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钠－葡萄糖共转运蛋白－2抑制剂治疗2型糖尿病1年有效性的网状Meta分析

黎 风[1,2],何 梅[1,2],刘 福[1,2△]

(1.川北医学院附属医院药剂科,四川 南充 637000; 2.川北医学院药学院,四川 南充 637000)

摘要:目的 系统评价钠－葡萄糖共转运蛋白－2抑制剂(SGLT－2i)治疗2型糖尿病(T2DM)1年的有效性。**方法** 计算机检索PubMed,Embase,The Cochrane Library,以及中国生物医学文献数据库、中国期刊全文数据库、维普期刊全文数据库、万方数据库及国际临床试验注册中心数据库,检索时限为各数据库自建库至2019年12月31日;收集SGLT－2i治疗T2DM的随机对照试验(RCT);提取资料,并按Cochrane偏倚风险量表评估文献质量;采用Stata 15.1软件对数据进行网状Meta分析。**结果** 共纳入37个RCT,包括28 973例患者。网状Meta分析结果显示,SGLT－2i降低糖化血红蛋白(HbA_{1C})水平的能力弱于胰高血糖素样肽－1受体激动剂(GPL－1RAs)和二甲双胍($P<0.05$),与磺脲类、噻唑烷二酮类(TZDs)、二肽基肽酶－4抑制剂(DPP－4i)相当($P>0.05$);各SGLT－2i间降低HbA_{1C}水平的能力相当($P>0.05$)。SGLT－2i降低空腹血糖(FBG)水平的能力与GLT－1RAs、二甲双胍和TZDs相当($P>0.05$),强于磺脲类、DPP－4i($P<0.05$);除卡格列净300 mg强于达格列净5 mg外($P<0.05$),其余SGLT－2i间降低FBG水平的能力相当($P>0.05$)。SGLT－2i降低体质量及血压的能力强于其他口服降糖药($P<0.05$);各SGLT－2i间降血压的能力相当($P>0.05$)。**结论** SGLT－2i能显著降低患者的HbA_{1C}和FBG水平及血压和体质量,卡格列净300 mg的疗效可能最好。上述结论尚需开展更大样本、更高质量的多中心RCT证实。

关键词:卡格列净;达格列净;恩格列净;钠－葡萄糖共转运蛋白－2抑制剂;网状Meta分析;2型糖尿病;有效性

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One－Year Efficacy of Sodium－Glucose－Transporter－2 Inhibitors in the Treatment of Type 2 Diabetes Mellitus:A Network Meta－Analysis

LI Feng[1,2], HE Mei[1,2], LIU Fu[1,2]

(*1. Department of Pharmacy, The Affiliated Hospital of North Sichuan Medical College, Nanchong, Sichuan, China 637000; 2. School of Pharmacy, North Sichuan Medical College, Nanchong, Sichuan, China 637000*)

Abstract: Objective To systematically review the one－year efficacy of sodium－glucose－transporter－2 inhibitors(SGLT－2i) in the treatment of type 2 diabetes mellitus(T2DM). **Methods** The randomized controlled trails(RCTs) of SGLT－2i in the treatment of T2DM were searched from PubMed, Embase, The Cochrane Library, CBM, CNKI, VIP, Wanfang database and International Clinical Trial Registry from inception to December 31st, 2019. The related data was extracted from RCTs and the quality of RCTs was evaluated according to the Cochrane bias risk scale. The network Meta－analysis was conducted on the data by the Stata 15.1 software. **Results** A total of 37 RCTs were included, including 28 973 patients. The results of network Meta－analysis showed that the ability of SGLT－2i to reduce the level of glycosylated hemoglobin(HbA_{1C}) was weaker than that of glucagon－like peptide－1 receptor agonists(GLP－1RAs) and metformin($P<0.05$), which was equivalent to that of sulfonylureas, thiazolidinediones(TZDs) and dipeptidyl peptidase－4 inhibitors($P>0.05$). The ability of each SGLT－2i to reduce the level of HbA_{1C} was similar($P>0.05$). The ability of SGLT－2i to reduce the level of fasting blood glucose(FBG) was equivalent to that of GLP－1RAs, metformin and TZDs($P>0.05$), which was stronger than that of sulfonylurea and dipeptidyl peptidase－4 inhibitors($P<0.05$). The ability of other SGLT－2i to reduce the level of FBG was similar($P>0.05$), except that of 300 mg of canagliflozin was stronger than that of 5 mg of dapagliflozin($P<0.05$). The ability of SGLT－2 inhibitors to reduce body weight and blood pressure was stronger than that of other oral hypoglycemic drugs($P<0.05$). The ability of each SGLT－2i to reduce blood pressure was similar($P>0.05$). **Conclusion** SGLT－2i can significantly reduce the levels of HbA_{1C} and FBG, blood pressure and body weight of patients. The curative effect of 300 mg of canagliflozin may be the best. However, the above conclusions need to be confirmed by a larger sample of higher－quality multi－center RCTs.

