large clinical trials that may change the paradigm of insulin use as the cornerstone of diabetes treatment for in-hospital setting in non-critical wards.

Data sharing

All data collected for the study will be available to others.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MJS: declares no conflict of interest. OMM: declares no conflict of interest. JPA: declares no conflict of interest. CEL: declares no conflict of interest. AMG: reports speaker's fees from Novo Nordisk, Elli Lilly, Boehringer Ingelheim, Sanofi, Abbott and Medtronic. DCH: reports speaker's fees from Novo Nordisk, Sanofi, Medtronic and Abbott.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.110019.

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