

中图分类号: R969.3; R587.1 文献标志码: A 文章编号: 1006-4931(2026)08-0124-11
doi:10.3969/j.issn.1006-4931.2026.08.024



GLP-1受体激动剂对2型糖尿病微血管病变影响的系统评价与Meta分析*

郑艳¹, 高葱葱¹, 骆岩¹, 刘文静¹, 施芳红², 姚佳晨¹, 李文艳^{1△}

(1. 上海市浦东新区公利医院, 上海 200135; 2. 上海交通大学医学院附属仁济医院, 上海 200127)

摘要:目的 探讨胰高血糖素样肽-1受体激动剂(GLP-1RA)对2型糖尿病(T2DM)微血管病变的影响。方法 检索PubMed、Embase、the Cochrane Library、中国知网(CNKI)、万方(WanFang)数据库、中国生物医学文献服务系统(SinoMed),检索时限为自建库起至2023年6月8日。纳入T2DM患者使用GLP-1RA(艾塞那肽、利司那肽、利拉鲁肽、司美格鲁肽、度拉糖肽)对微血管病变结局[糖尿病视网膜病变(DR)、视网膜脱落、视网膜出血、玻璃体出血、黄斑水肿、白内障、青光眼、糖尿病足]影响的临床随机对照试验(RCT)文献。采用Cochrane协作网推荐的偏倚风险评估标准评价文献质量。采用RevMan 5.3软件进行Meta分析。结果 共纳入文献39篇,涉及患者57902例。30篇文献的偏倚风险均较低。结果显示,纳入研究间的异质性较低($P < 50%$),差异主要由随机误差引起(结果 $P > 0.05$)。GLP-1RA对于微血管病变结局总体安全性较好,但可能增加DR的风险[$RR = 1.27, 95\%CI(1.08, 1.49), P = 0.003$],其中司美格鲁肽显著增加DR的风险[$RR = 1.47, 95\%CI(1.22, 1.78), P < 0.0001$]。亚组分析与主要结果一致。短期(≤ 52 周)治疗DR风险显著增加[$RR = 1.71, 95\%CI(1.31, 2.23), P < 0.0001$]。结论 GLP-1RA对T2DM患者微血管病变结局总体安全性较好,但在治疗初期使用司美格鲁肽时可能增加DR的发生。对于高风险患者(如已有微血管病变),建议使用GLP-1RA前筛查视网膜情况,尤其司美格鲁肽初始治疗52周内需加强监测。

关键词:胰高血糖素样肽-1受体激动剂;2型糖尿病;微血管病变;随机对照试验;Meta分析

Systematic Review and Meta-Analysis of the Effects of GLP-1 Receptor Agonists on Microangiopathy in Type 2 Diabetes Mellitus

ZHENG Yan¹, GAO Congcong¹, LUO Yan¹, LIU Wenjing¹, SHI Fanghong², YAO Jiachen¹, LI Wenyan^{1△}

(1. Gongli Hospital, Shanghai Pudong New Area, Shanghai 200135, China; 2. Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China)

Abstract: Objective To investigate the effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on microangiopathy in type 2 diabetes mellitus (T2DM). **Methods** Databases including PubMed, Embase, the Cochrane Library, CNKI, WanFang, and SinoMed were searched from establishment to June 8, 2023. Randomized controlled trials (RCTs) evaluating the effects of GLP-1RAs (including exenatide, lixisenatide, liraglutide, semaglutide, and dulaglutide) on microangiopathy outcomes [diabetic retinopathy (DR), retinal detachment, retinal hemorrhage, vitreous hemorrhage, macular edema, cataract, glaucoma, and diabetic foot] in patients with T2DM were included. The risk of bias was assessed using the Cochrane Collaboration. Meta-analysis was performed using RevMan 5.3 software. **Results** A total of 39 RCTs involving 57902 patients were included. The risk of bias was low in all 30 studies. The heterogeneity among the included studies was low ($P < 50%$), and the differences were mainly caused by random errors ($P > 0.05$). Overall, GLP-1RAs showed a favorable safety profile regarding microangiopathy outcomes but were associated with an increased risk of DR [$RR = 1.27, 95\%CI(1.08, 1.49), P = 0.003$]. Among these, semaglutide significantly increased the risk of DR [$RR = 1.47, 95\%CI(1.22, 1.78), P < 0.0001$]. Subgroup analyses were consistent with the primary findings. A significantly increased risk of DR was observed with short-term (≤ 52 weeks) treatment [$RR = 1.71, 95\%CI(1.31, 2.23), P < 0.0001$]. **Conclusion** GLP-1RAs demonstrate a favorable overall safety profile for microangiopathy outcomes in patients with T2DM; however, semaglutide may increase the risk of DR during the initial treatment period. For high-risk patients (such as those with pre-existing microangiopathy), retinal screening before initiating GLP-1RA therapy is recommended, and enhanced monitoring is warranted within the first 52 weeks of semaglutide treatment.

Key words: GLP-1; type 2 diabetes mellitus; microangiopathy; randomized controlled trials; Meta-analysis

近30年来,我国糖尿病患病率持续上升,其中2型糖尿病(T2DM)占90%以上^[1]。T2DM是一种因体内胰

*基金项目:上海市浦东新区卫生健康委员会学科建设计划项目[PWZxk2022-26]。

第一作者:郑艳,女,大学本科,主管药师,研究方向为临床药学,(电子信箱)zhengy0656@163.com。

△通信作者:李文艳,女,硕士,主任药师,研究方向为临床药学与中药新药,(电子信箱)liwenyan_linda@163.com。

胰岛素分泌不足或胰岛素抵抗导致的慢性进行性疾病,其慢性并发症[如糖尿病肾脏病、糖尿病视网膜病变(DR)、糖尿病神经病变、糖尿病下肢动脉病变、糖尿病足病等]是影响糖尿病患者生活质量和生命健康的主要因素^[1]。胰高血糖素样肽-1受体激动剂(GLP-1RA)为肠促胰岛素类降糖药,通过激活GLP-1受体升高环磷酸腺苷水平,从而以葡萄糖浓度依赖的方式刺激胰岛素分泌、抑制胰高血糖素分泌,增加肌肉和脂肪组织对葡萄糖的摄取,降低肝脏葡萄糖的生成,并可抑制胃排空及食欲^[2]。一项Meta分析结果显示,大部分GLP-1RA的糖化血红蛋白(HbA_{1c})水平比安慰剂降低1.0%~1.5%^[3]。目前关于GLP-1RA对糖尿病微血管病变(尤其是DR)结局的研究分析较少且存在争议。例如,SUSTAIN-6试验^[4]结果显示,相比安慰剂组,司美格鲁肽组DR风险增加(3.0% vs. 1.8%, HR = 1.76)。而REWIND事后分析结果显示,未发现度拉糖肽增加DR风险^[5]。HE等^[6]通过回顾队列研究从患者、小鼠、视网膜血管内皮细胞3个层面分析DR发生率,证明GLP-1RA对DR具有保护作用。上述研究中DR风险结果不一致,因此,本研究拟对T2DM患者涉及GLP-1RA微血管病变结局的随机对照试验(RCT)进行系统评价与Meta分析,评估GLP-1RA对T2DM患者微血管病变(尤其是DR)的影响,为临床应用提供参考。现报道如下。

1 资料与方法

1.1 检索范围及策略

检索范围:检索PubMed、Embase、the Cochrane Library、中国知网(CNKI)、万方(WanFang)数据库、中国生物医学文献服务系统(SinoMed)。检索时限为各数据库自建库起至2023年6月8日。并于ClinicalTrials.gov中通过文献试验登记号检索试验结果,手工检索其他相关会议论文、学位论文及灰色文献等。

检索策略:选择与GLP-1RA(贝那鲁肽、艾塞那肽、艾塞那肽微球、利司那肽、利拉鲁肽、司美格鲁肽、度拉糖肽、聚乙二醇洛塞那肽)相关的医学主题词(MeSH)及自由词,以及与T2DM、RCT相关的术语,组成检索式进行文献检索。

