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Position Paper

Practical management of glucagon-like peptide-1 receptor agonists in gastroenterology: a position paper by the Italian Society of Gastroenterology (SIGE)

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ABSTRACT

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly prescribed for type 2 diabetes and obesity, conditions frequently encountered in gastroenterological practice. Their pleiotropic effects along the gut–pancreas–liver axis have raised both therapeutic interest and safety concerns, particularly regarding hepatic outcomes, gastrointestinal cancers, peri-endoscopic management, and gastrointestinal adverse events.

This position paper, endorsed by the Italian Society of Gastroenterology (SIGE), was developed according to the GRADE framework and provides evidence-based recommendations for the safe and effective management of GLP-1RAs in gastroenterology, highlighting their favorable benefit–risk profile while identifying key knowledge gaps requiring future prospective studies.

GLP-1RAs may be safely used in patients with diabetes or obesity and metabolic dysfunction-associated steatotic liver disease. In cirrhotic patients with diabetes or obesity, GLP-1RAs appear safe and are associated with reduced hepatic decompensation. Available evidence does not support an increased risk of esophageal, gastric, colorectal, or pancreatic cancer, while a potential reduction in hepatocellular carcinoma incidence is suggested. Routine discontinuation of GLP-1RAs before upper gastrointestinal endoscopy is not recommended. GLP-1RAs increase the risk of mild, transient gastrointestinal adverse events and cholelithiasis but are not associated with severe gastrointestinal complications or acute pancreatitis.

1. Introduction

Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs), including the dual receptor agonists acting concurrently on receptors for glucose-dependent insulinotropic polypeptide (GIP), represent new

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and effective drugs for the management of both type 2 diabetes (T2DM) and obesity.

GLP-1 RAs, including albiglutide, dulaglutide, efpeglenatide, exenatide, liraglutide, lixisenatide, orforglipron, and semaglutide, mimic the action of endogenous GLP-1, a gut hormone. Activation of GLP-1 receptors on pancreatic beta cells increases glucose-dependent insulin secretion, inhibits glucagon release, slows gastric emptying, and promotes satiety through the regulation of multiple metabolic pathways [1,2].

Therefore, based on the aforementioned mechanisms, GLP-1 RAs reduce hyperglycemia in people with type 2 diabetes and decrease food intake and body weight, making them an effective treatment for obesity [3]. In addition to significantly improving the glycemic control and determining substantial weight loss in obese patients, GLP-1RAs reduce the risk of cardiovascular and renal disease [4–6], inhibit inflammatory signalling pathways in the liver, thus decreasing steatosis and inflammation [7–9], and are associated to a reduced risk of several gastrointestinal cancers [10–13].

From a pathophysiological perspective, GLP-1 receptor agonists exert complex and heterogeneous effects along the gut–pancreas–liver axis [14–17].

However, some concerns were raised about the safety profile of these drugs, particularly on the gastrointestinal effects of both short-acting and long-acting GLP-1RAs, specifically in relation to their effect on delaying gastric emptying.

The goal of this document, endorsed by the Italian Society of Gastroenterology and Endoscopy (SIGE) is to provide evidence-based recommendations (based on Grading of Recommendations Assessment, Development and Evaluation [GRADE] criteria) [18] to offer a univocal societal guidance for safely managing patients needing GLP-1RA therapy with a particular focus on the gastrointestinal therapeutic options and side effects.

The document is focused on four separate sections: hepatological indications to GLP-1RA therapy; effects on gastrointestinal cancers; peri-endoscopic management of GLP-1RAs; management of gastrointestinal side effects.

2. Methods

The position paper was developed using the GRADE framework [18] (Table 1). The relevant clinical questions were developed a priori and listed in the PICO format (Supplementary Table 1).

Each TF performed a systematic literature search using PubMed/MEDLINE, Embase, Scopus, and the Cochrane library to identify publications from inception till May 2025 (restricted to papers published in the English language), focusing on meta-analyses and published prospective studies, particularly RCTs, performed in humans (Supplementary Table 2). Retrospective analyses and non-randomized studies were also included if they addressed topics not covered in the RCTs.

After further exploration of their content, all the relevant articles were included and summarized in the literature tables for the key topics.

Several web meetings were held between the leader of the project (A.F.) and the TF leaders to discuss and resolve issues, and to finalize the recommendations.

By July 2025, a draft of all of the recommendations in this position paper was prepared by the listed authors. Following approval by the Leader (A.F.), the draft was reviewed by the SIGE Governing Board and, after agreement on a final version, the manuscript was submitted to the journal *Digestive and Liver Disease* for publication. All authors agreed on the final version of the manuscript.

3. Results and recommendations

A summary of all recommendations is provided in Table 2.

3.1. Hepatological indications to GLP-1RA therapy

RECOMMENDATION 1:

The panel suggests that semaglutide should be considered as a disease-modifying therapy in adults with non-cirrhotic MASH and F2–F3 fibrosis, according to current labeling, and supports the use of GLP-1RAs in patients with type 2 diabetes or obesity and MASH, given their favorable safety profile and established cardiometabolic benefits. However, national reimbursement criteria and patient selection policies may influence real-world implementation.

