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1 **Glucagon-like peptide-1 receptor agonists across the spectrum of heart failure**

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42

43 **Abstract**

44 Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have been used to reduce
45 body weight in overweight or people with obesity and to improve glycemic control
46 and cardiovascular outcomes among people with type 2 diabetes (T2D) and a high
47 cardiovascular risk. However, the effects of GLP-1 RA may be modified by the
48 presence of heart failure (HF). In this review, we summarize the evidence for the use
49 of GLP-1 RA across patient's risk with a particular focus in HF. After a careful review
50 of the literature, we challenge the current views about the use of GLP-1 RA and
51 suggest performing an active HF screening (with directed clinical history, physical
52 examination, an echocardiogram, and natriuretic peptides) before initiating a GLP-1
53 RA. After HF screening, we suggest GLP-1 RA treatment decisions as follows: 1) in
54 people with T2D without HF, GLP-1 RA should be used for reducing the risk of
55 myocardial infarction and stroke, with a possible effect to reduce the risk of heart
56 failure hospitalizations; 2) in patients with a heart failure and preserved ejection
57 fraction (HFpEF), GLP-1 RA do not reduce HF hospitalizations but may reduce
58 atherosclerotic events, and their use may be considered in an individualized manner;
59 and 3) in patients with heart failure and reduced ejection fraction (HFrEF), the use of
60 GLP-1RA warrants caution due to potential risk of worsening HF events and
61 arrhythmias, pending risk-benefit data from further studies.

62

63 Key-words: Glucagon-like peptide-1 receptor agonists; Heart failure; Risk
64 modification.

65

66 **Introduction**

67 Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have been used to reduce
68 body weight in overweight or people with obesity and to improve glycemic control
69 and cardiovascular outcomes among people with type 2 diabetes (T2D) and a high
70 cardiovascular risk.¹⁻³

71 Despite the well-documented benefits of GLP-1 RA, these may not be generalized to
72 all patient-populations. For example, in patients with heart failure (HF), particularly
73 heart failure with reduced ejection fraction (HFrEF), some studies suggested that
74 GLP-1 RA may produce harmful effects, increasing the risk of HF hospitalizations
75 and ventricular arrhythmias.⁴⁻⁶ Despite these data, current recommendations do not
76 provide guidance on GLP-1 RA prescription to patients with HF nor they differentiate
77 between the prevention of HF in those at risk versus the treatment of patients with
78 overt HF. Furthermore, these documents do not differentiate among those with
79 different HF phenotypes.⁷

80 Based on the available data, we postulate that the decision to use a GLP-1 RA
81 should be weighted versus the risk of each individual patient, particularly according
82 to HF status, symptoms, and ejection fraction (EF). In this review, we provide a
83 practical guidance for the use of GLP-1 RA according to patient's risk and HF status,
84 backed by data from randomized controlled trials (RCTs).

85

86 **Overweight or obesity without diabetes or heart failure**

87 Obesity is a major public health issue affecting approximately 40% of the adult
88 population worldwide, and is associated with an increased risk of cardiovascular
89 events¹. GLP-1 RA reduce body weight, as adjuncts to lifestyle intervention.

90 The potential cardiovascular benefits of GLP-1 RA in overweight or people with
91 obesity without T2D are not well-established, mainly because GLP-1 RA trials in
92 overweight people or with obesity were relatively small or with a short follow-up time.
93 Moreover, overweight or people with obesity without T2D or additional
94 cardiovascular risk factors have low rate of cardiovascular events.

95 Still, a meta-analysis of RCTs including 11430 people overweight or people with
96 obesity without T2D randomized to either a GLP-1 RA or placebo, suggested that
97 GLP-1 RA might reduce the risk of any adverse cardiovascular event.³ The
98 occurrence of HF events or cardiac arrhythmias was rare, in concordance with the low
99 cardiovascular risk of this population.