Key words: canagliflozin; dapagliflozin; empagliflozin; sodium－glucose－transporter－2 inhibitors; network Meta－analysis; type 2 diabetes mellitus; efficacy

2型糖尿病(T2DM)属慢性代谢性疾病,以高血糖和胰岛素－葡萄糖反馈机制的渐进性失调为特征[1]。研究表明,强化血糖控制对于减少T2DM患者的长期微血管和大血管并发症具有重要意义[2]。钠－葡萄糖共转运蛋白－2抑制剂(SGLT－2i)是治疗T2DM高血糖的新型口服降糖药,通过抑制近端肾小管SGLT－2表达来减少尿糖的重吸收,从而起到降血糖的作用[3]。此外,SGLT－2i还可通过利尿和利钠作用来降低心力衰竭患

第一作者:黎风,女,硕士,药师,研究方向为临床药学及循证药学,(电子信箱)pharmacylf90@163.com。

△**通信作者:**刘福,男,教授,主任药师,研究方向为医院药学及临床药学,(电话)0817－2262246(电子信箱)nclf91@163.com。

者的住院率，降低心血管病死亡率，并减缓 T2DM 肾病的进展[4]。美国糖尿病协会、欧洲糖尿病研究协会和我国 T2DM 防治指南均推荐 SGLT－2i 用于 T2DM 的二线治疗[5－6]。目前已有 SGLT－2i 与安慰剂（PBO）、其他降糖药如磺脲类降糖药（SU）、二肽基肽酶－4 抑制剂（DPP－4i）和二甲双胍（MET）等的临床随机对照试验（RCT），但尚无 SGLT－2i 之间“头对头”的直接比较试验，故无法直接评估 SGLT－2i 间疗效的差异。当缺乏直接比较数据时，可通过网状 Meta 分析对多个干预中措施的疗效进行评估[7]，且网状 Meta 分析在卫生保健决策方面的价值也日益得到认可[8]。本研究中采用网状 Meta 分析方法评估 SGLT－2i 治疗 T2DM 1 年的有效性，旨在为临床选药、医保药物遴选、药品价格调整或制订合理用药指南等提供参考。现报道如下。

1 资料与方法

1.1 检索策略

计算机检索 PubMed，Embase，The Cochrane Library，以及中国期刊全数据库、万方数据库、维普期刊全文数据库、中国生物医学文献数据库及国际临床试验注册平台。检索时限为各数据库自建库起至 2019 年 12 月 31 日。此外，追溯纳入研究的参考文献，以补充获取相关文献。中英文主题词和关键词包括“Diabetes mellitus type 2”“sodium－glucose－transporter－2 inhibitors”“SGLT－2 inhibitors”“ipragliflozin”“dapagliflozin”“canagliflozin”“luseogliflozin”“empagliflozin”“ertugliflozin”“randomized control trial”“2 型糖尿病”“钠－葡萄糖共转运蛋白－2 抑制剂”“SGLT－2 抑制剂”“伊格列净”“达格列净”“卡格列净”“鲁格列净”“恩格列净”“埃格列净”“随机对照”。

1.2 文献纳入与排除标准

纳入标准：1）纳入人群，年龄≥18 岁；性别不限；以美国糖尿病协会或世界卫生组织标准确诊的 T2DM。2）干预措施，试验组予 SGLT－2i，对照组予安慰剂或活性对照药物；治疗剂量不限。3）结局指标，①糖化血红蛋白（HbA_{1C}）水平；②空腹血糖（FBG）水平；③体质量；④收缩压（SBP）；⑤舒张压（DBP）。4）研究类型为 RCT，随访时间约 1 年，语言不限。

排除标准：1 型糖尿病；未包含前述任一结局指标；数据有误、数据报道不全；重复发表，不能获取全文；未提供原始数据，且向作者联系无果。

1.3 文献筛选、资料提取与文献质量评价

两位研究人员根据事先制定的检索策略、文献纳入与排除标准和数据资料提取表独立地进行文献检索、筛选和资料提取，并按 Cochrane 偏倚风险评估工具独立对所纳入研究的方法学进行质量评价，若有分歧，则通过协商解决，若仍不能达成一致则交由第三方协助裁定。

1.4 统计学处理及数据分析

采用 Stata 15.1 统计学软件分析。研究间的异质性用 I^2 值来定量描述；若 $I^2>50\%$，表明研究间存在显著异质性，则采用随机效应模型分析；若 $I^2\leqslant 50\%$，表明研究间的异质性较小，则采用固定效应模型分析。采用 Network 包进行数据预处理、绘制网状证据图，通过 SUCRA 功能进行疗效排序。采用环不一致性检测图对结果的不一致性进行检验，若差异无统计学意义（$P>0.05$），提示直接比较与间接比较结果一致。本研究中结局资料类型均为计量资料，采用加权均数差（*WMD*）和 95% 置信区间（*CI*）作为效应指标。

2 结果

2.1 纳入文献信息

共检索出 3 154 篇文献，经层层筛选，最终纳入 37 篇文献，共 28 973 例患者。网状 Meta 分析中共涉及的干预措施有：卡格列净（CANA）100 mg 和 300 mg，达格列净（DAPA）5 mg 和 10 mg，恩格列净（EMPA）10 mg 和 25 mg，PBO、MET、SU、噻唑烷二酮类降糖药（TZDs）、DPP－4i、胰高糖素样肽－1 受体激动剂（GLP－1RAs）。纳入文献偏倚风险见图 1，纳入研究降糖药使用情况网状关系见图 2，纳入研究的基本特征见表 1。