3.1.1. Conditional recommendation, low quality of evidence

Metabolic dysfunction-associated liver disease (MASLD), formerly nonalcoholic fatty liver disease (NAFLD), is a multisystemic disease defined by the presence of hepatic steatosis in 5% of hepatocytes, in addition to at least 1 of 5 cardiometabolic risk factors (overweight/obesity, hypertension, hyperglycemia, dyslipidemia with either low plasma high-density lipoprotein cholesterol or high triglycerides, or treatment for these conditions) and absence of other causes of steatosis (medications, excessive alcohol use, viral hepatitis or other liver diseases) [19]. MASLD represents the most common etiology of chronic liver disease worldwide and it encompasses a broad range of chronic liver conditions, from isolated hepatic steatosis to metabolic dysfunction-associated steatohepatitis (MASH) and the presence of liver fibrosis may lead to cirrhosis, and/or hepatocellular carcinoma (HCC) [20].

The studies testing GLP-1RAs in T2D or obesity showed a significant reduction in liver enzymes and hepatic lipid content, thus suggesting a potential role of these pharmacological agents in MAFLD and MASH [17].

Beyond weight loss–mediated effects, experimental and clinical data suggest that GLP-1RAs exert direct actions on hepatocellular lipid handling and inflammatory signalling, contributing to reductions in steatosis and necroinflammation even in the absence of consistent antifibrotic effects, thus supporting their biological plausibility in MASH [17]. Specifically, GLP-1 RAs have been shown to affect the liver indirectly via their effect on hepatic insulin resistance, weight loss, peripheral plasma insulin and glucose, and improvement in lipotoxicity [21].

However, the results concerning histological improvement with GLP-1 RAs in patients with MASH remain inconclusive. Both a phase 2 trial with liraglutide [22] and a larger RCT evaluating semaglutide [23] demonstrated significant resolution of MASH compared to placebo. Nonetheless, neither study achieved a statistically significant improvement in liver fibrosis. On the other hand, in the interim analysis of the phase 3 ESSENCE study, semaglutide demonstrated significant improvements also in fibrosis stage, alongside MASH resolution, thus raising hope for the final results of the trial [24].

Histological data on combination therapies (semaglutide combined with lipogenesis inhibitors) are not yet available. Nonetheless, early-phase studies with dual agonists such as tirzepatide and survodutide have yielded promising results, demonstrating significant improvements in both MASH resolution and fibrosis stage [9,25].

On the other hand, a clear improvement of liver steatosis, liver enzymes and indexes of fibrosis has been shown in several studies [26–28] and case-control studies have suggested that exposure to GLP1-RAs in patients with T2D is associated with a reduction in liver-related outcomes [29–30].

However, it should be noted that the only available RCT of semaglutide in cirrhotic patients did not demonstrate a histological improvement [31].

As a result, a recent network meta-analysis of 29 RCTs ranked survodutide and tirzepatide among the most effective treatments

Table 1
Interpretation of the certainty in evidence of effects and of strong and conditional recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.

Certainty	Description	
High	We are very confident that the true effect lies close to that of the estimate of the effect	
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect	
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect	
Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not	Most individuals in this situation would want the suggested course of action, but many would not
For clinicians	Most individuals should receive the intervention. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Different choices will be appropriate for individual patients consistent with their values and preferences. Use shared decision-making. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values, and preferences
For policymakers	The recommendation can be adapted as policy or performance measure in most situations	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate

Table 2
Panel recommendations on the management of GLP-1 RAs in gastroenterology.

	Recommendations	Strength of recommendation	Quality of evidence
1.	The panel suggests that semaglutide should be considered as a disease-modifying therapy in adults with non-cirrhotic MASH and F2–F3 fibrosis, according to current labeling, and supports the use of GLP-1RAs in patients with type 2 diabetes or obesity and MASH, given their favorable safety profile and established cardiometabolic benefits. However, national reimbursement criteria and patient selection policies may influence real-world implementation.	Conditional	Low
2.	The panel suggests the use of GLP-1RAs in cirrhotic patients with type 2 diabetes or obesity as they are safe to use and associated with a decreased rate of hepatic decompensation	Conditional	Low
3.	The panel suggests that GLP-1RA therapy could be associated with a decreased incidence of hepatocellular carcinoma in diabetic patients	Conditional	Very low
4.	The use of GLP1-RAs does not increase the risk of esophageal, gastric, or colorectal cancer in patients with type 2 diabetes or obesity.	Strong	High
5.	The panel suggests that the use of GLP1-RAs could be associated with a decreased risk of pancreatic cancer.	Conditional	Very low
6.	The panel suggests against the routine interruption of GLP-1RA therapy before upper gastrointestinal endoscopy; the panel suggests a liquid diet the day before longer and more complex endoscopic procedures and in patients with symptoms suggesting possible retained gastric contents.	Conditional	Very low
7.	The panel does not suggest additional preparation recommendations in patients on GLP-1RA therapy undergoing colonoscopy.	Conditional	Very Low
8.	The use of GLP-1 RAs is not associated with an increased risk of acute pancreatitis	Strong	Moderate
9.	The panel suggests that GLP-1RA therapy increases the incidence of cholelithiasis in patients with diabetes, overweight/obesity and MASH/MAFLD.	Strong	Moderate
10.	The use of GLP-1 RAs is associated with an increased risk of GERD and mild gastrointestinal side effects, typically transient and dose-dependent. The use of GLP-1 RAs is not associated with an increased risk of severe gastrointestinal adverse events compared to placebo.	Strong	Moderate

for achieving MASH resolution without worsening of fibrosis but not as the best choice to achieve fibrosis regression [32].