100 The ongoing Semaglutide Effects on Heart Disease and Stroke in Patients With
101 Overweight or Obesity trial (SELECT; NCT03574597) and Study of Tirzepatide on
102 the Reduction on Morbidity and Mortality in Adults With Obesity (SURMOUNT-MMO;
103 NCT05556512) will provide more robust evidence on the effect of the GLP-1 RA on
104 cardiovascular outcomes in overweight or people with obesity without T2D. However,
105 a recent meta-analysis suggested that GLP-1 RA potentially reduce cardiovascular
106 events in overweight or people with obesity without HF.³

107

108 **Type 2 diabetes without heart failure**

109 Patients with T2D with high cardiovascular risk but without HF, benefit from GLP-1
110 RA for the reduction of atherosclerotic cardiovascular events (i.e., myocardial
111 infarction, ischemic stroke, or cardiovascular death: 3P-MACE).

112 Several trials comparing GLP-1 RA vs. placebo performed analysis stratified on HF
113 status. However, it is important to highlight that in these trials 80% or more of the
114 enrolled patients did not have HF diagnosis, although an echocardiogram or
115 natriuretic peptides were rarely available in these trials.⁸⁻¹⁵

116 Overall, the findings suggest that GLP-1 RA may be useful to prevent HF
117 hospitalizations among patients without HF.^{9-14,16-21} Specifically, the effect of GLP-1
118 RA vs. placebo on the composite of HF hospitalizations or cardiovascular death in
119 patients without HF history, gave a meta-analyzed pooled hazard ratio (HR) of 0.85,
120 with a 95% confidence interval (95%CI) ranging from 0.76 to 0.94. More specifically,
121 the effect of GLP-1 RA vs. placebo on HF hospitalizations alone yielded a borderline
122 result, with a HR of 0.81, with 95%CI ranging from 0.63 to 1.03. The effect of GLP-1
123 RA vs. placebo on cardiovascular mortality gave a meta-analyzed HR of 0.85, with
124 95%CI ranging from 0.76 to 0.94. GLP-1 RA were also superior to placebo in
125 reducing 3P-MACE, with a meta-analyzed HR of 0.88, 95%CI 0.83 to 0.93.²²

126 The GRADE (A Comparative Effectiveness Study of Major Glycemia-lowering
127 Medications for Treatment of Type 2 Diabetes; NCT01794143) trial compared the
128 effectiveness of four commonly used glucose-lowering medications (insulin glargine,
129 glimepiride, liraglutide, and sitagliptin) on top of metformin.²³ Compared to all other
130 treatments, assignment to liraglutide resulted in lower rate of HF hospitalizations with
131 an HR of 0.49, 95%CI 0.28 to 0.86, but the number of heart failure events was small.
132 and lower rate of death from cardiovascular causes with an HR of 0.47, 95%CI 0.23
133 to 0.93. Liraglutide also tended to reduce 3P-MACE with an HR of 0.75, 95%CI 0.54
134 to 1.03. Results according to HF subgroups were not presented in this analysis;
135 however, few patients were expected to have symptomatic HF. The GRADE

136 population had a low cardiovascular risk, with overall HF hospitalization rates inferior
137 to 0.4 events per 100 patient-years and cardiovascular death rates inferior to 0.3
138 events per 100 patient-years due to the exclusion of patients with a history of a major
139 cardiovascular event in the year before randomization, HF with a New York Heart
140 Association (NYHA) functional classification of III or higher, and an estimated
141 glomerular filtration rate (eGFR) of less than 30 ml/min/1.73m².

142 Together, these results support the use of GLP-1 RA for reducing atherosclerotic
143 events in patients with T2D without HF, with a possible effect to reduce heart failure
144 hospitalizations.

145

146 **Type 2 diabetes with heart failure and preserved ejection fraction**

147 In contrast to patients with T2D without HF, those with HF (representing 15-20% of
148 patients in trials) did not seem to benefit from GLP-1 RA for reducing HF
149 hospitalizations or cardiovascular death. Still, GLP-1 RA may reduce atherosclerotic
150 events in patients with T2D and HF.⁸⁻¹⁵