1.2 纳入与排除标准

纳入标准:RCT研究;研究对象均为T2DM患者,接受GLP-1RA(贝那鲁肽、艾塞那肽、艾塞那肽微球、利司那肽、利拉鲁肽、司美格鲁肽、度拉糖肽、聚乙二醇洛塞那肽)降糖治疗,检测报告包括微血管病变结局指标(DR、视网膜脱落、视网膜出血、玻璃体出血、黄斑水肿、白内障、青光眼、糖尿病足等)。

排除标准:回顾性研究、真实世界研究、非随机对照研究;个案报道、会议、摘要、系统评价、综述、成本效益研究、满意度研究、机制研究、药物代谢动力学研究、

动物实验;研究对象未使用GLP-1RA治疗;研究对象为1型糖尿病或妊娠期糖尿病患者;无法利用、获得全文及研究所需数据。

1.3 文献筛选、数据提取及质量评价

文献筛选与数据提取:由3名研究人员对检索到的文献标题和摘要进行筛选,并评估全文,如遇分歧则请第4名研究人员协助裁定。提取文献的基本信息(标题、作者、临床试验登记号、研究持续时间、病例数量)、干预的过程及方法、患者基线特征(年龄、HbA_{1c}、糖尿病病程)、微血管病变结局指标的发生情况。

质量评价:由2名研究人员根据Cochrane协作网推荐的风险偏倚评估标准对纳入文献的质量独立进行评估,评估内容包括随机序列生成、分配隐藏、是否采用盲法、结果数据的完整性及其他偏倚。

1.4 结局指标

包括DR、视网膜脱落、视网膜出血、玻璃体出血、黄斑水肿、白内障、青光眼、糖尿病足。

1.5 统计学处理

采用RevMan 5.3软件进行Meta分析。计数资料以相对危险度(RR)及其95%置信区间(CI)表示。对纳入研究进行异质性检验,当 $P \geq 0.05$ 且 $I^2 \leq 50\%$ 时提示组间无异质性,采用固定效应模型分析;当 $P < 0.05$ 且 $I^2 > 50\%$ 时提示组间存在异质性,采用随机效应模型分析。研究结果的稳定性采用敏感性分析;研究发表偏倚采用倒漏斗图评价。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 文献筛选结果

初筛共检索获得文献2469篇,筛选后最终纳入39篇^[4,7-44]。涉及患者57902例。其中,艾塞那肽5篇,利司那肽7篇,利拉鲁肽12篇,司美格鲁肽9篇,度拉糖肽6篇(其余3种药0篇)。文献筛选流程见图1。纳入研究的基本信息见表1、表2。

2.2 文献质量评价

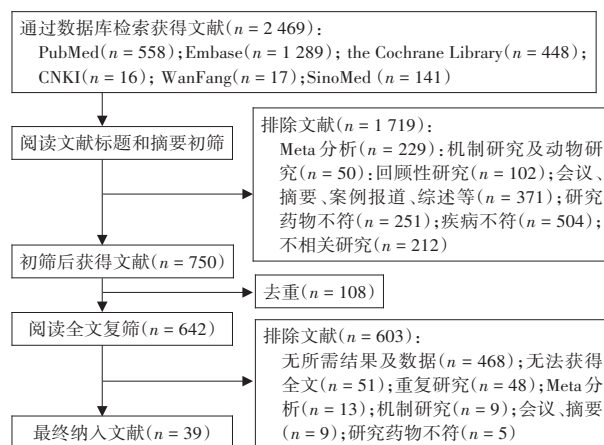


图1 文献筛选流程图

Fig. 1 Flowchart of literature screening

表1 GLP-1RA 药物组患者基本情况

Tab. 1 Baseline characteristics of patients in the GLP - 1RA drug group

微血管病变	纳入文献(篇)	例数	年龄(\bar{X} ,岁)	病程(\bar{X} ,年)	HbA _{1c} (\bar{X} ,%)
DR	21	25 940	61.4	11.69	8.47
视网膜脱落	12	40 855	62.03	11.64	8.20
视网膜出血	7	29 516	62.69	12.5	8.26
玻璃体出血	10	40 000	62.33	11.87	8.21
黄斑水肿	7	32 394	62.99	12.45	8.05
白内障	21	48 285	61.25	11.44	8.21
青光眼	7	35 912	62.1	11.81	8.21
糖尿病足	6	12 078	61.04	10.66	7.98

注:因 NCT01644500 和 NCT01648582 未收集到基线病程及 HbA_{1c} 相关数据,故以上平均病程及平均 HbA_{1c} 结果(DR、视网膜出血、白内障、青光眼)不包含此试验。表2同。

Note: Due to the absence of baseline disease duration and HbA_{1c} - related datas from NCT01644500 and NCT01648582, the mean disease duration and mean HbA_{1c} results (for DR, retinal hemorrhage, cataract, and glaucoma) do not include these trials (for Tab. 1 - 2).

39 篇文献中参与者和研究人员盲法具有高风险的有 2 篇,结局指标评估盲法具有高风险的有 4 篇,选择性报告具有高风险的有 3 篇,低风险 30 篇。详见图 2。

2.3 Meta 分析结果

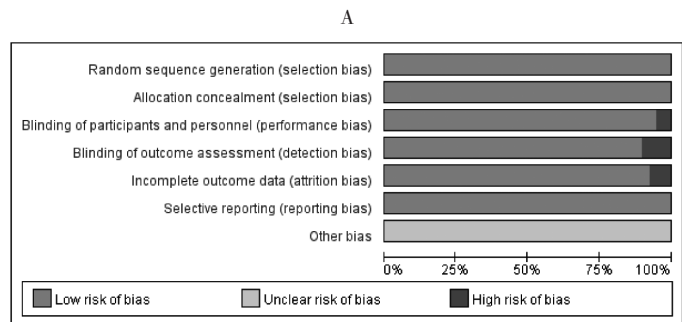
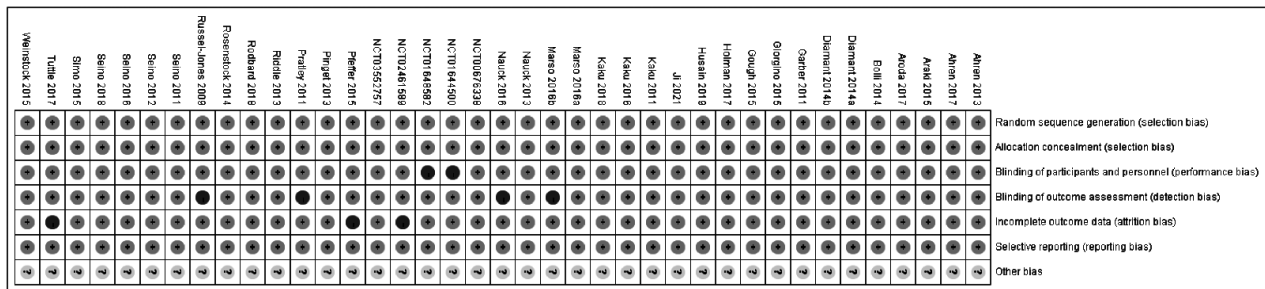
2.3.1 GLP-1RA 的微血管病变结局

DR:共纳入 21 项研究^[4,7,11-12,14,19-20,22-26,31,35,37-41,43-44]。各研究间无异质性($I^2 = 29\%$, $P = 0.10$),采用固定效应