Based on the evidence reported above, semaglutide has received accelerated approval by the Food and Drug Administration (FDA) and, more recently, the European Medicines Agency (EMA) granted marketing authorization for the treatment of adults with non-cirrhotic MASH and moderate to advanced fibrosis (F2–F3). Moreover, major society guidelines consider their use in patients with diabetes or obesity associated with MASLD [19,33,34].

The TF performed a literature search finding 6 RCTs comparing GLP-1RAs vs placebo in terms of MASH resolution and ≥1 point reduction in fibrosis [9,22–25,31] (Supplementary Table 3). The results of the meta-analysis are reported in the Supplementary Table 4.

GLP-1RAs determined a significantly higher rate of MASH resolution (RR 5.36, 3.08-9.34, I^2=36.8%) and reduction in fibrosis both overall (RR 1.32, 1.13-1.56; I^2=0%) and in the subset of non-cirrhotic patients (RR 2.08, 1.40-3.07; I^2=4.4%).

Therefore, emerging evidence indicates that, in MASH individuals with F2-F3 liver fibrosis, once-weekly semaglutide at a dose of 2.4 mg improved liver histology independently of diabetes [24]. However, national reimbursement criteria and patient selection policies may influence real-world implementation.

3.1.2. Quality of evidence

The risk of bias assessment for each study was reported in the Supplementary Table 5. Overall, the included studies were felt to be at good quality. The certainty of evidence for the clinical outcomes in this PICO question was downgraded due to the high inconsistency related to high heterogeneity in the estimates and indirectness due to different drugs, duration of therapy and dosage of GLP-1RAs (Supplementary Table 6).

RECOMMENDATION 2:

The panel suggests the use of GLP-1RAs in cirrhotic patients with type 2 diabetes or obesity as they are safe to use and associated with a decreased rate of hepatic decompensation.

3.1.3. Conditional recommendation, low quality of evidence

Liver cirrhosis determines the dysfunction in metabolism of drugs with consequent reduced drug elimination. Therefore, some concerns have been raised on the use of antidiabetic drugs in patients with liver cirrhosis [35].

However, GLP-1RAs undergo minimal hepatic metabolism and display a pharmacokinetic profile that is largely preserved across stages of liver dysfunction, providing a mechanistic rationale for their favourable safety profile in patients with compensated and decompensated cirrhosis [36]. Once cirrhosis is present, the prevention of cirrhotic decompensation can be challenging and preliminary studies seem to suggest a beneficial role of GLP-1RAs in this regard.

RCTs usually exclude cirrhotic populations and they are commonly underpowered to detect potential differences in terms of liver-related events.

An RCT enrolling 71 patients with NASH-related cirrhosis and T2D showed that semaglutide does not increase overall AEs and liver-related events as compared to placebo [31]. However, the limited sample size and the relatively short follow-up length prevented a valid assessment of the risk of liver decompensation. A recent phase-I open-label prospective series testing survodutide found it generally tolerable in patients with compensated or decompensated cirrhosis, not requiring pharmacokinetic-related dose adjustment [36].

The TF performed a literature search finding 3 propensity score adjusted series comparing GLP-1RAs use vs non-use in cirrhotic patients [29,37–38] (Supplementary Table 7). As reported in Supplementary Figure 1, the adjusted HR for liver decompensation was significantly lower in GLP-1RAs users (aHR 0.71, 0.61-0.82; I^2=0%). Notably, the study by Yen et al. [37] reported also a significantly lower risk of death (aHR 0.47, 0.32-0.69) and of major cardiovascular events (aHR 0.6, 0.41-0.87) in GLP-1RAs users as compared to non-users.

Therefore, based on the currently available evidence, the panel suggested the use of GLP-1RAs in patients with cirrhosis and T2D and/or obesity.

3.1.4. Quality of evidence

The risk of bias assessment for each study was reported in the Supplementary Table 8. Overall, the included studies were felt to be at good quality. The certainty of evidence for the clinical outcomes in this PICO question was downgraded because the evidence was based on non-randomized studies (Supplementary Table 6). Therefore, the TF concluded by making a conditional recommendation supporting the use of GLP-1RAs in cirrhotic patients with T2D and/or diabetes, with low quality of evidence.

3.2. Effects of GLP-1RAs on gastrointestinal cancers

RECOMMENDATION 3:

The panel suggests that GLP-1RA therapy could be associated with a decreased incidence of hepatocellular carcinoma in diabetic patients.