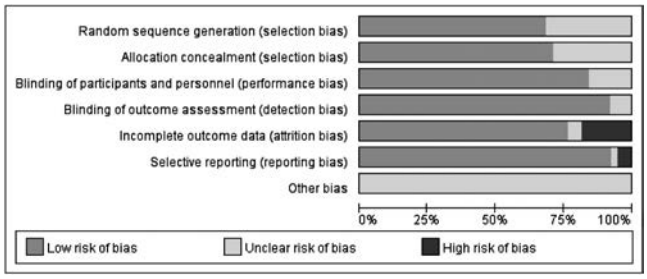

图 1 纳入文献偏倚风险条形图

Fig. 1 Bar chart of bias risk of included studies

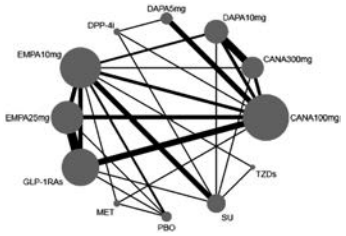

图 2 纳入研究的网状关系图

Fig. 2 Network diagram of included studies

2.2 网状 Meta 分析结果

HbA_{1C}：有 37 篇文献[9－45]报道。环不一致性检测图结果提示，一致性差异无统计学意义（$P>0.05$）。异质性检验显示，直接比较中各研究间统计学异质性均较小（$P>0.1$，$I^2<50\%$）。网状 Meta 分析结果显示，SGLT－2i 降 HbA_{1C} 的能力弱于 GLP－1RAs 和 MET（$P<0.05$），与 SU，TZDs，DPP－4i 相当；各 SGLT－2i 间降 HbA_{1C} 能力相当（见表 2）。根据 Sucra 值对干预措施排序，GLP－

表1 纳入研究的基本特征($\overline{X} \pm s$)

Tab. 1 Basic characteristics of the included studies($\overline{X} \pm s$)