表2 GLP-1RA 不同药物亚组患者基本情况

Tab. 2 Baseline characteristics in different GLP - 1RA subgroup

微血管病变	药物亚组	纳入研究(项)	例数	年龄(\bar{X} ,岁)	病程(\bar{X} ,年)	HbA _{1c} (\bar{X} ,%)	
DR	利拉鲁肽	8	12 008	62.84	11.91	8.65	
	司美格鲁肽	8	11 087	61.32	11.69	8.31	
	度拉糖肽	3	1 851	54.48	8.9	8.10	
	视网膜脱落	艾塞那肽	2	15 208	61.88	11.88	8.01
	利司那肽	3	7 034	59.70	8.99	7.75	
	利拉鲁肽	3	10 344	63.28	12.21	8.66	
	司美格鲁肽	3	7 348	63.84	13.44	8.41	
	视网膜出血	利司那肽	3	1 486	56.22	9.86	8.23
	玻璃体出血	艾塞那肽	2	15 262	61.91	11.98	8.01
	利司那肽	4	8 091	59.24	8.96	7.82	
黄斑水肿	利拉鲁肽	2	10 167	63.54	12.43	8.67	
	司美格鲁肽	2	6 480	65.29	14.39	8.45	
	艾塞那肽	2	15 729	61.63	11.61	7.96	
	司美格鲁肽	2	6 480	65.29	14.39	8.45	
	白内障	艾塞那肽	2	15 262	61.91	11.98	8.01
	利司那肽	3	7 422	59.73	9.51	7.82	
	利拉鲁肽	5	11 629	62.87	11.99	8.63	
	司美格鲁肽	6	10 393	61.77	12.09	8.34	
	度拉糖肽	5	3 579	54.86	8.1	8.1	
	青光眼	艾塞那肽	2	15 262	61.91	11.98	8.01
糖尿病足	司美格鲁肽	2	4 507	62.11	12.32	8.54	
	艾塞那肽	2	1 330	55.91	6.06	8.4	
	度拉糖肽	2	1 497	58.08	11.27	8.29	



A. 偏倚风险分析 B. 偏倚风险柱状图

图2 偏倚风险质量评价

A. Risk of bias summary B. Risk of bias bar chart

Fig. 2 Risk of bias assessment

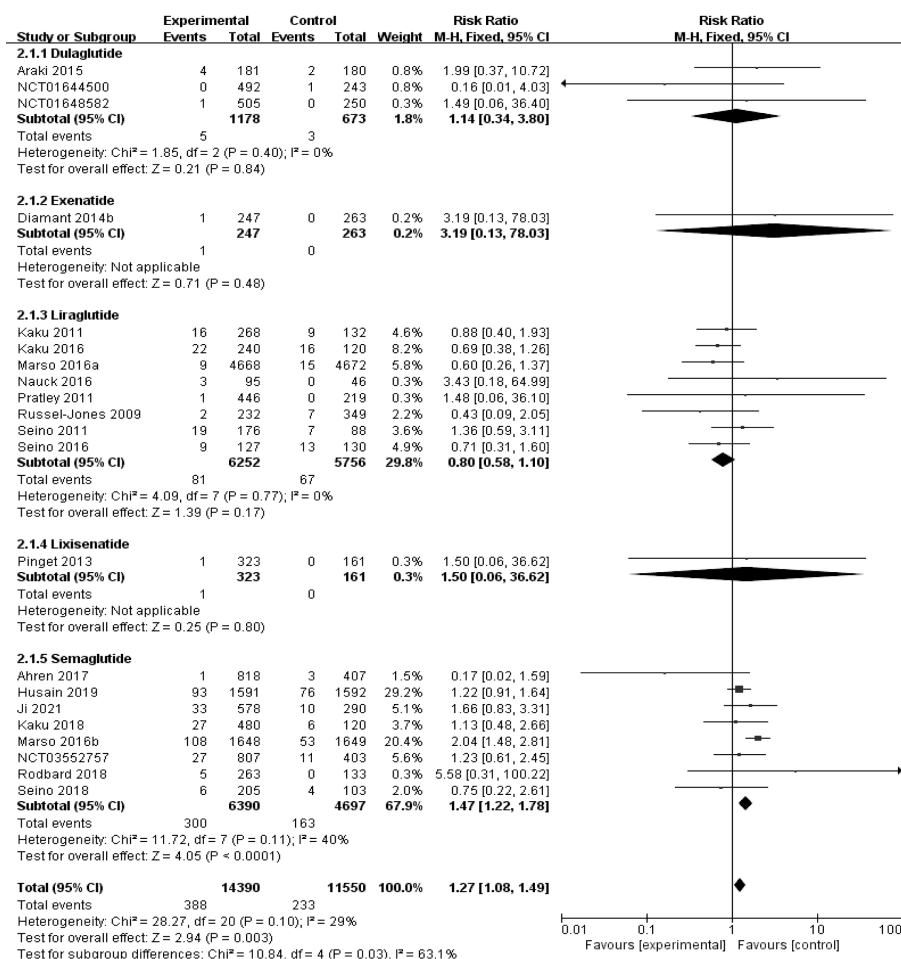


图3 DR的Meta分析森林图

Fig. 3 Forest plot for Meta - analysis of DR

模型。结果显示,试验组DR发生率显著高于对照组 [RR = 1.27, 95%CI(1.08, 1.49), P = 0.003]。详见图3。

其他微血管病变结局: 纳入32项研究^[4,7-18,20-21,26-36,38,40-44]。异质性结果显示,视网膜脱落 (I² = 0, P = 0.95)、视网膜出血 (I² = 0, P = 0.74)、玻璃体出血 (I² = 0, P = 0.89)、黄斑水肿 (I² = 0, P = 0.93)、白内障 (I² = 0, P = 0.98)、青光眼 (I² = 0, P = 0.85)、糖尿病足 (I² = 0, P = 0.60), 各研究间无异质性。结果显示, 试验组视网膜脱落 [RR = 1.12, 95%CI(0.54, 2.31)]、视网膜出血 [RR = 0.79, 95%CI(0.29, 2.16)]、玻璃体出血 [RR = 1.57, 95%CI(0.81, 3.04)]、黄斑水肿 [RR = 0.61, 95%CI(0.27, 1.41)]、白内障 [RR = 0.82, 95%CI(0.63, 1.07)]、青光眼 [RR = 0.48, 95%CI(0.18, 1.28)]、糖尿病足 [RR = 0.97, 95%CI(0.45, 2.07)] 的发生率与对照组比较, 均无统计学意义 (P > 0.05)。详见图4至图10。

2.3.2 GLP-1RA 不同药物亚组的微血管病变结局

DR: 8项研究^[4,35,37-41,44]报道司美格鲁肽。异质性结果显示, 各研究间无异质性 (I² = 40%, P = 0.11), 采用固定效应模型。结果显示, 试验组DR发生率显著高

于对照组 [RR = 1.47, 95%CI(1.22, 1.78), P < 0.0001], 需进一步评估。详见图3。8项研究^[19,20,22-26,43]报道利拉鲁肽, 3项研究^[7,11,12]报道度拉糖肽。异质性结果显示, 利拉鲁肽 (I² = 0, P = 0.77) 和度拉糖肽 (I² = 0, P = 0.40) 各研究间无异质性, 采用固定效应模型。结果显示, 试验组利拉鲁肽 [RR = 0.80, 95%CI(0.58, 1.10)] 和度拉糖肽 [RR = 1.14, 95%CI(0.34, 3.80)] 的发生率与对照组比较, 均无统计学意义 (P > 0.05)。见图3。

其他微血管病变结局: 共纳入32项研究^[4,7-18,20,21,26-36,38,40-44]。异质性结果显示, 各研究间无异质性 (I² < 50%, P > 0.05), 采用固定效应模型。结果显示, 试验组的其他微血管病变结局发生率 (95%CI 均包含1) 与对照组比较, 均无统计学意义 (P > 0.05)。详见图4至图10。

2.3.3 司美格鲁肽对DR结局的影响

共纳入8项研究^[4,35,37-41,44]。各研究间无异质性 (I² < 50%, P > 0.05), 采用固定效应模型。按随访时间分层 (< 52周 vs. > 52周), 长期 (> 52周) 治疗DR风险虽有增加但无统计学意义 [RR = 1.27, 95%CI(0.97, 1.66), P = 0.08]。短期 (< 52周) 治疗DR风险显著增加