3.2.1. Conditional recommendation, very low quality of evidence

The metabolic syndrome, characterized by a high prevalence of T2DM, is well known to significantly increase the incidence of liver-related events in patients with chronic liver disease and cirrhosis, including liver decompensation and HCC [39–41].

Therefore, GLP-1RAs, which proved to be effective in the therapeutic management of T2DM, could be associated with a decreased risk of the major liver-related outcomes, although the evidence supporting this effect still seems weak and not robust enough to draw definitive conclusions in this regard [17].

From a biological standpoint, the potential chemoprotective effect of GLP-1RAs on hepatocellular carcinoma may be mediated by improvements in insulin resistance, chronic inflammation, and hepatic steatosis, all of which are established drivers of hepatocarcinogenesis [17,39].

A preliminary meta-analysis of RCTs did not find a significant chemoprotective effects of GLP-1RAs against liver and other specific abdominal cancers [13].

On the other hand, several meta-analyses of large retrospective nationwide databases showed that GLP-1RA therapy was associated with a consistent decrease in HCC incidence [42–44].

Furthermore, a recent umbrella review of systematic reviews and meta-analyses assessing several different lifestyle-related and pharmacological risk factors for HCC confirmed the protective role of these drugs, along with other medications such as statins [45], aspirin [46] and metformin [47], although still with limited evidence [48].

While the highest evidence should be based on results of RCTs, it should be noted that RCTs specifically designed to detect the correlation between GLP-1RAs use and HCC incidence are lacking and the studies included in the aforementioned meta-analysis of RCTs [13] were not adequately powered and did not report a follow-up time long enough to capture a potential association between GLP-1RAs use and abdominal cancers, including HCC. Ideally, the best evidence that may be currently available should be based mainly on large nationwide cohort studies, properly matched with a control group of non-users and reporting adjusted outcomes according to several potential confounders such as presence of diabetes, other medications, and cirrhosis.

Following these premises, the TF decided to base the evidence on a recent meta-analysis [42] of five cohort studies [12,38,49–51] adjusting the analysis of the outcomes for potential confounding factors such as age, sex, race, family history of cancer, obesity, complications of T2DM, and comorbidities. All these studies were based on a propensity score (matching or weighting) analysis (Supplementary Table 9).

GLP-1 RAs were found to significantly decrease the risk of HCC both in the overall population (aHR: 0.42, 0.19-0.93; Supplementary Figure 2a) and in the subset of patients with cirrhosis (aHR: 0.44, 0.25-0.76; Supplementary Figure 2b). Of note, the high heterogeneity observed (I^2= 93%, p<0.00001) was mainly due to the different magnitude of the effect rather than its different direction.

3.2.2. Quality of evidence

The risk of bias assessment for each study was reported in the Supplementary Table 10. Overall, the included studies were felt to be at good quality. The certainty of evidence for the clinical outcomes in this PICO question was downgraded owing to the fact that there were only observational studies included and due to the high inconsistency related to high heterogeneity in the estimates and indirectness due to different drugs, duration of therapy and dosage of GLP-1RAs (Supplementary Table 6). Therefore, the TF concluded by making a conditional recommendation in favour of the chemoprotective role of GLP-1RAs against the incidence of HCC, with very low quality of evidence.

RECOMMENDATION 4:

The use of GLP1-RAs does not increase the risk of esophageal, gastric, or colorectal cancer in patients with type 2 diabetes or obesity.

3.2.3. Strong recommendation, high quality of evidence

Concerns regarding a potential carcinogenic effect of GLP1-RAs on gastrointestinal cancers have been extensively investigated.

In a study published in 2025 by Ungvari et al. [52] based on a database of 7007 patients with various types of cancer (including 80 esophageal carcinomas, 375 stomach cancer, 454 colorectal cancers), overall survival appeared to vary according to GLP-1 receptor gene expression. Nevertheless, large clinical studies have consistently failed to demonstrate any association between GLP-1 RAs use and increased risk of esophageal, gastric, or colorectal malig-

nancies [53–58]. The association between GLP-1 RAs use and colorectal cancer has been more extensively evaluated. A recent meta-analysis including over 2 million patients showed that GLP-1 RA use was associated with a significant reduction in colorectal cancer risk compared to insulin (RR 0.57, 95% CI 0.32–0.81), thiazolidinediones (RR 0.82, 95% CI 0.68–0.96), and SGLT2 inhibitors (RR 0.77, 95% CI 0.59–0.95) [59]. Conversely, when compared to metformin, DPP-4 inhibitors, or sulfonylureas, no significant risk differences were found. However, in a systematic review of RCTs only no differences respect to placebo control group were found (RR 1.13, 95% CI 0.92–1.39) [13].

The TF decided to base the evidence on the above reported recent meta-analysis [13] of RCTs as no new evidence was available, hence highlighting the lack of association between GLP-1RAs use and increased risk of gastrointestinal cancers.