第一作者及发表年份	干预措施	例数	年龄(岁)	体质量(kg)	HbA_{1C}(%)	结局指标
FERRANNINI2013[9]	恩格列净10 mg	106	58.3±8.5	82.9±16.4	7.89±0.9	①②③
	恩格列净25 mg	109	58.5±10.0	84.6±18.1	8.00±0.93	
	二甲双胍	56	56.8±8.9	85.8±15.6	8.15±1.0	
FERRANNINI2013[9]	恩格列净10 mg	166	58.4±8.3	89.6±15.0	7.88±0.7	①②③
	恩格列净25 mg	166	59.9±7.8	89.5±16.2	7.91±0.8	
	西格列汀	56	58.3±10.5	88.6±14.9	8.03±0.9	
INAGAKI2015[11]	卡格列净100 mg	127	57.7±10.8	68.54±15.9	7.84±0.7	①②③④⑤
	卡格列净300 mg	253	58.5±11.7	67.57±12.9	7.95±0.7	
STENLOF2014[12]	卡格列净100 mg	195	55.1±10.8	85.8±21.4	8.1±1.0	①②③④
	卡格列净300 mg	197	55.3±10.2	86.9±20.5	8.0±1.0	
KADOWAKI2015[13]	恩格列净10 mg	267	57.3±9.8	69.3±14.5	7.94±0.7	①②③④⑤
	恩格列净25 mg	265	57.9±10.1	68.8±12.7	7.93±0.7	
RODEN2015[14]	安慰剂	228	54.9±10.9	78.2±19.9	7.91±0.8	①②③④⑤
	恩格列净10 mg	224	56.2±11.6	78.4±18.7	7.87±0.9	
	恩格列净25 mg	224	53.8±11.6	77.8±18.0	7.86±0.93	
	西格列汀	223	55.1±9.9	79.3±20.4	7.85±0.8	
LEWIN2015[15]	恩格列净25 mg	133	56.0±9.3	86.7±19.7	7.99±1.0	①②③④⑤
	恩格列净10mg	132	53.9±10.5	87.8±24.0	8.05±1.0	
	利格列汀	133	53.8±11.5	89.5±20.1	8.05±0.9	
NAUCK2011[16]	达格列净10 mg	400	58.1±9.4	88.4	7.69±0.9	①③
	格列吡嗪	401	58.6±9.8	87.6	7.74±0.9	
CEFALU2013[17]	格列美脲	482	56.3±9.0	86.5±19.8	7.8±0.8	①②③④⑤
	卡格列净100 mg	483	56.4±9.5	86.9±20.1	7.8±0.8	
	卡格列净300 mg	485	55.8±9.2	86.6±19.5	7.8±0.8	
LAVALLE-GONZALEZ2013[18]	西格列汀	366	55.5±9.6	87.7±21.6	7.9±0.9	①②③④⑤
	卡格列净100 mg	368	55.5±9.4	88.8±22.2	7.9±0.9	
	卡格列净300 mg	367	55.3±9.2	85.4±20.9	7.9±0.9	
RIDDERSTRALE2014[19]	格列美脲	780	55.7±10.4	83.0±19.2	7.92±0.9	①②③④⑤
	恩格列净25 mg	765	56.2±10.3	82.5±19.2	7.92±0.8	
DEFRONZO2015[20]	恩格列净25 mg	140	55.5±10.0	87.7±17.6	8.02±0.8	①②③④⑤
	恩格列净10 mg	137	56.1±10.5	85.7±18.4	8.00±0.9	
	利格列汀	128	56.2±10.0	85.0±18.3	8.02±0.9	
MERKER2015[21]	安慰剂	207	56.0±9.7	79.7±18.6	7.9±0.9	①②③④⑤
	恩格列净10 mg	217	55.5±9.9	81.6±18.5	7.9±0.8	
	恩格列净25 mg	213	55.6±10.2	82.2±19.3	7.9±0.9	
YALE2017[22]	安慰剂	69	64.3±7.8	84.2±18.9	8.4±1.1	①②
	卡格列净100 mg	74	64.3±8.5	80.7±16.6	8.3±1.0	
	卡格列净300 mg	72	65.8±7.9	80.5±18.9	8.1±1.0	
SCHERNTHANER2013[23]	西格列汀	378	56.7±9.3	89.1±23.2	8.1±0.9	①②③④
	卡格列净300 mg	377	56.6±9.6	87.4±23.2	8.1±0.9	
WILDING2013[24]	安慰剂	156	56.8±8.3	91.2±22.6	8.1±0.9	①②③④⑤
	卡格列净100 mg	157	57.4±10.5	93.8±22.6	8.1±0.9	
	卡格列净300 mg	156	56.1±8.9	93.5±22.0	8.1±0.9	
HAERING2015[25]	安慰剂	225	56.9±9.2	76.2±16.9	8.2±0.8	①②③④⑤
	恩格列净10 mg	225	57.0±9.2	77.1±18.3	8.1±0.8	
	恩格列净25 mg	216	57.4±9.3	77.5±18.8	8.1±0.8	
MATTHAEI2015[26]	安慰剂	108	60.9±9.2	90.1±16.2	8.2±0.9	①②③④
	达格列净10 mg	108	61.1±9.7	88.6±17.6	8.1±0.9	
MATHIEU2016[27]	安慰剂	160	55.0±9.6	32.2±5.3#	8.17±1.0	①②③
	达格列净10 mg	160	55.2±8.6	31.2±4.7#	8.24±1.0	
MATTHAEI2016[28]	安慰剂	162	54.5±9.3	87.9±17.1	7.86±1.0	①②
	沙格列汀	153	54.7±9.8	88.1±20.0	7.97±0.8	
KOHAN2014[29]	安慰剂	84	67±8.6	89.61±20.1	8.53±1.3	①②③
	达格列净5 mg	83	66±8.9	95.23±20.9	8.30±1.0	
	达格列净10 mg	85	68±7.7	93.25±17.3	8.22±1.0	
BARNETT2014[10]	安慰剂	95	62.6±8.1	86.0±20.0	8.09±0.8	①②③④⑤
	恩格列净10 mg	98	63.2±8.5	92.1±21.4	8.02±0.8	
	恩格列净25 mg	97	62.0±8.4	88.1±21.7	7.96±0.7	
BARNETT2014[10]	安慰剂	187	65.1±8.2	82.5±18.0	8.09±0.8	①②③④⑤
	恩格列净25 mg	187	64.6±8.9	83.2±19.5	8.02±0.8	
BARNETT2014[10]	安慰剂	37	62.9±11.9	84.1±21.1	8.16±1.0	①②③④⑤
	恩格列净25 mg	37	65.4±10.2	77.9±16.4	8.06±1.1	
LEITER2014[30]	安慰剂	482	63.6±7.0	93.2±16.8	8.1±0.8	①③
	达格列净10 mg	480	63.9±7.6	94.5±17.8	8.0±0.8	
YALE2014[31]	安慰剂	90	68.2±8.4	92.8±17.4	8.0±0.9	
	卡格列净100 mg	90	69.5±8.2	90.5±18.4	7.9±0.9	
	卡格列净300 mg	89	67.9±8.2	90.2±18.1	8.0±0.8	
CEFALU2015[32]	安慰剂	459	63.0±7.7	93.6±19.5	8.08±0.8	①②③④
	达格列净10 mg	455	62.8±7.0	92.6±20.5	8.18±0.8	
REUSCH2014[33]	安慰剂	151	54.9±9.4	100.2±23.1	8.1±0.9	①②③
	阿必鲁肽	152	55.2±9.9	97.6±22.0	8.1±1	
MATTHEWS2005[34]	吡格列酮	317	56±9.2	91.8±16.2	8.71±1	①②
	格列齐特	313	57±9.0	92.7±17.4	8.53±0.9	
UMPIERREZ2014[35]	度拉糖肽	539	56±10.5	92.5±19	7.6±0.9	①②③④⑤
	二甲双胍	268	55±10.0	92±19	7.6±0.8	
NAUCK2014[36]	度拉糖肽	606	54±10.0	86.5±17.5	8.2±1.1	①②③④⑤
	西格列汀	315	54±10.0	86±17	8.1±1.1	
GALLWITZ2012[37]	利格列汀	776	59.8±9.4	86.1±17.6	7.7±0.9	①②③
	格列美脲	775	59.8±9.4	86.8±16.7	7.7±0.9	
BARNETT2013[38]	沙格列汀	304	57.2±9.4	87.7±18.6	8.7±0.9	①④⑤
	安慰剂	151	57.3±9.3	86.2±16.5	8.6±0.9	
PFUTZNER2011[39]	沙格列汀	335	52.1±10.2		9.6±1.3	①
	二甲双胍	328	51.8±10.7		9.4±1.3	
GOKE2010[40]	沙格列汀	428	57.5±10.3	88.7±18.6	7.7±0.9	①②③
	格列吡嗪	430	57.6±10.4	88.6±19.6	7.7±0.9	
BOLLI2009[41]	度拉糖肽	295	56.3±9.3	91.8±18.5	8.4±1.0	①②③
	吡格列酮	281	57.0±9.7	91.2±16.9	8.4±0.9	
SCHWEIZER2007[42]	维格列汀	526	52.8±11.7	32.4±5.7#	8.7±1.1	①②③
	二甲双胍	254	53.6±10.2	32.5±5.7#	8.7±1.1	
FERRANNINI2009[43]	维格列汀	1 396	57.5±9.1	31.8±5.3#	7.31±0.6	①②
	格列美脲	1 393	57.46±9.3	31.69±5.3#	7.30±0.7	