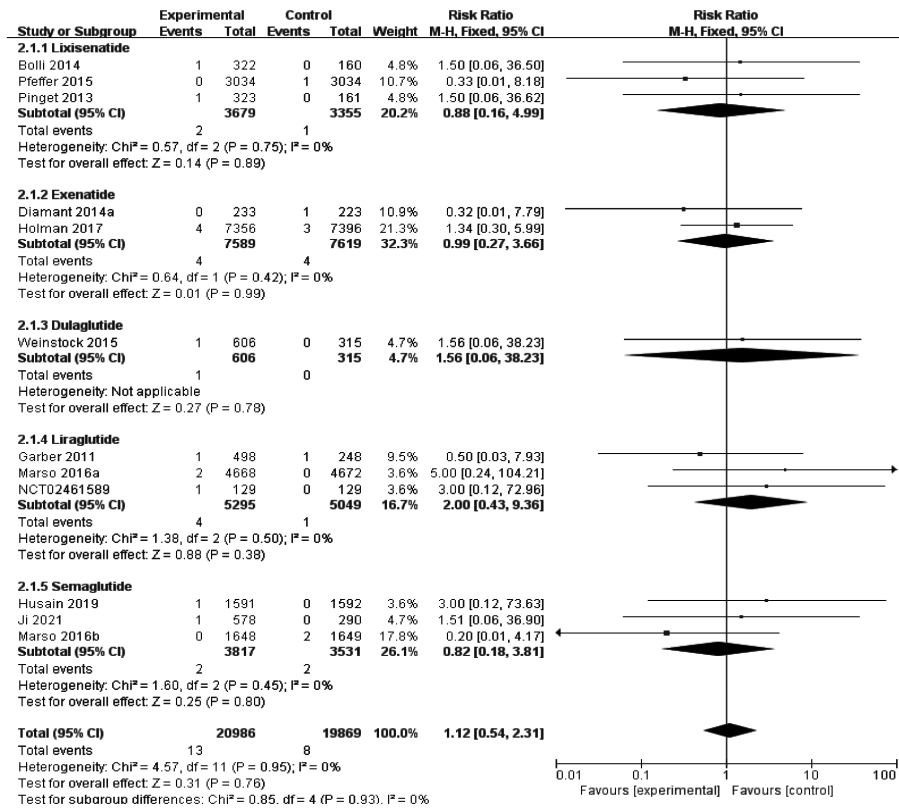


图4 视网膜脱落的Meta分析森林图

Fig. 4 Forest plot for Meta-analysis of retinal detachment

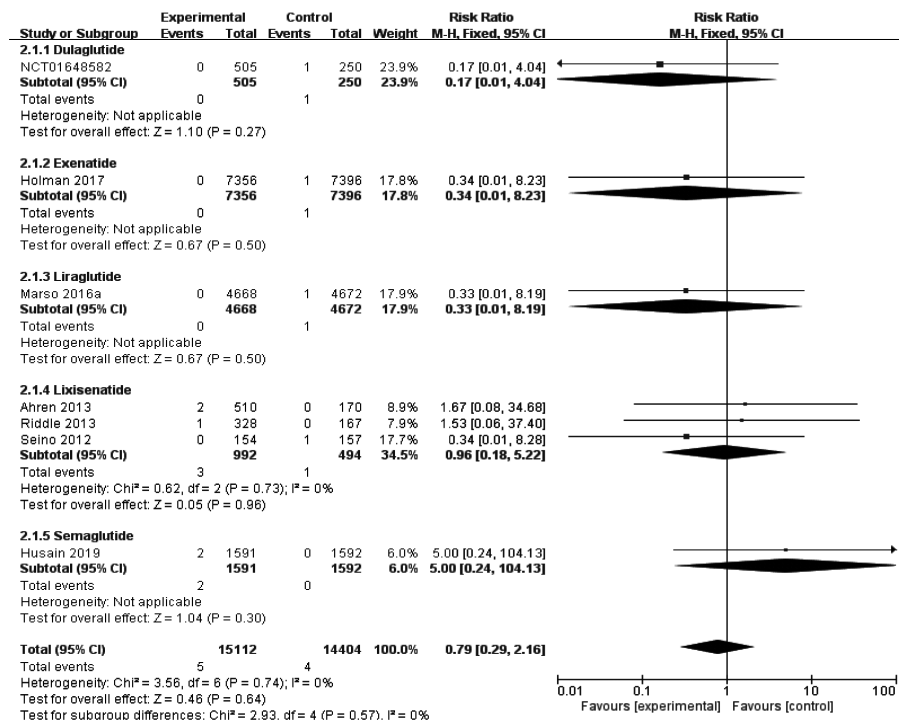


图5 视网膜出血的Meta分析森林图

Fig. 5 Forest plot for Meta-analysis of retinal hemorrhage

[$RR = 1.71, 95\%CI(1.31, 2.23)$], $P < 0.0001$ 。详见图11。

2.3.4 敏感性分析和发表偏倚

对司美格鲁肽主要结局DR进行敏感性分析,结果

显示,各结局指标的统计学结果均无显著变化,未能识别出任何单个研究对主要结果有影响,提示结果相对稳健。通过漏斗图进行发表偏倚分析,未观察到DR结局潜在的发表偏倚,详见图12。