3.2.4. Quality of evidence

As reported in the meta-analysis of RCTs by Figlioli et al. [13], all the RCTs were deemed at high quality and there was no evidence of indirectness, publication bias, inconsistency and imprecision. Of note, although the 95 % CIs for the summary estimates included 1, they did not cross any of the thresholds selected regarding the magnitude of effect (the three thresholds selected were absolute effects of 0.5 % for small effect, 1.3 % for moderate effect, and 2.6 % for large effect); hence, the quality of evidence was not downgraded for imprecision [13].

Therefore, the TF provided a strong recommendation with high quality of evidence supporting the non-association between GLP-1RAs use and the incidence of major gastrointestinal cancers.

RECOMMENDATION 5:

The panel suggests that the use of GLP1-RAs could be associated with a decreased risk of pancreatic cancer.

3.2.5. Conditional recommendation, very low quality of evidence

Incretins have pleiotropic effects on digestive functions and the exocrine pancreas, such as stimulating cell proliferation. For this reason, concerns have been raised about the possible adverse effects of GLP-1RAs on the pancreas. Some preliminary studies, such as animal toxicology studies [60], epidemiological research [61], and case reports [62] reported a higher risk of developing pancreatic dysplasia and neuroendocrine tumors. A recent pharmacovigilance study by Cao et al. [63] using the FDA Adverse Event Reporting System (FAERS) database provided a warning regarding a high risk of pancreatic cancer in patient using all types of GLP1-RAs (except for albiglutide). However, many clinical studies [10,64–67] based on large databases with long follow-up (even superior to 7 years) did not find association of GLP1-RAs with the risk of pancreatic cancer.

Two meta-analyses [13,68] involving 11869 patients in 15 RCTs and 94279 patients in 49 studies confirmed the absence of an increased risk of pancreatic cancer. However, these results are derived from studies that were not specifically designed to assess the incidence of pancreatic cancer, but rather from RCTs or large cohort studies with broader outcomes, so probably underpowered to detect this specific endpoint.

The TF conducted a meta-analysis that included these data along with studies specifically investigating pancreatic cancer risk. A total of 47 RCTs (all included in the meta-analysis by Figlioli et al.) [13] and 4 additional retrospective studies [10,64–66] were included, encompassing 26,426,551 patients (Supplementary table 11).

GLP-1 RAs users demonstrated a significantly lower risk of pancreatic cancer (OR 0.667, 95% CI 0.510–0.873, I^2 = 74.53%, p < 0.001) (Supplementary Figure 3). Subgroup analysis restricted to “pancreatic cancer-specific studies” confirmed these findings. No specific studies on the risk of developing pancreatic neuroendocrine tumors are currently available.

3.2.6. Quality of evidence

The studies were deemed mainly at high quality (Supplementary Table 12) and there was evidence of indirectness, and inconsistence; hence, the quality of evidence was downgraded to very low.

Therefore, the TF provided a conditional recommendation with very low quality of evidence suggesting a decreased incidence of pancreatic cancer in patients using GLP-1RAs.

3.3. Peri-endoscopic management of GLP-1RA therapy

RECOMMENDATION 6:

The panel suggests against the routine interruption of GLP-1RA therapy before upper gastrointestinal endoscopy; the panel suggests a liquid diet the day before longer and more complex endoscopic procedures and in patients with symptoms suggesting possible retained gastric contents.

3.3.1. Conditional recommendation, very low quality of evidence

GLP-1RAs are well-known to delay gastric emptying and this effect has raised concerns in patients undergoing surgical and endoscopic procedures, particularly upper endoscopies, due to the alleged increased risk of aspiration and reduced diagnostic yield of the examinations related to the risk of retained gastric content (RGC).

Based on preliminary studies [69–71], the American Society of Anesthesiologists (ASA) has recently issued consensus-based perioperative guidance suggesting that GLP-1RAs should be withheld prior to the procedure or surgery, regardless of the indication (T2DM or weight loss), dose, or the type of procedure/surgery [72]. On the other hand, the American Gastroenterology Association (AGA) has recommended an individualized approach to managing patients on GLP-1 RAs in the pre-endoscopic setting, pointing out the scarce data supporting this policy, and they emphasized the importance of not withholding the therapy in patients who do not exhibit symptoms suggesting RGC, being the risk of withholding the therapy, particularly in diabetic patients, considerably higher than the risk of aspiration.

Despite conflicting results of individual studies, a meta-analysis showed only mild gastric emptying delay (~36 minutes per T1/2) on solid phase scintigraphy and no significant differences on modalities reflective of liquid emptying with GLP-1 RA use [73]. Another recent meta-analysis of 13 studies (84,065 patients) found that GLP-1RA therapy exhibited significantly higher rates of RGC (adjusted odds ratio [aOR] 4.20, 3.42-5.15), of aborted and repeated procedures (OR 5.13, 3.01-8.75, and OR 2.19, 1.43-3.35; respectively); however, no significant differences were found in adverse events (AE) and aspiration rates between the two groups (OR 4.04, 0.63-26.03, and OR 1.75, 0.64-4.77; respectively) [74]. These results were confirmed in other two recent meta-analyses of observational studies [75–76].