151 The effect of GLP-1 RA vs. placebo on the composite of HF hospitalizations or
152 cardiovascular death in patients with HF gave a meta-analyzed HR of 0.96, 95%CI
153 0.84 to 1.08. The meta-analyzed effect on HF hospitalizations alone gave an HR of
154 0.95, 95%CI 0.81 to 1.11. The meta-analyzed effect on cardiovascular death gave
155 an HR of 0.96, 95%CI 0.82 to 1.12.²²

156 Despite the neutral effect on HF hospitalizations and cardiovascular death, GLP-1
157 RA may be superior to placebo for reducing major atherosclerotic events in patients
158 with T2D and HF, with a pooled 3P-MACE HR of 0.85, 95%CI 0.75 to 0.97.²²

159 The characterization of HF in T2D trials with GLP-1 RA was poor, mostly lacking
160 detailed description on signs and symptoms, as well as natriuretic peptides and
161 echocardiogram. Still, it is likely that most HF patients enrolled in T2D trials were
162 stable outpatients with heart failure with preserved ejection fraction (HFpEF). This
163 statement is supported with data from the EXSCEL (Exenatide Study of
164 Cardiovascular Event Lowering Trial; NCT01144338) trial where ejection fraction
165 (EF) data was available for 33.2% (n =4892) of the patients with 9.6% (n =469)
166 having an ejection fraction lower than 40% i.e., >90% of the patients with
167 echocardiographic data available had an ejection fraction of 40% or greater.¹⁷

168 Dedicated HFpEF trials with GLP-1 RA are ongoing (e.g., NCT04847557 and
169 NCT04788511) and will provide more evidence about the effect of these agents in
170 patients with HFpEF.

171 Based on available data, GLP1-RA did not reduce HF-related events in patients with
172 T2D and HF, most of whom presumably had HFpEF. However, GLP-1 RA may be
173 considered for reducing ischemic events in HFpEF patients with a high
174 atherosclerotic risk. Notwithstanding, adequately powered trials should be conducted
175 to test the effect of GLP-1 RA on cardiovascular (including HF) outcomes.

176

177 **Heart failure with reduced ejection fraction**

178 The effect of the GLP-1 RA liraglutide was studied in three small trials enrolling
179 patients with heart failure with reduced ejection fraction (HFrEF).

180 Patients with severely symptomatic HFrEF who had been recently hospitalized for
181 worsening HF were included in the FIGHT trial (the Heart Failure Network Functional

182 Impact of GLP-1 for Heart Failure Treatment; NCT01800968) and randomly
183 assigned to either liraglutide (n =154) or placebo (n =146), and followed for 180
184 days.⁵ Despite no differences between liraglutide and placebo on the global rank
185 score including time to death, time to HF rehospitalization, and time-averaged
186 change in NT-pro BNP (primary outcome), and no differences in echocardiographic
187 parameters or health status, liraglutide treatment showed a tendency for increasing
188 the risk of rehospitalization for cardiovascular reasons (HR 1.33, 95%CI 0.95 to
189 1.85), HF re-hospitalizations (HR 1.33, 95%CI 0.83-2.12), and the risk of emergency
190 department visit, HF hospitalization, or all-cause death (HR 1.36, 95%CI 0.99 to
191 1.85).⁵ In a post-hoc analysis of the FIGHT trial, reassessing the trial outcomes using
192 total events (first and recurrent), a tendency towards increased risk of total HF
193 hospitalizations or all-cause deaths (incidence rate ratio [IRR] 1.41, 95%CI 0.98-
194 2.04) and total arrhythmias (IRR 1.76, 95%CI 0.92-3.37) was found with liraglutide.
195 Of note, the risk of HF hospitalizations or all-cause deaths was higher among
196 patients in NYHA class III-IV (interactionP=0.008), and the risk of arrhythmic events
197 was higher among those without an implanted cardiac device (interactionP=0.047).⁴
198 Another relatively small (N =241) trial with a short follow-up (180 days) studying the
199 effect of liraglutide vs. placebo in stable HFrEF was the LIVE trial (Effect of
200 Liraglutide on Left Ventricular Function in Stable Chronic Heart Failure Patients with
201 and without Diabetes). Despite patients in LIVE were more stable than in FIGHT, the
202 results from LIVE also suggested an increased risk of adverse cardiac events with
203 liraglutide, particularly ventricular tachycardias and atrial fibrillation.⁶
204 Another small trial (A Multi-center, Placebo-controlled Study to Evaluate the Safety
205 of GSK716155 and Its Effects on Myocardial Metabolism, Myocardial Function, and
206 Exercise Capacity in Patients With NYHA Class II/III Congestive Heart Failure;