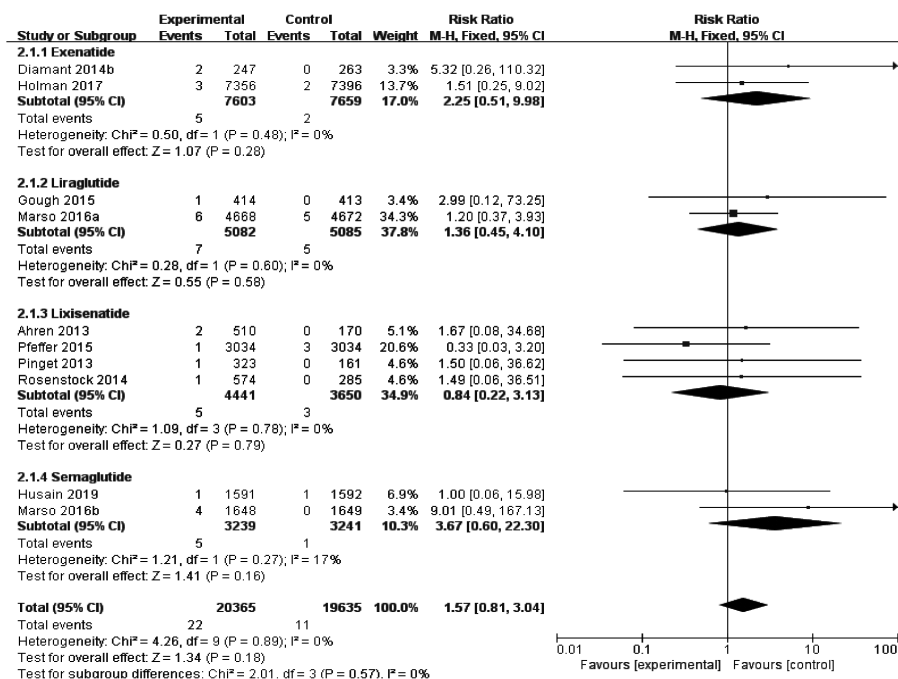


图6 玻璃体出血的Meta分析森林图

Fig. 6 Forest plot for Meta - analysis of vitreous hemorrhage

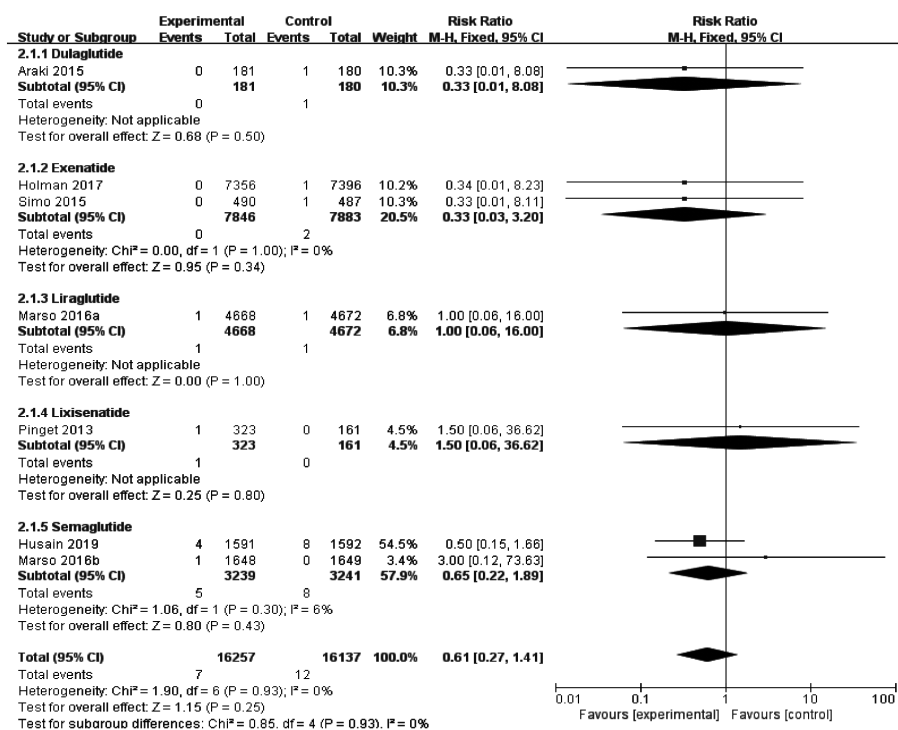


图7 黄斑水肿的Meta分析森林图

Fig. 7 Forest plot for Meta - analysis of macular edema

3 讨论

本研究中基于39项RCT研究,涉及57 902例患者,系统评价了GLP-1RA对于T2DM患者微血管病变结局的影响。研究结果显示,GLP-1RA对于微血管病变结局总体安全性较好,但与对照组比较显著增加DR风险[RR = 1.27, 95%CI(1.08, 1.49), P = 0.003],其中司美格鲁肽显著增加DR的风险[RR = 1.47, 95%CI

(1.22, 1.78), P < 0.000 1]。亚组分析与主要结果一致。短期(≤ 52周)治疗DR风险显著增加[OR = 1.71, 95%CI(1.31, 2.23), P < 0.000 1]。

AVGERINOS等^[45]通过Meta分析得出,与安慰剂或其他降糖药比较,GLP-1RA治疗对于视网膜病变相关结果总体是安全的,不增加DR、黄斑水肿、视网膜脱落及视网膜出血的发生率,但与安慰剂比较,GLP-