续表 1 纳入研究的基本特征（$\bar{X} \pm s$）

Continued Tab. 1 Basic characteristics of the included studies（$\bar{X} \pm s$）

研究	干预措施	例数	年龄(岁)	体质量(kg)	HbA_{1C}(%)	结局指标	研究	干预措施	例数	年龄(岁)	体质量(kg)	HbA_{1C}(%)	结局指标
FILOZOF2010[44]	维格列汀	513	59.2±9.9	85.7±16.6	8.5±1.0	①	NAUCK2007[45]	西格列汀	588	56.8±9.3	89.5±17.4	7.7±0.9	①②③
	格列齐特	494	59.7±10.2	84.2±17.9	8.5±1.0			格列吡嗪	584	56.6±9.8	89.7±17.5	7.6±0.9	

表 2 HbA_{1C} 的网状 Meta 分析结果汇总[*WMD*(95% *CI*)]

Tab. 2 Results of network Meta－analysis of HbA_{1C}[*WMD*(95% *CI*)]

GLP-1RAs	-0.11(-0.28,0.05)	*	*	*	*	*	*	*	*	-0.59(-0.74,-0.45)	-0.76(-0.96,-0.56)
-0.09(-0.28,0.10)	二甲双胍	*	-0.42(-0.70,-0.14)	*	-0.47(-0.75,-0.19)	*	*	*	*	-0.28(-0.44,-0.13)	*
-0.23(-0.43,-0.03)	-0.14(-0.33,0.06)	卡格列净300 mg	*	*	*	-0.12(-0.23,-0.01)	-0.16(-0.22,-0.10)	*	*	-0.26(-0.48,-0.04)	-0.68(-1.03,-0.33)
-0.30(-0.48,-0.12)	-0.21(-0.38,-0.03)	-0.07(0.07,-0.21)	恩格列净25 mg	*	-0.09(-0.15,-0.03)	-0.07(-0.15,0.01)	*	*	*	-0.23(-0.41,-0.05)	-0.59(-0.79,-0.40)
-0.33(-0.55,-0.12)	-0.24(-0.45,-0.03)	-0.10(0.07,-0.28)	-0.03(-0.19,0.12)	达格列净10 mg	*	0.00(-0.74,0.74)	*	*	0.00(-0.28,0.28)	*	-0.60(-0.75,-0.45)
-0.34(-0.53,-0.15)	-0.25(-0.43,-0.07)	-0.11(0.04,-0.25)	-0.04(-0.13,0.05)	-0.01(0.15,-0.17)	恩格列净10 mg	*	*	*	*	-0.12(-0.29,0.05)	-0.69(-0.77,-0.62)
-0.40(-0.21,-0.58)	-0.30(-0.12,-0.48)	-0.17(-0.04,-0.29)	-0.10(0.02,-0.21)	-0.06(0.11,-0.23)	-0.06(0.07,-0.18)	维格列汀	-0.01(-0.12,0.10)	-0.02(-0.03,-0.01)	*	-0.09(-0.15,-0.02)	*
-0.40(-0.61,-0.20)	-0.31(-0.51,-0.11)	-0.17(-0.27,-0.07)	-0.10(-0.25,0.04)	-0.07(-0.25,0.11)	-0.06(-0.21,0.09)	-0.01(-0.14,0.13)	卡格列净100 mg	*	*	0.00(-0.14,0.14)	-0.55(-0.83,-0.27)
-0.44(-0.20,-0.68)	-0.35(-0.11,-0.59)	-0.21(-0.00,-0.41)	-0.14(0.06,-0.34)	-0.11(0.13,-0.34)	-0.10(0.10,-0.30)	-0.04(0.13,-0.21)	-0.04(0.17,-0.25)	TZDs	*	0.00(0.18,0.18)	*
-0.51(-0.83,-0.19)	-0.42(-0.74,-0.09)	-0.28(0.02,-0.58)	-0.21(-0.50,0.08)	-0.18(0.11,-0.46)	-0.17(-0.46,0.12)	-0.11(-0.41,0.18)	-0.11(0.19,-0.41)	-0.07(-0.40,0.26)	达格列净5 mg	*	-0.28(-0.51,-0.05)
-0.48(-0.65,-0.31)	-0.39(-0.55,-0.23)	-0.25(-0.13,-0.37)	-0.18(-0.28,-0.08)	-0.15(0.01,-0.30)	-0.14(-0.25,-0.03)	-0.08(-0.17,0.00)	-0.08(0.05,-0.21)	-0.04(-0.22,0.14)	0.03(0.32,-0.26)	DPP-4i	-0.5(-0.69,-0.31)
-0.93(-1.11,-0.76)	-0.84(-1.02,-0.66)	-0.70(-0.83,-0.58)	-0.63(-0.73,-0.53)	-0.60(-0.72,-0.48)	-0.59(-0.70,-0.49)	-0.54(-0.65,-0.42)	-0.53(-0.66,-0.40)	-0.49(-0.69,-0.29)	-0.42(-0.70,-0.15)	-0.45(-0.55,-0.35)	安慰剂

注：TZDs 为噻唑烷二酮类药物，表格右上部分为直接比较的结果，左下部分为网状 Meta 分析结果；* 表示无直接比较结果。表 3 至表 5 同。

Note：TZDs is short for thiazolidinediones，the upper right part of the table shows the results of direct comparison，and the lower left part of the table shows the results of network Meta－analysis；* indicates that there is no direct comparison result；as well as Tab. 3 to Tab. 5.