207 NCT01357850) compared weekly placebo (n =30) to albiglutide 30 mg (n =27)
208 during 12 weeks. No detectable effect of albiglutide on cardiac function or myocardial
209 glucose use was found, but a modest increase in peak oxygen consumption was
210 observed with albiglutide, which the authors attributed to noncardiac effects of
211 albiglutide.²⁴

212 A post-hoc analysis of published EXSCEL data,¹⁷ suggested that patients with an EF
213 <40% had an increased risk of HF hospitalizations with exenatide vs. placebo. In
214 EXSCEL, there were 249 first HFH during a median follow-up of 3.2 years among
215 the 4892 participants with baseline LVEF available (33.2% of EXSCEL population). A
216 significant interaction of LVEF with the effect of exenatide on HFH was found with an
217 increased risk of HF hospitalizations observed in patients with a LVEF <40%: LVEF
218 >55% OR 0.73, 95%CI 0.48-1.13; LVEF 40-55% OR 0.77, 95% CI 0.50-1.20; LVEF
219 <40% OR 1.70, 95%CI 1.02-2.83; interactionP=0.027. A meta-analysis of ESCEL
220 and FIGHT trials suggested an increased risk of HF hospitalizations with GLP-1 RA
221 in patients with LVEF <40% with little heterogeneity across studies: meta-analyzed
222 OR 1.49, 95%CI 1.05-2.10 (overall treatment effect p-value =0.02 and heterogeneity
223 $I^2=0\%$).²⁵

224 Together, these results suggest that GLP-1 RA may be associated with an increased
225 risk of HF hospitalizations in patients with HFrEF and, until further randomized
226 studies are available, GLP-1 RA should be avoided in patients with HFrEF.

227

228 **Integrated view of the role of GLP-1 RA across the spectrum of heart function**

229 The evidence summarized above supports that the effects of GLP-1 RA are modified
230 by HF status (*Figure 1*). Among people with T2D or obesity without HF treatment

231 with GLP-1 RA may be used to improve metabolic status and reduce atherosclerotic
232 events, with a possible effect to reduce HF hospitalizations. In patients with stable
233 HFpEF (15-20% of people with T2D) GLP-1 RA have not reduced HF
234 hospitalizations or cardiovascular mortality but reduced atherosclerotic events and
235 may be used in selected high-risk patients. In patients with HFrEF, GLP-1 RA may
236 increase the risk of adverse outcomes, particularly worsening HF and ventricular
237 arrhythmias, and the use of these agents should not be recommended (*Figure 1*).

238 Current guidelines support the use of GLP-1 RA or SGLT2 inhibitors (with or without
239 metformin) for patients with T2D and cardiovascular disease, including HF.¹ The
240 evidence here summarized challenges this “conventional” view by providing an
241 “updated” view whereby ruling out the presence of HF, particularly HFrEF, is relevant
242 for treatment decisions.

243

244 **Practical guidance for the use of GLP-1 RA**

245 The decision to use GLP-1 RA must be individualized. Before starting GLP-1 RA, all
246 patients should be evaluated for symptoms and signs of HF and have natriuretic
247 peptides (either BNP or NT-pro BNP) measured. If natriuretic peptides are elevated
248 (>35 pg/mL for BNP and >125 pg/mL for NT-pro BNP) an echocardiogram should be
249 performed, as recommended by international guidelines.^{26,27} This active HF
250 screening allows the categorization of the patients in 3 categories:

251 1) No HF: GLP-1 RA are recommended for reducing atherosclerotic
252 cardiovascular events in high-risk patients, with a possible effect to reduce HF
253 hospitalizations.