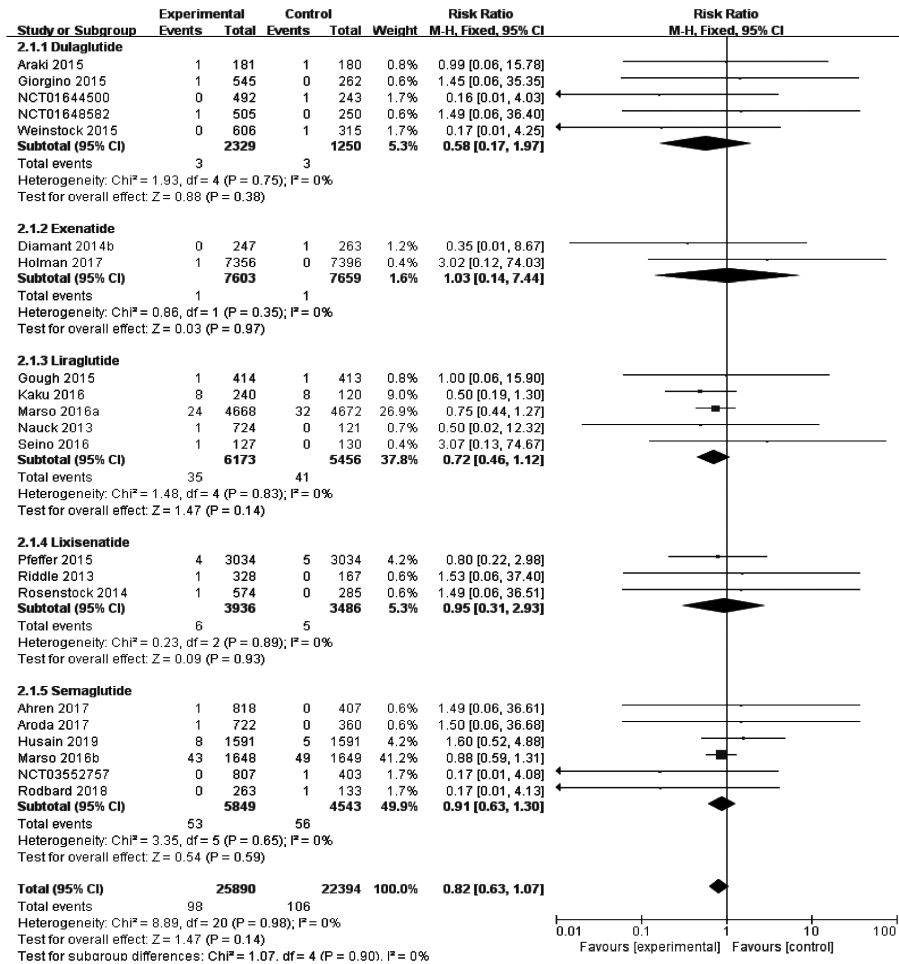


图8 白内障的Meta分析森林图

Fig. 8 Forest plot for Meta - analysis of cataract

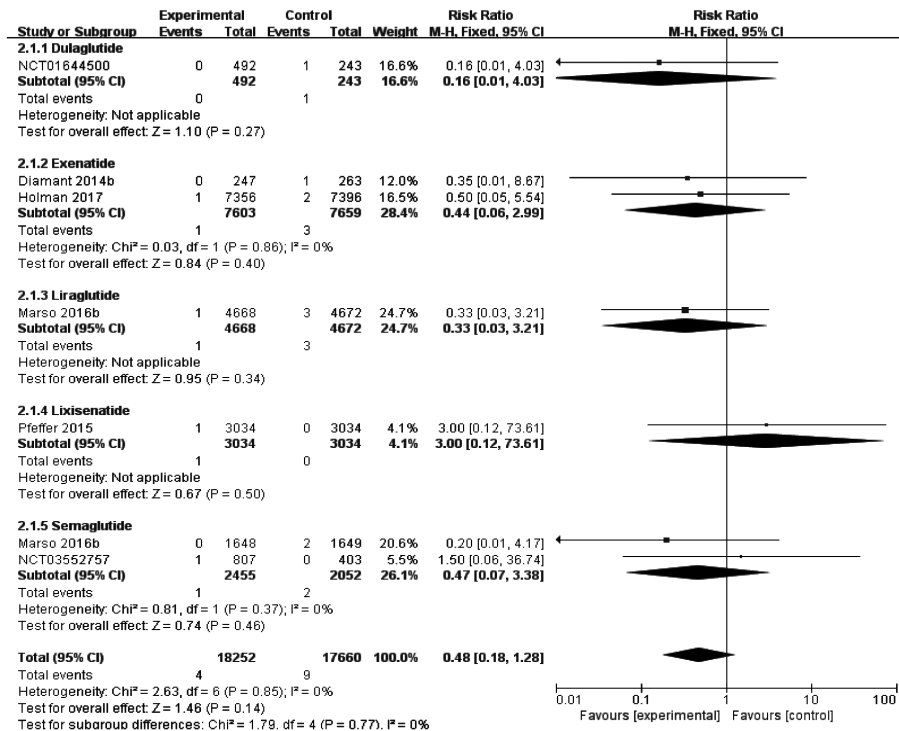


图9 青光眼的Meta分析森林图

Fig. 9 Forest plot for Meta - analysis of glaucoma

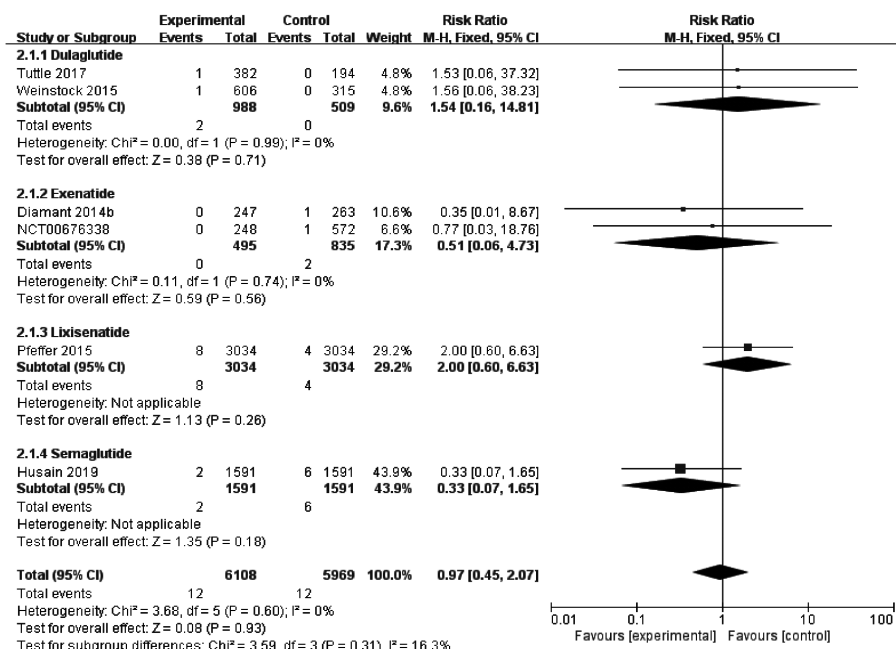


图10 糖尿病足的Meta分析森林图

Fig. 10 Forest plot for Meta - analysis of diabetic foot

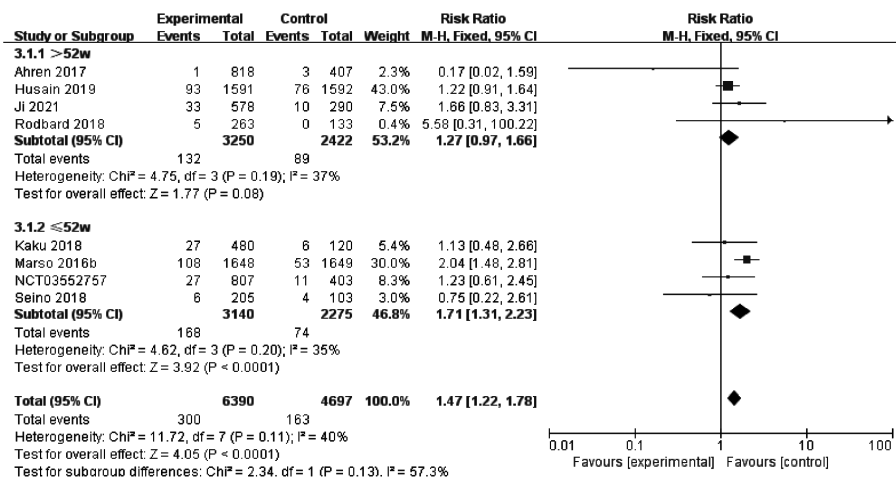


图11 司美格鲁肽DR的Meta分析森林图

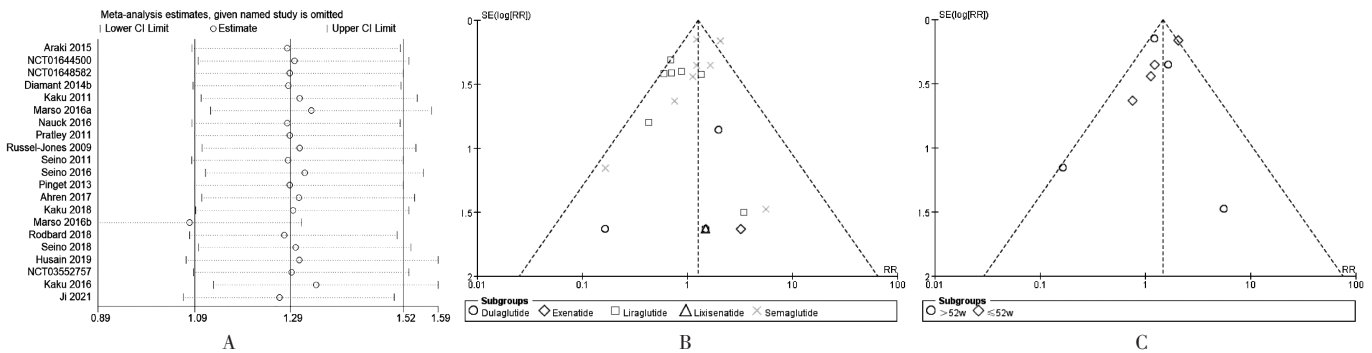
Fig. 11 Forest plot for Meta - analysis of DR of semaglutide

1RA 治疗后玻璃体出血的发生率更高[OR = 1.93, 95% (1.09, 3.42)],这一结果主要受到LEADER试验^[20]结果的推动。本研究中更新了2018年6月至2023年6月的新研究,并增加对青光眼、白内障、糖尿病足相关微血管病变结局指标的研究。

DR 属慢性进行性致盲性眼病,研究表明,糖尿病病程是DR最重要的危险因素,血糖是影响DR发生和进展的关键因素,高血压、血脂异常也是DR发生的重要危险因素^[46]。糖尿病控制与并发症试验(DCCT)研究^[47]、英国前瞻性糖尿病(UKPDS)研究^[48]等临床研究结果显示,处于糖尿病早期阶段的患者严格控制血糖,可显著降低糖尿病微血管病变的发生风险;此外,GLP-1RA 还可通过抗氧化应激、抗炎及对血管-视网膜屏障的保护作用对DR产生有益影响^[49]。在司美格鲁肽的

药品说明书中,T2DM 患者中的DR为其常见药品不良反应(ADR)。对司美格鲁肽ADR 个案报道分析结果显示,ADR 多于2个月内发生,主要累及消化系统^[50]。目前司美格鲁肽公开报道的ADR 仍较少,临床应重点关注其胃肠道ADR、急性胰腺炎、肠梗阻、胃排空延长。

基于美国食品和药物管理局(FDA)不良事件报告系统(FAERS)的司美格鲁肽相关报告挖掘不良事件,视网膜病变是排名第2的不良反应,提示司美格鲁肽的使用与DR 发生有一定关联^[51-52]。SUSTAIN-6 试验^[4]为司美格鲁肽对于心血管安全性事件研究,结果显示,接受司美格鲁肽治疗的患者,DR 相关并发症的发生率高于安慰剂组。但在基线无DR 基础疾病的患者中,司美格鲁肽组与安慰剂组的DR 发生率相当。这可能与司美格鲁肽快速降糖导致早期恶化、视网膜短暂缺血有



A. DR敏感性分析图 B. DR漏斗图 C. 司美格鲁肽DR漏斗图

图 12 司美格鲁肽DR敏感性分析及发表偏倚结果

A. Sensitivity analysis for DR B. Funnel plot for DR C. Funnel plot DR of semaglutide

Fig. 12 Sensitivity analysis and publication bias results for DR of semaglutide

关,也可能与司美格鲁肽影响血管内皮生长因子(VEGF)通路激活,加剧已有DR相关并发症有关。由于SUSTAIN-6试验的主要终点是心血管事件,微血管相关数据来自次要终点,未针对视网膜病变进行前瞻性设计,可能受到基线视网膜病变严重程度、药物剂量、用药疗程等其他因素影响。

在其他微血管病变结局中,视网膜脱落[RR = 1.12, 95%CI(0.54, 2.31)]、视网膜出血[RR = 0.79, 95%CI(0.29, 2.16)]、青光眼[RR = 0.48, 95%CI(0.18, 1.28)]、糖尿病足[RR = 0.97, 95%CI(0.45, 2.07)]、黄斑水肿[RR = 0.61, 95%CI(0.27, 1.41)]、白内障[RR = 0.82, 95%CI(0.63, 1.07)],现有结果差异无统计学意义,尚不能证明GLP-1RA会增加或减少以上微血管病变结局的风险。GLP-1RA对玻璃体出血[RR = 1.57, 95%CI(0.81, 3.04)]结果倾向于风险增加,与AVGERINOS等^[45]Meta分析结果一致,但无统计学意义。在临床使用GLP-1RA过程中,T2DM患者应定期进行规范的眼底检查,如患者已有眼部病变(如活动性或严重视网膜病变),开始治疗后应密切监测眼部症状(如视力迅速下降)。