表 3 FBG 的网状 Meta 分析结果汇总[*WMD*(95% *CI*)]

Tab. 3 Results of network Meta－analysis of FBG[*WMD*(95% *CI*)]

卡格列净300 mg	*	*	*	*	*	-0.39(-0.56,-0.21)	*	-0.50(-0.75,-0.25)	*	-1.15(-1.47,-0.83)	-1.67(-2.41,-0.92)
-0.02(0.48,-0.52)	GLP-1RAs	-0.11(-0.51,0.29)	*	*	*	*	*	*	*	-1.11(-1.38,-0.83)	-1.63(-2.17,-1.09)
-0.15(0.38,-0.67)	-0.13(0.36,-0.61)	二甲双胍	-0.05(-0.70,0.60)	*	-0.01(-0.66,0.64)	*	*	*	*	-1.00(-1.43,-0.57)	*
-0.24(0.12,-0.60)	-0.22(-0.68,0.24)	-0.09(-0.56,0.37)	恩格列净25 mg	*	-0.15(-0.30,0.00)	*	*	-0.60(-0.76,-0.44)	*	-0.85(-1.25,-0.44)	-1.44(-1.82,-1.05)
-0.32(0.16,-0.81)	-0.30(-0.87,0.27)	-0.18(-0.77,0.42)	-0.08(-0.51,0.35)	达格列净10 mg	*	*	*	*	-0.09(-0.71,0.53)	*	-1.40(-2.15,-0.64)
-0.32(0.05,-0.70)	-0.30(-0.77,0.16)	-0.18(-0.65,0.30)	-0.08(-0.31,0.14)	-0.00(0.44,-0.44)	恩格列净10 mg	*	*	*	*	-0.68(-1.08,-0.28)	-1.56(-1.77,-1.35)
-0.40(-0.66,-0.14)	-0.38(-0.90,0.14)	-0.25(-0.79,0.28)	-0.16(-0.54,0.21)	-0.08(-0.57,0.42)	-0.08(-0.46,0.31)	卡格列净100 mg	*	-0.33(-0.58,-0.08)	*	-0.50(-0.77,-0.23)	-1.49(-2.23,-0.75)
-0.55(-0.02,-1.07)	-0.53(0.09,-1.14)	-0.40(0.23,-1.03)	-0.31(0.19,-0.81)	-0.23(0.39,-0.84)	-0.22(0.29,-0.74)	-0.15(0.39,-0.68)	TZDs	-0.20(-0.23,-0.17)	*	-0.60(-1.05,-0.15)	*
-0.80(-0.46,-1.13)	-0.78(-0.30,-1.25)	-0.65(-0.16,-1.14)	-0.56(-0.26,-0.86)	-0.48(0.00,-0.95)	-0.47(-0.15,-0.80)	-0.40(-0.05,-0.75)	-0.25(-0.69,0.19)	维格列汀	*	-0.22(-0.42,-0.02)	*
-0.93(-0.13,-1.73)	-0.91(-1.76,-0.06)	-0.79(-1.65,0.08)	-0.69(-1.46,0.07)	-0.61(0.12,-1.34)	-0.61(-1.38,0.16)	-0.53(0.27,-1.34)	-0.38(-1.27,0.50)	-0.13(-0.92,0.66)	达格列净5 mg	*	-0.35(-0.94,0.24)
-1.06(-0.76,-1.37)	-1.04(-1.47,-0.62)	-0.92(-1.36,-0.47)	-0.83(-1.08,-0.57)	-0.74(-0.30,-1.18)	-0.74(-1.01,-0.47)	-0.67(-0.34,-0.99)	-0.52(-0.97,-0.07)	-0.27(-0.50,-0.03)	-0.13(0.64,-0.90)	DPP-4i	-0.72(-1.22,-0.22)
-1.73(-2.07,-1.39)	-1.71(-2.16,-1.26)	-1.58(-2.06,-1.11)	-1.49(-1.74,-1.24)	-1.41(-1.76,-1.06)	-1.41(-1.67,-1.14)	-1.33(-1.68,-0.98)	-1.18(-1.69,-0.67)	-0.93(-1.25,-0.61)	-0.80(-1.52,-0.08)	-0.67(-0.93,-0.40)	安慰剂

1RAs > MET，CANA 300 mg > EMPA 25 mg > DAPA 10 mg > EMPA 10 mg > SU > CANA 100 mg > TZDs > DAPA 5 mg > DPP－4i > PBO。

FBG：有 31 篇文献[9－15，17－21，23－29，31－37，40－43，45]报道。环不一致性检测图结果提示，一致性差异无统计学意义（$P > 0.05$）。异质性检验显示，直接比较中各研究间统计学异质性均较小（$P > 0.10$，$I^2 < 50\%$）。网状 Meta 分析结果显示，SGLT－2i 降 FBG 的能力与 GLP－1RAs，MET，TZDs 相当，强于 SU 和 DPP－4i（$P < 0.05$）；除 CANA 300 mg 强于 DAPA 5 mg 外（$P < 0.05$），余 SGLT－2i 间降 FBG 能力相当（见表 3）。根据 Sucra 值对干预措施排序，CANA 300 mg > GLP－1RAs > MET > EMPA 25 mg > DAPA 10 mg > EMPA 10 mg > CANA 100 mg > TZDs > SU > DAPA 5 mg > DPP－4i > PBO。