- 254 2) HFpEF: After a SGLT2 inhibitor (first line agent), GLP-1 RA may be used in
255 selected patients to reduce atherosclerotic cardiovascular events if the
256 atherosclerotic risk is high.
- 257 3) HFrEF: GLP-1 RA should be avoided in patients with HFrEF, until further
258 evidence is produced. SGLT2 inhibitor (first line) and metformin (second line)
259 should be preferred. Given that other antidiabetic drugs may also not be
260 appropriate in this setting (e.g., DDP4 inhibitors and thiazolidinediones may
261 increase the risk of HF hospitalization, and sulfonylureas and insulin increase
262 the risk of hypoglycemic events),²⁸ a higher HbA1c level may be acceptable in
263 patients with HFrEF already on SGLT2 inhibitor and metformin. The risk of
264 adverse events with GLP-1 RA in HFrEF may be particularly increased in
265 those in NYHA class III-IV and in patients without an implanted cardiac
266 device.⁴

267 These bullet-points are illustrated in *Figure 2* which may serve as a tool to support
268 routine clinical decisions.

269

270 **Mechanisms supporting the use of GLP-1 RA according to HF status**

271 The mechanisms underlying the GLP-1 RA beneficial effects on HF prevention
272 (among patients without HF), the neutral (HFpEF) or potentially harmful (HFrEF)
273 effect in patients with HF are probably multifactorial. GLP-1 RA can reduce epicardial
274 fat,^{28,29} an effect (together with the reduction of atherosclerotic cardiovascular
275 disease) may explain why GLP-1 RA may possibly reduce HF hospitalizations
276 (*Figure 1*). On the other hand, GLP-1 RA are known to increase heart rate which
277 may be deleterious to HF patients.³⁰ Furthermore, the GLP-1 receptor, expressed in

278 cardiomyocytes and sinoatrial node cells, signals through a cyclic AMP (cAMP)-
279 dependent pathway which may induce intracellular calcium overload and increase
280 the risk of ventricular ectopy in high-risk patients, such as those with severely
281 depressed LVEF.^{7,17,31-33}

282

283 **Future perspectives**

284 Notwithstanding the current evidence about the relevance of HF status for GLP-1 RA
285 cardiovascular effects, further research in this field is required. Namely, more
286 research is needed on the combined use of GLP-1 RA and SGLT2 inhibitors and on
287 the efficacy and safety of GLP-1 RA (and dual glucose-dependent insulinotropic
288 polypeptide [GIP] and GLP-1 RA agonists) among patients with HFpEF. In this
289 regard, the effect of semaglutide in HFpEF will be studied in the STEP-HFpEF
290 (Research Study to Investigate How Well Semaglutide Works in People Living With
291 Heart Failure and Obesity; NCT04788511) trial, enrolling 516 patients with HFpEF
292 and obesity, and in the STEP-HFpEF-DM (Research Study to Look at How Well
293 Semaglutide Works in People Living With Heart Failure, Obesity and Type 2
294 Diabetes) trial, enrolling 610 patients with HFpEF and T2D. The ongoing SUMMIT (A
295 Study of Tirzepatide in Participants With Heart Failure With Preserved Ejection
296 Fraction and Obesity; NCT04847557) trial will assess the effect of tirzepatide in 700
297 patients with HFpEF and obesity. Despite the clinical importance of these trials, they
298 will likely be underpowered to assess the impact of GLP-1 RA (or dual GIP/GLP-1
299 RA) on HF hospitalizations or mortality.

300 Ideally, further research on the use of GLP-1 RA in patients with HF (including
301 HFpEF) should be incentivized by regulatory agencies, with further and larger

302 outcome RCTs testing the efficacy and safety of GLP-1 RA in HF patients across a
303 wide range of ejection fractions. Nonetheless, based on the available data, enrolling
304 patients with EF <40% possibly raises ethical issues. Still, based on the available
305 evidence, these agents should be avoided in patients with HFrEF, until further
306 evidence is produced.