现有GLP-1RA相关研究多数针对有效性、安全性、心血管事件等方面,暂无针对微血管病变结局作为主要终点的研究,无法按剂量或基线微血管病变状态进行分析。微血管风险研究需通过微血管结局试验进一步验证。目前FOCUS研究(NCT03811561)^[53]为针对司美格鲁肽设计的为期5年、纳入1500例T2DM患者关于眼科的专项研究,预计2027年完成,期待能更好地明确司美格鲁肽对DR的影响。

本研究中主要优势在于基于39项RCT研究中的57902例患者,通过对2023年6月之前的最新数据进行系统分析,全面评估了GLP-1RA对T2DM患者微血管病变结局的影响,且本研究为首个针对司美格鲁肽DR风险的亚组分析。本研究也存在一定局限性:微血管病变结局的产生可能需要较长时间,所纳入的RCT研究疗程不等,可能影响微血管结局的产生及收集;纳入研

究间GLP-1RA剂量差异未分析;由于眼部微血管病变事件总体发生例数较少且分类较多,所收集的眼部微血管病变仅为其中部分类别;多数研究未报告微血管病变严重程度分级(如非增殖性DR vs. 增殖性DR);本研究未对基线合并微血管病变的患者进行亚组分析,未评估结局指标的产生是否与基线微血管病变相关。部分GLP-1RA的使用对微血管病变结局无统计学意义,需进一步的研究验证。

综上所述,GLP-1RA对T2DM患者微血管病变结局总体安全性较好,但在治疗初期使用司美格鲁肽时应注意可能增加DR的发生。对于高风险患者(如已有微血管病变),建议使用GLP-1RA前筛查视网膜情况,尤其司美格鲁肽初始治疗52周内需加强监测。

参考文献

- [1] 中华医学会糖尿病学分会. 中国糖尿病防治指南(2024版)[J]. 中华糖尿病杂志, 2025, 17(1): 16-139.
- [2] GUPTA V. Glucagon-like peptide-1 analogues: an overview[J]. Indian J Endocrinol Metab, 2013, 17(3): 413-421.
- [3] YAO H, ZHANG A, LI D, et al. Comparative effectiveness of GLP-1 receptor agonists on glycaemic control, body weight, and lipid profile for type 2 diabetes: systematic review and network meta-analysis[J]. BMJ, 2024, 384: e076410.
- [4] MARSO SP, BAIN SC, CONSOLI A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes[J]. N Engl J Med, 2016, 375(19): 1834-1844.
- [5] GERSTEIN HC, COLHOUN HM, DAGENAIS GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial[J]. Lancet, 2019, 394(10193): 121-130.
- [6] HE XM, WEN SY, TANG XX, et al. Glucagon-like peptide-1 receptor agonists rescued diabetic vascular endothelial damage through suppression of aberrant STING signaling[J]. Acta Pharm Sin B, 2024, 14: 2613-2630.
- [7] ARAKI E, INAGAKI N, TANIZAWA Y, et al. Efficacy and safety of once-weekly dulaglutide in combination with

- sulphonylurea and / or biguanide compared with once - daily insulin glargine in Japanese patients with type 2 diabetes: a randomized, open - label, phase III, non - inferiority study[J]. *Diabetes Obes Metab*, 2015, 17(10):994 - 1002.
- [8] GIORGINO F, BENROUBI M, SUN JH, et al. Efficacy and Safety of Once - Weekly Dulaglutide Versus Insulin Glargine in Patients With Type 2 Diabetes on Metformin and Glimepiride (AWARD - 2)[J]. *Diabetes Care*, 2015, 38(12):2241 - 2249.
- [9] TUTTLE KR, RAYNER B, LAKSHMANAN MGJ, et al. Dulaglutide vs. Glargine, Both Combined with Lispro, Mitigated eGFR Decline in People with Type 2 Diabetes and Moderate - to - Severe Chronic Kidney Disease (AWARD - 7) [J]. *Diabetes Care*, 2018, 41(6):1237 - 1246.
- [10] WEINSTOCK RS, GUERCI B, UMPIERREZ G, et al. Safety and efficacy of once - weekly dulaglutide versus sitagliptin after 2 years in metformin - treated patients with type 2 diabetes (AWARD - 5): a randomized, phase III study[J]. *Diabetes, Obes Metab*, 2015, 17(9):849 - 858.
- [11] A Study Comparing the Effects and Safety of Dulaglutide With Glimepiride in Type 2 Diabetes Mellitus, NCT01644500[EB/OL]. (2017 - 09 - 10) [2025 - 04 - 19]. <https://clinicaltrials.gov/ct2/show/NCT01644500>.
- [12] A Study Comparing the Effects and Safety of Dulaglutide With Insulin Glargine in Type 2 Diabetes Mellitus, NCT01648582[EB/OL]. (2017 - 09 - 10) [2025 - 04 - 19]. <https://clinicaltrials.gov/ct2/show/NCT01648582>.
- [13] DIAMANT M, VAN GAAL L, GUERCI B, et al. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION - 3): 3 - year results of an open - label randomised trial[J]. *Lancet Diabetes Endocrinol*, 2014, 2(6):464 - 473.
- [14] DIAMANT M, NAUCK MA, SHAGINIAN R, et al. Glucagon - Like Peptide 1 Receptor Agonist or Bolus Insulin With Optimized Basal Insulin in Type 2 Diabetes [J]. *Diabetes Care*, 2014, 37(10):2763 - 2773.
- [15] HOLMAN RR, BETHEL MA, MENTZ RJ, et al. Effects of Once - Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes[J]. *N Engl J Med*, 2017, 377(13):1228 - 1239.
- [16] SIMO R, GUERCI B, SCHERNTHANER G, et al. Long - term changes in cardiovascular risk markers during administration of exenatide twice daily or glimepiride: results from the European exenatide study[J]. *Cardiovasc Diabetol*, 2015, 14(1):116.
- [17] GARBER A, HENRY RR, RATNER R, et al. Liraglutide, a once - daily human glucagon - like peptide 1 analogue, provides sustained improvements in glycaemic control and weight for 2 years as monotherapy compared with glimepiride in patients with type 2 diabetes [J]. *Diabetes Obes Metab*, 2011, 13(4):348 - 356.
- [18] GOUGH SCL, BODE BW, WOO VC, et al. One - year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26 - week extension to a 26 - week main trial [J]. *Diabetes Obes Metab*, 2015, 17(10):965 - 973.
- [19] KAKU K, RASMUSSEN MF, NISHIDA T, et al. Fifty - two - week, randomized, multicenter trial to compare the safety and efficacy of the novel glucagon - like peptide - 1 analog liraglutide vs glibenclamide in patients with type 2 diabetes[J]. *J Diabetes Investig*, 2011, 2(6):441 - 447.
- [20] MARSO SP, DANIELS GH, BROWN - FRANSEN K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes[J]. *N Engl J Med*, 2016, 375(4):311 - 322.
- [21] NAUCK M, FRID A, HERMANSEN K, et al. Long - term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2 - year results from the LEAD - 2 study [J]. *Diabetes Obes Metab*, 2013, 15(3):204 - 212.
- [22] NAUCK MA, PETRIE JR, SESTI G, et al. A Phase 2, Randomized, Dose - Finding Study of the Novel Once - Weekly Human GLP - 1 Analog, Semaglutide, Compared With Placebo and Open - Label Liraglutide in Patients With Type 2 Diabetes [J]. *Diabetes Care*, 2016, 39(2):231 - 241.
- [23] PRATLEY R, NAUCK M, BAILEY T, et al. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel - group, open - label trial [J]. *Int J Clin Pract*, 2011, 65(4):397 - 407.
- [24] RUSSELL - JONES D, VAAG A, SCHMITZ O, et al. Liraglutide vs insulin glargine and placebo in combination with metformin and sulphonylurea therapy in type 2 diabetes mellitus (LEAD - 5 met + SU): a randomised controlled trial [J]. *Diabetologia*, 2009, 52(10):2046 - 2055.
- [25] SEINO Y, RASMUSSEN MF, NISHIDA T, et al. Glucagon - like peptide - 1 analog liraglutide in combination with sulphonylurea safely improves blood glucose measures vs sulphonylurea monotherapy in Japanese patients with type 2 diabetes: Results of a 52 - week, randomized, multicenter trial [J]. *J Diabetes Investig*, 2011, 2(4):280 - 286.
- [26] SEINO Y, KANEKO S, FUKUDA S, et al. Combination therapy with liraglutide and insulin in Japanese patients with type 2 diabetes: A 36 - week, randomized, double - blind, parallel - group trial [J]. *J Diabetes Investig*, 2016, 7(4):565 - 573.
- [27] Dose - finding of Semaglutide Administered Subcutaneously Once Daily Versus Placebo and Liraglutide in Subjects With Type 2 Diabetes, NCT02464589[EB/OL]. (2018 - 07 - 09) [2025 - 04 - 19]. <https://clinicaltrials.gov/ct2/show/NCT02464589>.
- [28] AHRÉN B, LEGUIZAMO DIMAS A, MIOSSEC P, et al. Efficacy and Safety of Lixisenatide Once - Daily Morning or Evening Injections in Type 2 Diabetes Inadequately Controlled on Metformin (GetGoal - M) [J]. *Diabetes Care*, 2013, 36(9):2543 - 2550.
- [29] BOLLI GB, MUNTEANU M, DOTSENKO S, et al. Efficacy and safety of lixisenatide once daily vs. placebo in people with Type 2 diabetes insufficiently controlled on metformin