体质量：有 30 篇文献[9－21，23－27，29－33，35－37，40－42，45]报道。环不一致性检测图结果提示，一致性差异无统计学意义（$P > 0.05$）。异质性检验显示，直接比较中各研究间统计学异质性均较小（$P > 0.10$，$I^2 < 50\%$）。网状Meta 分析结果显示，SGLT2i 减轻体质量的能力强于 GLP－1RAs，MET，TZDs，SU 和 DPP－4i（$P < 0.05$）；除 DAPA 5 mg 外，其他 SGLT－2i 均强于 CANA 100 mg（$P < 0.05$），余 SGLT－2i 间减轻体质量的能力相当（见表 4）。根据

SUCRA值对干预措施排序，DAPA 10 mg > EMPA 25 mg > EMPA 10 mg > DAPA 5 mg > CANA 300 mg > CANA 100 mg > MET > GLP－1RAs > PBO > DPP－4i > SU > TZDs。

SBP：有20篇文献[10－15，17－21，23－26，31－32，35－36，38]报道。环不一致性检测图结果提示，一致性差异无统计学意义（$P>0.05$）。异质性检验显示，直接比较中各研究间统计学异质性均较小（$P>0.10$，$I^2<50\%$）。网状Meta分析结果显示，SGLT－2i降SBP的能力强于GLP－1RAs，MET，SU，DPP－4i（$P<0.05$）；各SGLT－2i间降SBP的能力相当（见表5）。根据SUCRA值对干预措施排序：CANA 300 mg > EMPA 25 mg > EMPA 10 mg > DAPA 10 mg > CANA 100 mg > GLP－1RAs > DPP－4i > PBO > MET > SU。

DBP：有15篇文献[10－11，13－15，17－21，24－25，35－36，38]报道。环不一致性检测图结果提示，一致性差异无统计学意义（$P>0.05$）。异质性检验显示，直接比较中各研究间统计学异质性均较小（$P>0.10$，$I^2<50\%$）。网状Meta分析结果显示，SGLT－2i降DBP的能力强于GLP－1RAs，MET，SU，DPP－4i（$P<0.05$）；各SGLT－2i间降DBP的能力相当（见表6）。根据SUCRA值对干预措施排序：EMPA 25 mg > CANA 300 mg > EMPA 10 mg > CANA 100 mg >

表4 体质量的网状Meta分析结果汇总[*WMD*(95% *CI*)]

Tab. 4 Results of network Meta－analysis of body weight[*WMD*(95% *CI*)]

达格列净10 mg	*	*	-0.58(-1.93,0.76)	*	*	*	*	-2.09(-2.45,-1.73)	*	-4.66(-5.15,-4.17)	*
-0.08(0.25,-0.41)	恩格列净25 mg	-0.16(0.41,0.08)	*	*	*	-1.17(-2.14,-0.20)	*	-1.90(-2.29,-1.50)	-2.62(-3.02,-2.22)	-4.80(-5.12,-4.48)	*
-0.14(0.21,-0.50)	-0.07(-0.31,0.18)	恩格列净10 mg	*	*	*	-1.04(-2.01,-0.07)	*	-1.94(-2.22,-1.65)	-2.66(-3.05,-2.26)	*	*
-0.13(1.04,-1.31)	-0.06(-1.25,1.14)	0.01(-1.19,1.21)	达格列净5 mg	*	*	*	*	-2.27(-3.59,-0.95)	*	*	*
-0.21(-0.63,0.21)	-0.13(-0.49,0.23)	-0.06(-0.45,0.33)	-0.07(-1.30,1.15)	卡格列净300 mg	-0.51(-0.80,-0.23)	*	*	-1.79(-2.56,-1.01)	-2.45(-2.84,-2.06)	-4.70(-5.25,-4.15)	*
-0.72(-1.16,-0.28)	-0.64(-1.03,-0.25)	-0.57(-0.99,-0.16)	-0.59(-1.81,0.64)	-0.51(-0.80,-0.22)	卡格列净100 mg	*	*	-0.93(-1.59,-0.27)	-2.10(-2.65,-1.55)	-4.40(-4.95,-3.85)	*
-0.78(-0.22,-1.35)	-0.70(-0.20,-1.21)	-0.64(-0.12,-1.15)	-0.65(0.63,-1.93)	-0.57(-0.02,-1.13)	-0.06(0.51,-0.63)	二甲双胍	-0.69(-1.39,0.00)	*	-2.20(-2.90,-1.50)	*	*
-1.48(-0.95,-2.01)	-1.40(-0.92,-1.89)	-1.34(-0.84,-1.83)	-1.35(-0.08,-2.61)	-1.27(-0.75,-1.80)	-0.76(-0.22,-1.30)	-0.70(-1.22,-0.18)	GLP－1RAs	-0.17(-1.13,0.79)	-1.29(-1.82,-0.75)	*	*
-1.99(-2.25,-1.72)	-1.91(-2.14,-1.68)	-1.84(-2.11,-1.58)	-1.86(-3.03,-0.68)	-1.78(-2.14,-1.42)	-1.27(-1.65,-0.89)	-1.21(-1.73,-0.69)	-0.51(-0.99,-0.02)	安慰剂	-0.62(-1.15,-0.09)	*	*
-2.66(-2.31,-3.01)	-2.58(-2.85,-2.32)	-2.52(-2.81,-2.22)	-2.53(-1.33,-3.73)	-2.45(-2.14,-2.76)	-1.94(-1.60,-2.28)	-1.88(-2.35,-1.41)	-1.18(-1.61,-0.74)	-0.67(-0.39,-0.96)	DPP－4i	-2.42(-2.68,-2.16)	-2.40(-3.11,-1.69)
-4.96(-4.62,-5.30)	-4.88(-4.62,-5.14)	-4.82(-4.50,-5.13)	-4.83(-3.63,-6.02)	-4.75(-4.42,-5.08)	-4.24(-3.89,-4.59)	-4.18(-3.67,-4.69)	-3.48(-3.00,-3.95)	-2.97(-2.69,-3.26)	-2.30(-2.07,-2.53)	维格列汀	*
-5.06(-4.25,-5.87)	-4.98(-4.21,-5.76)	-4.92(-4.13,-5.70)	-4.93(-3.52,-6.33)	-4.85(-4.06,-5.65)	-4.34(-3.54,-5.15)	-4.28(-3.41,-5.15)	-3.58(-2.73,-4.43)	-3.07(-2.29,-3.86)	-2.40(-1.67,-3.13)	-0.10(0.66,-0.87)	TZDs