The TF updated these previous meta-analyses and found 18 observational studies, of which 4 conference abstracts, comparing the incidence of RGC and aspiration between patients on GLP-1RA therapy and matched controls [69–71,77–91] (Supplementary Table 13). The TF did not find any relevant RCTs.

GLP-1 RAs were found to significantly increase the risk of RGC (OR 5.43, 3.72-7.91; I^2=78%; Supplementary Figure 4a), while they did not increase the risk of repeated procedures (OR 3.90, 0.86-17.82; I^2=45%; Supplementary Figure 4b) nor of aspiration (OR 1.75, 0.64-4.77; I^2=61%; Supplementary Figure 4c). Particularly, pooled rates of bronchial aspiration were found to be 0.3% (0.001%-

0.1%) and 0.2% (0.001%-1%), respectively, with a number needed to scope to observe one event of aspiration of 794 (-500 to 950) [74].

Previous studies found RGC might not represent an issue in patients undergoing combined esophagogastroduodenoscopy and colonoscopy, unlike esophagogastroduodenoscopy alone, presumably because of fasting and consumption of only a liquid diet the day before the procedures [69,86].

The real impact of RGC on the diagnostic yield and the feasibility of the procedure is variable and although its incidence was significantly superior as compared to controls, the incidence of aborted and repeated procedures was overall low with a reported rate of 1.5% and 2.4%, respectively, in the largest series [78]. Therefore, the routine interruption of GLP-1RAs before upper gastrointestinal endoscopy does not seem to be supported by the evidence; on the other hand, an individualized approach based on the indication of GLP-1RAs use (withholding the drug in patients with diabetes could lead to more harm than benefits) and the presence of symptoms related to RGC could represent the best choice in this setting, as suggested by the AGA [92].

Based on the observation of reduced risk of RGC in patients on GLP-1RA therapy undergoing same day gastroscopy and colonoscopy, a potential strategy could be to place patients on a liquid diet the day before endoscopy thus prolonging the duration of fasting for solid for at least 12 hours, particularly in the case of longer and more complex procedures and in patients with symptoms suggestive of RGC such as dyspepsia, nausea or vomiting.

It should be noted that the limited data on newer and more potent GLP-1RAs such as semaglutide or tirzepatide calls for a note of caution in this regard. A recent large retrospective study showed 0.4% risk of bronchial aspiration with semaglutide, not superior to another new class of drugs, the sodium-glucose cotransporter-2 (SGLT-2) inhibitors [93]; however, further data are needed to provide definitive recommendations.

3.3.2. Quality of evidence

The risk of bias assessment for each study was reported in the Supplementary Table 14. Overall, the included studies were felt to be at good quality. The certainty of evidence for all clinical outcomes in this PICO question was downgraded owing to the fact that there were only observational studies included and due to the high inconsistency related to high heterogeneity in the estimates and indirectness due to different drugs and dosage of GLP-1RAs (Supplementary Table 6). Therefore, the TF concluded by making a conditional recommendation against the routine interruption of GLP-1RA therapy before upper gastrointestinal endoscopy with very low quality of evidence.

RECOMMENDATION 7:

The panel does not suggest additional preparation recommendations in patients on GLP-1RA therapy undergoing colonoscopy.

3.3.3. Conditional recommendation, very low quality of evidence

The effectiveness and the diagnostic yield of colonoscopy is strictly dependent on a proper bowel preparation, defined as Boston bowel preparation score (BPPS) $\geq$ 6 in which all three colon segments have scores $\geq$ 2 [94].

Several factors were associated with incomplete bowel preparation (IBP), including diabetes, obesity, constipation, and several medications.

The aforementioned effects of GLP-1 RAs in slowing gastrointestinal motility raised concerns about their potential detrimental impact on bowel preparation. However, although GLP-1RAs may slow gastrointestinal transit, their effect on colonic motility appears modest and insufficient, on average, to significantly impair bowel cleansing when standard preparation regimens are appropriately followed [75].

Data on the impact of GLP-1RA therapy on colonoscopy cleansing are scarce and conflicting. While a preliminary study showed a lower BBPS score in GLP-1RA users than in non-users (P = 0.046) [95], other two studies in diabetics found no significant difference in the two groups [96–97].

More recently, a large Israeli study with a propensity score matched analysis found a significantly higher rate of IBP among GLP-1RA users (10%) compared with the non-GLP-1RA group (4%; P<0.001) [98].

The TF performed a meta-analysis of 7 studies, of which 3 conference abstracts [96–102] (Supplementary Table 15).

Although mean BPPS score was lower in patients in GLP-1 RA therapy (-0.27, -0.46 to -0.07; I^2=64%; Supplementary Figure 5a), the rate of IBP was not significantly different between the two groups (OR 1.39, 0.96-2.02; I^2=87%; Supplementary Figure 5b). These results were in line with a previous meta-analysis published before the Israeli study [75].

Based on the limited available evidence and with the caveat of further studies needed to draw definitive conclusion in this regard, the TF decided to not suggest additional recommendations about bowel preparation for patients in GLP-1RA therapy undergoing colonoscopy.