- (GetGoal - F1)[J]. *Diabet Med*, 2014, 31(2): 176 - 184.
- [30] PFEFFER MA, CLAGGETT B, DIAZ R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome[J]. *N Engl J Med*, 2015, 373(23): 2247 - 2257.
- [31] PINGET M, GOLDENBERG R, NIEMOELLER E, et al. Efficacy and safety of lixisenatide once daily versus placebo in type 2 diabetes insufficiently controlled on pioglitazone (GetGoal-P)[J]. *Diabetes Obes Metab*, 2013, 15(11): 1000 - 1007.
- [32] RIDDLE MC, ARONSON R, HOME P, et al. Adding once - daily lixisenatide for type 2 diabetes inadequately controlled by established basal insulin: a 24 - week, randomized, placebo - controlled comparison (GetGoal - L)[J]. *Diabetes Care*, 2013, 36(9): 2489 - 2496.
- [33] ROSENSTOCK J, HANEFELD M, SHAMANNA P, et al. Beneficial effects of once - daily lixisenatide on overall and postprandial glycemic levels without significant excess of hypoglycemia in Type 2 diabetes inadequately controlled on a sulfonylurea with or without metformin (GetGoal - S)[J]. *J Diabetes Complications*, 2014, 28(3): 386 - 392.
- [34] SEINO Y, MIN KW, NIEMOELLER E, et al. Randomized, double - blind, placebo - controlled trial of the once - daily GLP - 1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal - L - Asia)[J]. *Diabetes Obes Metab*, 2012, 14(10): 910 - 917.
- [35] AHRÉN B, MASMIQUEL L, KUMAR H, et al. Efficacy and safety of once - weekly semaglutide versus once - daily sitagliptin as an add - on to metformin, thiazolidinediones, or both, in patients with type 2 diabetes (SUSTAIN 2): a 56 - week, double - blind, phase 3a, randomised trial [J]. *Lancet Diabetes Endocrinol*, 2017, 5(5): 341 - 354.
- [36] ARODA VR, BAIN SC, CARIOU B, et al. Efficacy and safety of once - weekly semaglutide versus once - daily insulin glargine as add - on to metformin (with or without sulfonylureas) in insulin - naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open - label, parallel - group, multicentre, mul[J]. *Lancet Diabetes Endocrinol*, 2017, 5(5): 355 - 366.
- [37] KAKU K, YAMADA Y, WATADA H, et al. Safety and efficacy of once - weekly semaglutide vs additional oral antidiabetic drugs in Japanese people with inadequately controlled type 2 diabetes: A randomized trial [J]. *Diabetes Obes Metab*, 2018, 20(5): 1202 - 1212.
- [38] RODBARD HW, LINGVAY I, REED J, et al. Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A Randomized, Controlled Trial [J]. *J Clin Endocrinol Metab*, 2018, 103(6): 2291 - 2301.
- [39] SEINO Y, TERAUCHI Y, OSONOI T, et al. Safety and efficacy of semaglutide once weekly vs sitagliptin once daily, both as monotherapy in Japanese people with type 2 diabetes[J]. *Diabetes Obes Metab*, 2018, 20(2): 378 - 388.
- [40] HUSAIN M, BIRKENFELD AL, DONSMARK M, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes [J]. *N Engl J Med*, 2019, 381(9): 841 - 851.
- [41] DAVIES M, FÆRCH L, JEPPESEN OK, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, doubleblind, double - dummy, placebo - controlled, phase 3 trial [J]. *Lancet*, 2021, 397(10278): 971 - 984.
- [42] Safety and Efficacy of Exenatide Once Weekly Injection Versus Metformin, Dipeptidyl Peptidase - 4 Inhibitor, or Thiazolidinedione as Monotherapy in Drug - Naive Patients With Type 2 Diabetes (DURATION - 4), NCT00676338 [EB/OL]. (2015 - 04 - 09) [2025 - 04 - 19]. <https://clinicaltrials.gov/ct2/show/NCT00676338>.
- [43] KAKU K, KIYOSUE A, ONO Y, et al. Liraglutide is effective and well tolerated in combination with an oral antidiabetic drug in Japanese patients with type 2 diabetes: A randomized, 52 - week, open - label, parallelgroup trial [J]. *J Diabetes Investig*, 2016, 7(1): 76 - 84.
- [44] JI LN, DONG XL, LI YM, et al. Efficacy and safety of once - weekly semaglutide versus once - daily sitagliptin as add - on to metformin in patients with type 2 diabetes in SUSTAIN China: A 30 - week, double - blind, phase 3a, randomized trial [J]. *Diabetes Obes Metab*, 2021, 23(2): 404 - 414.
- [45] AVGERINOS I, KARAGIANNIS T, MALANDRIS K, et al. Glu - cagon - like peptide - 1 receptor agonists and microvascular outcomes in type 2 diabetes: A systematic review and meta - analysis [J]. *Diabetes Obes Metab*, 2019, 21(1): 188 - 193.
- [46] 中华医学会眼科学分会眼底病学组, 中国医师协会眼科医师分会眼底病学组. 我国糖尿病视网膜病变临床诊疗指南(2022年)[J]. *中华眼底病杂志*, 2023, 39(2): 99 - 124.
- [47] NATHAN DM, CLEARY PA, BACKLUND JY, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes [J]. *N Engl J Med*, 2005, 353(25): 2643 - 2653.
- [48] HOLMAN RR, PAUL SK, BETHEL MA, et al. 10 - year follow - up of intensive glucose control in type 2 diabetes [J]. *N Engl J Med*, 2008, 359(15): 1577 - 1589.
- [49] 张俊清. 胰高糖素样肽 - 1 受体激动剂对糖尿病微血管病变的保护作用及应用前景 [J]. *中华糖尿病杂志*, 2022, 14(11): 1136 - 1142.
- [50] 徐辉祥, 康力敏, 樊帆, 等. 司美格鲁肽药品不良反应国内外文献分析 [J]. *中国药业*, 2025, 34(12): 116 - 120.
- [51] 蒋王艳, 刘少华, 郭洁茹, 等. 基于美国 FAERS 数据库的司美格鲁肽不良事件信号挖掘 [J]. *药物流行病学杂志*, 2022, 31(3): 167 - 172.
- [52] 郭艳琼, 彭晶, 李庆德, 等. 基于 OpenFDA 数据挖掘和分析司美格鲁肽的不良事件报告信号 [J]. *中国药师*, 2022, 25(3): 475 - 478.
- [53] A Research Study to Look at How Semaglutide Compared to Placebo Affects Diabetic Eye Disease in People With Type 2 Diabetes (FOCUS) [EB/OL]. (2019 - 12 - 01) [2025 - 04 - 19]. <https://clinicaltrials.gov/ct2/show/NCT03811561>.

(收稿日期: 2025 - 05 - 27; 修回日期: 2025 - 12 - 01)