307

308 **Conclusion**

309 This paper provides evidence for an “updated” view of the use of GLP-1 RA in
310 clinical practice based on HF status. After an active HF screening, if the patient has
311 T2D and atherosclerotic risk without HF, then GLP-1 RA should be considered for
312 improving cardiovascular outcomes. If the patient has T2D and HFpEF a GLP-1 RA
313 may be considered, after a SGLT2 inhibitor (first line agent) if the atherosclerotic risk
314 is high. However, if the patient has HFrEF GLP-1 RA should be avoided, until further
315 evidence is produced.

316

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321

322 **Data Availability Statement**

323 All data used in this manuscript is fully available in the respective publications cited
324 throughout the manuscript.

325

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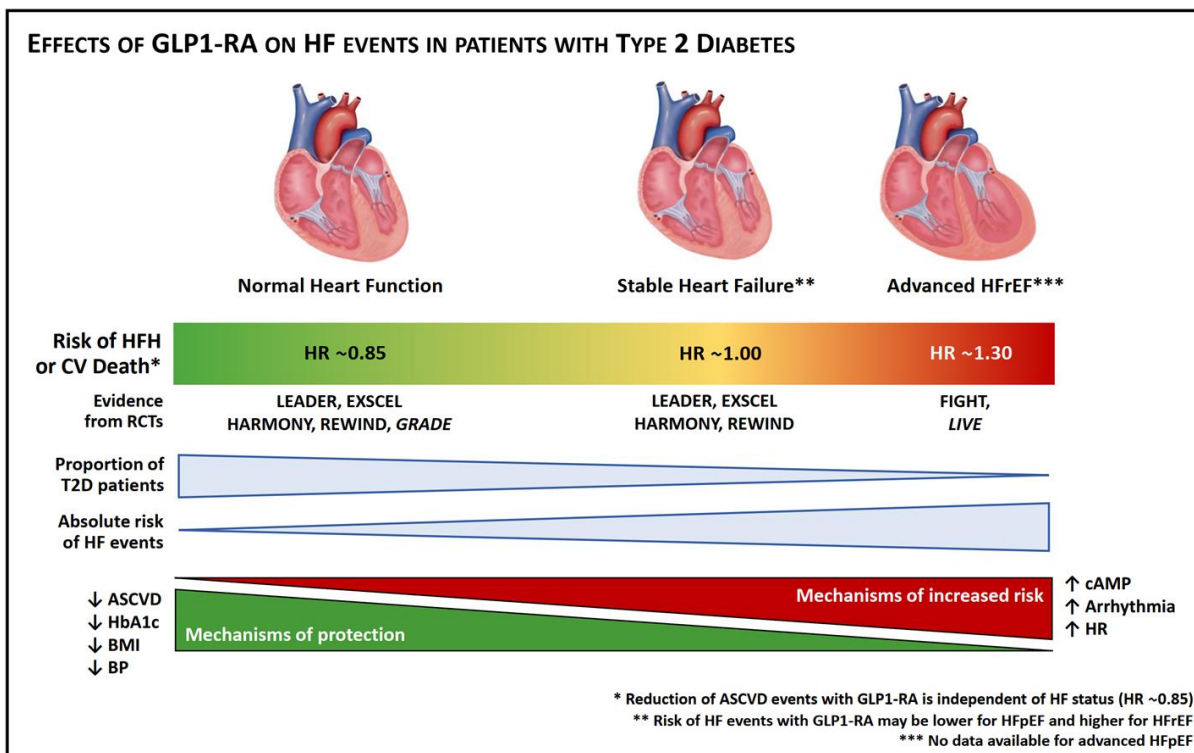
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483 Figure 1. GLP-1RA and heart failure outcomes across patient's risk.