3.3.4. Quality of evidence

The risk of bias assessment for each study was reported in the Supplementary Table 16. Overall, the included studies were felt to be at low quality. The certainty of evidence for all clinical outcomes in this PICO question was downgraded owing to the fact that there were only observational studies included and due to the high inconsistency related to high heterogeneity in the estimates, the indirectness due to different drugs and dosage of GLP-1RAs, and the high risk of bias in the literature (Supplementary Table 6). Therefore, the TF concluded by making a conditional recommendation against additional prescriptions about bowel preparation in patients in GLP-1RA therapy before colonoscopy with very low quality of evidence.

3.4. GI adverse events

RECOMMENDATION 8:

The use of GLP-1 RAs is not associated with an increased risk of acute pancreatitis.

3.4.1. Strong recommendation, moderate quality of evidence

After approval for clinical use of the first GLP-1 RA, exenatide in 2005, several cases of acute pancreatitis apparently associated with this drug were reported to the Food and Drug Administration (FDA) through MedWatch (the US FDA Adverse Event Reporting System or FAERS), prompting the FDA to issue a label update for both GLP-1 RAs as well as DPP-4 inhibitors warning about acute pancreatitis as a possible adverse effect.

In the most recent report from the FAERS, Osei et al. [103] found Exenatide and Liraglutide to be associated with claims of pancreatitis. However, such records are prone to bias and pancreatitis might have been reported because of an increase in pancreatic enzyme values associated with unspecified abdominal complaints, in the absence of an established acute pancreatitis. This distinction is particularly relevant in clinical practice, as asymptomatic elevations of pancreatic enzymes are relatively common in patients with diabetes and obesity and should not be misinterpreted as acute pancreatitis in the absence of clinical and imaging criteria [104,105].

Interestingly, in a small RCT on patients with diabetes, liraglutide increased lipase levels after 6 weeks and plasma trypsinogen after 12 weeks and tended to increase pancreatic volume, that was in turn associated with increased amylase levels [67].

Moreover, patients with diabetes and obesity may have an unspecific increase of amylase or lipase levels, independently from the use of GLP-1 RAs.

Finally, patients with diabetes, obesity and cardiac disorders with indication to treatment with GLP-1 RAs, carry an increased risk of pancreatitis due to higher odds of biliary stones and alcohol use and of concurrent pancreato-toxic drugs, prompting cautions when evaluating data from non-controlled studies where association might not be causation.

In the setting of RCTs of GLP-1 RAs, there is no increased risk for acute pancreatitis associated with GLP-1RA use compared to placebo [106–109].

The TF reviewed the literature and did not find any additional studies on the topic; therefore, the statement was based on the results of the above reported meta-analyses of RCTs (Supplementary Table 17).

Specifically, the recent meta-analysis by Badve et al. [107] reported 0.3% pancreatitis rate in both GLP-1 RAs users and non-users (HR 1.02, 0.78-1.33), thus excluding any significant differences between the two groups. However, it needs to be acknowledged that most registrative trials and several large observational studies did exclude patients with a history of pancreatitis or other conditions considered to confer a high baseline risk of pancreatitis, such as alcohol abuse, while evidence in patients with a history of pancreatitis remains limited.

3.4.2. Quality of evidence

The level of evidence in this PICO question was considered moderate due to the risk of indirectness related to different drugs and dosage of GLP-1RAs (Supplementary Table 6). Therefore, the TF concluded that GLP-1RAs do not increase the risk of pancreatitis, based on a strong recommendation with moderate quality of evidence.

RECOMMENDATION 9:

The panel suggests that GLP-1RA therapy increases the incidence of cholelithiasis in patients with diabetes, overweight/obesity and MASH/MAFLD.

3.4.3. Strong recommendation, moderate quality of evidence

The use of GLP-1RAs has been associated with a potential risk of gallbladder or biliary tract diseases. This is secondary to the mechanism of GLP-1RAs that may suppress cholecystokinin secretion, inhibit gallbladder motility, and delay gallbladder emptying. These mechanisms may lead to bile sludging and stone formation. In this context, the inhibition of gallbladder contractility represents a direct pharmacodynamic effect of GLP-1RAs, independent of weight loss, providing a coherent pathophysiological explanation for the increased risk of cholelithiasis observed across randomized trials and real-world studies [110].

Additionally, the rapid weight loss often induced by GLP-1RAs may result in bile supersaturated with cholesterol, increasing the risk of gallstone formation [110–111].

Furthermore, diabetes itself is an independent risk factor for cholelithiasis.

The TF performed a literature search and found 37 RCTs, already included in the meta-analysis by Chiang et al. [112], comparing GLP-1RAs vs placebo in patients with type 2 diabetes mellitus and MASLD and reporting the incidence of cholelithiasis. The results of the meta-analysis are reported in the Supplementary Table 18.

The pooled analysis (37 RCT, 90,299 participants) found that GLP-1RAs increased the risk of cholelithiasis (RR=1.33; 95% CI 1.10–1.60, P=0.003, I^2=0%) (Supplementary Figure 6).

The subgroup analysis by molecule confirmed a higher risk of cholelithiasis for semaglutide (P=0.04) and liraglutide (P=0.002) (Supplementary Figure 7).