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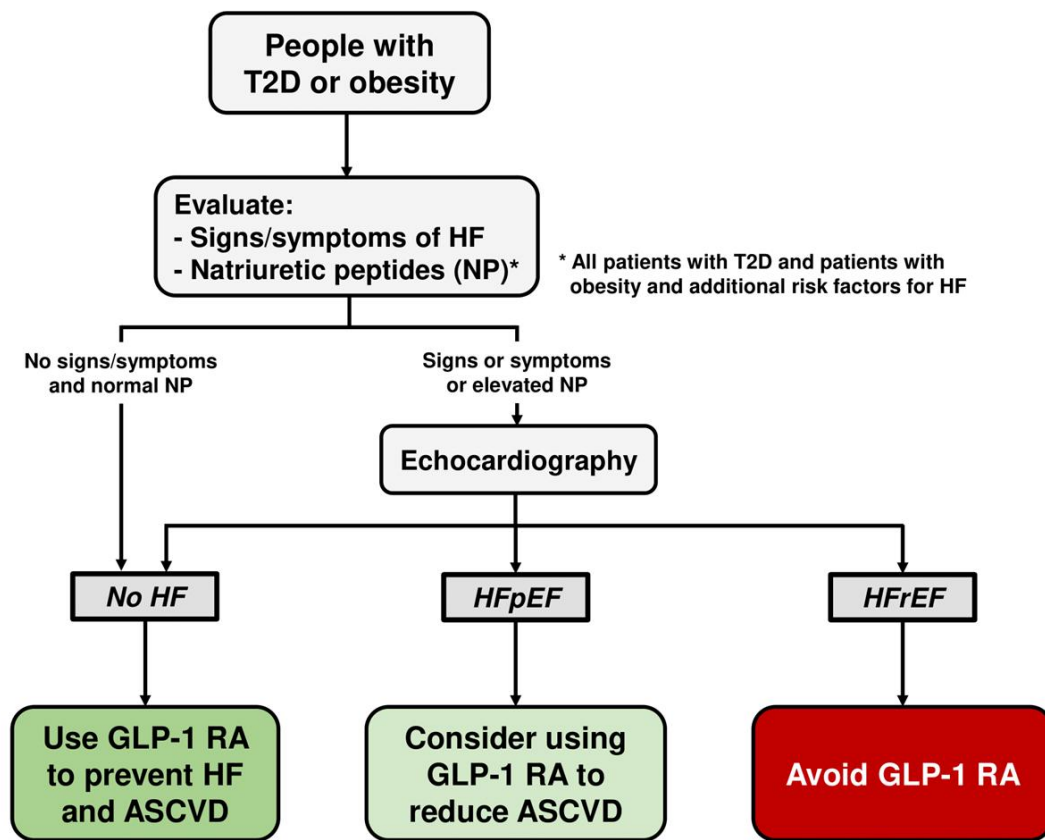
485 Legend: GLP-1RA, glucagon-like peptide-1 receptor agonists; HFH, heart failure
 486 hospitalization; CV, cardiovascular; RCT, randomized controlled trial; T2D, type 2
 487 diabetes; ASCVD, atherosclerotic cardiovascular disease; HbA1c, glycated
 488 hemoglobin; BMI, body mass index; BP, blood pressure; HR, heart rate; HFpEF,
 489 heart failure with preserved ejection fraction; HFrEF, heart failure with reduced
 490 ejection fraction.

491 Caption: GLP-1 RA reduce HF hospitalizations or cardiovascular death in patients
 492 with T2D without HF, are neutral regarding HF-related events in patients with T2D
 493 with HFpEF and may be harmful to patients with HFrEF.

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496 Figure 2. Updated guidance for GLP-1 RA use



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498 Legend: ASCVD, atherosclerotic cardiovascular disease; GLP-1 RA, glucagon-like
499 peptide-1 receptor agonists; HF, heart failure; T2D, type 2 diabetes; HFpEF, heart
500 failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection
501 fraction, NP, natriuretic peptides.

502 Caption: Patients should be screened for heart failure before starting GLP-1 RA.
503 Signs and symptoms of HF must be evaluated in all patients, and natriuretic peptides
504 should be evaluated in all patients with T2D and in patients with obesity and
505 additional risk factors for HF. Echocardiography should be performed in patients with
506 signs/symptoms of HF or with elevated natriuretic peptides. GLP-1 RA should be
507 used in patients without HF to reduce atherosclerotic events and prevent new-onset
508 HF. GLP-1 RA may be used in selected patients with HFpEF to reduce ASCVD but
509 not to reduce HF hospitalizations or cardiovascular death. GLP-1 RA should be
510 avoided in patients with HFrEF, where the potential harms outweigh the potential
511 benefits.

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