These findings are in line with those of a recent real-world, multicenter observational study involving 308 patients with type 2 diabetes mellitus, which found that GLP-1 Ras, above all liraglutide followed by semaglutide, were significantly associated with a higher risk of clinically relevant (i.e., symptomatic) cholelithiasis [113].

3.4.4. Quality of evidence

The level of evidence was considered moderate due to the risk of indirectness related to different drugs and dosage of GLP-1RAs (Supplementary Table 6). Therefore, the TF concluded that GLP-1RAs increase the risk of cholelithiasis, based on a strong recommendation with moderate quality of evidence.

RECOMMENDATION 10:

The use of GLP-1 RAs is associated with an increased risk of GERD and gastrointestinal side effects, typically transient and dose-dependent. The use of GLP-1 RAs is not associated with an increased risk of severe gastrointestinal adverse events compared to placebo.

3.4.5. Strong recommendation, moderate quality of evidence

The pharmacologic action of delaying gastric emptying and reducing appetite of GLP-1RAs is closely related to mild gastrointestinal (GI) side effects, mainly nausea, vomiting, diarrhea, and constipation [114]. These effects are generally dose-dependent and class-related, arising from the mechanism of slowed gastric motility and central appetite suppression.

Across trials, nausea is the most frequently reported GLP-1 RA side effect, affecting roughly 20–40% of patients depending on the study population, agent and dose [108]. The incidence of diarrhea and vomiting is also increased, each occurring in approximately 10–20% of patients, while constipation is reported in a smaller fraction (typically 5–15%) [115–116].

Constipation, although less frequently reported than nausea or diarrhea, may be more persistent over time, particularly in patients with pre-existing slow colonic transit or reduced physical activity [16,117].

Most GI events are mild to moderate and patients usually experience these symptoms early in the first 4–8 weeks and symptoms tend to diminish over time as tolerance develops [115]. Consistently, short-term use of GLP-1 RAs is associated with more frequent GI symptoms, whereas by around 20–30 weeks of continued therapy the incidence of new GI events declines toward rates observed in control groups [108].

Serious GI complications (such as dehydration, perforation or rare bowel obstruction) are uncommon, and severe AEs are comparable to placebo in clinical trials [108,116].

The GI tolerability of GLP-1 RAs is clearly dose-related. A systematic analysis of phase III trials confirmed that nausea and diarrhea increase in a dose-dependent manner across the GLP-1 RA class ($P<0.01$ for trend) [114].

Vomiting showed a similar dose trend, though not always statistically significant. These findings support the recommended practice of gradual dose escalation with GLP-1 RAs to improve tolerability.

While GI AEs are a class-wide effect, their incidence can differ slightly among individual GLP-1 RAs. Head-to-head evidence and real-world data suggest that newer, more potent agents may have higher rates of certain GI events [114,116,118].

Drug titration and patient education are crucial to manage GI AEs: subjects should be counseled on eating smaller, more frequent meals and avoiding large high-fat meals to lessen nausea. Maintaining adequate hydration is important, especially if vomiting or diarrhea occurs. If nausea is significant, over-the-counter or prescribed antiemetic agents can be used. For diarrhea, if dietary

adjustments fail, anti-diarrheal agents such as loperamide or probiotics may be considered for a limited time [119]. Constipation, though less common than nausea, may have a longer duration; increasing fluid and fiber intake, physical activity, or using stool softeners can mitigate this issue. In all cases, if side effects remain intolerable despite supportive measures, a reduction in the GLP-1 RA dose or a switch to an alternative agent might be necessary to improve patient comfort [119].

The TF performed a literature search and found 55 RCTs comparing GLP-1RAs vs placebo in patients with type 2 diabetes mellitus and MASLD in terms of GI AEs, thus confirming the studies included and the results of a previous meta-analysis [112].

The pooled analysis found that GLP-1RAs increased the risk of GERD (RR= 2.19; 95% CI, 1.48–3.25; I^2=59.3%) whereas no difference in terms of severe GI complications was found [112].

3.4.6. Quality of evidence

The level of evidence was considered moderate due to the risk of indirectness related to different drugs and dosage of GLP-1RAs (Supplementary Table 6). Therefore, the TF concluded that GLP-1RAs increase the risk of GERD and mild GI AEs, based on a strong recommendation with moderate quality of evidence.

4. Unmet needs and evidence gaps

As it is evident above, the majority of the recommendations in this document are based on low or very low quality evidence owing to the lack of RCTs on these topics. The low quality of the evidence points out the pressing need for prospective studies and RCTs in this field. Various unmet needs, such as the impact of duration of therapy, the dosage of these drugs, and the impact of different molecules on the aforementioned outcomes, still need to be addressed in the literature. Moreover, the relationship between objective measures of gastrointestinal motility and the occurrence or severity of symptoms such as nausea and vomiting remains incompletely understood, suggesting that mechanisms beyond delayed gastric emptying, including central pathways, deserve further investigation [120].

Declaration of competing interest

All the other authors have no proprietary, financial, professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the position presented in, or the review of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2026.02.018.

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