表5 SBP的网状Meta分析结果汇总[*WMD*(95% *CI*)]

Tab. 5 Results of network Meta－analysis of SBP[*WMD*(95% *CI*)]

卡格列净300 mg	*	*	*	-1.44(-2.33,-0.56)	*	-4.91(-6.78,-3.04)	-4.49(-8.04,-0.94)	*	-4.80(-6.46,-3.14)
-0.60(0.77,-1.97)	恩格列净25 mg	-0.39(-1.55,0.77)	*	*	*	-3.22(-4.69,-1.74)	-4.47(-6.22,-2.73)	*	-5.80(-7.04,-4.56)
-1.20(0.29,-2.69)	-0.60(-1.60,0.40)	达格列净10 mg	*	*	*	-3.59(-5.24,-1.93)	-3.04(-4.15,-1.92)	*	*
-1.49(0.77,-3.75)	-0.90(-2.92,1.13)	-0.29(-2.36,1.77)	恩格列净10 mg	*	*	*	-3.21(-4.76,-1.67)	*	*
-1.59(-2.57,-0.61)	-1.00(-2.43,0.44)	-0.39(-1.94,1.16)	-0.10(-2.40,2.20)	卡格列净100 mg	*	-2.80(-4.45,-1.15)	-4.31(-6.60,-2.01)	*	-3.50(-5.16,-1.84)
-4.41(-2.13,-6.69)	-3.81(-1.52,-6.11)	-3.21(-0.88,-5.54)	-2.92(0.00,-5.83)	-2.82(-0.48,-5.16)	GLP－1RAs	-0.15(-1.83,1.53)	*	-0.40(-2.51,1.71)	*
-4.56(-3.41,-5.71)	-3.96(-5.14,-2.79)	-3.36(-4.61,-2.11)	-3.07(-0.91,-5.22)	-2.97(-1.70,-4.23)	-0.15(-2.12,1.82)	DPP－4i	-0.03(-2.08,2.05)	*	*
-4.65(-6.05,-3.26)	-4.06(-5.06,-3.05)	-3.45(-4.54,-2.36)	-3.16(-4.91,-1.41)	-3.06(-4.51,-1.60)	-0.24(-2.56,2.07)	-0.09(-1.31,1.13)	安慰剂	*	*
-4.81(-1.53,-8.08)	-4.21(-0.93,-7.50)	-3.61(-0.30,-6.92)	-3.32(0.43,-7.06)	-3.22(0.10,-6.53)	-0.40(1.95,-2.75)	-0.25(2.82,-3.32)	-0.16(3.14,-3.46)	二甲双胍	*
-5.71(-4.29,-7.12)	-5.11(-3.76,-6.46)	-4.51(-2.92,-6.09)	-4.21(-1.85,-6.58)	-4.11(-2.67,-5.56)	-1.30(1.18,-3.77)	-1.15(0.35,-2.65)	-1.05(0.50,-2.61)	-0.90(2.52,-4.31)	安慰剂

表6 DBP的网状Meta分析结果汇总[*WMD*(95% *CI*)]

Tab. 6 Results of network Meta－analysis of DBP[*WMD*(95% *CI*)]

恩格列净25 mg	*	-0.32(-0.93,0.29)	*	-1.51(-2.41,-0.62)	-2.15(-3.32,-0.97)	*	*	-2.80(-3.54,-2.06)
-0.21(-1.04,0.63)	卡格列净300 mg	*	-0.42(-1.16,0.33)	-1.50(-2.60,-0.40)	-1.00(-2.64,0.64)	*	*	-2.40(-3.50,-1.30)
-0.39(-0.98,0.21)	-0.18(0.74,-1.10)	恩格列净10 mg	*	-1.03(-1.93,-0.13)	-1.42(-2.18,-0.66)	*	*	*
-0.62(-1.46,0.22)	-0.41(-1.06,0.23)	-0.23(-1.16,0.69)	卡格列净100 mg	-1.50(-2.60,-0.40)	-1.50(-3.14,0.14)	*	*	-1.70(-2.80,-0.60)
-1.62(-2.30,-0.94)	-1.41(-0.61,-2.22)	-1.23(-1.96,-0.51)	-1.00(-0.20,-1.81)	DPP－4i	-0.29(-1.38,0.80)	-0.45(-1.65,0.75)	*	*
-1.85(-2.45,-1.26)	-1.65(-2.51,-0.78)	-1.47(-2.12,-0.82)	-1.23(-2.10,-0.37)	-0.23(-0.95,0.49)	安慰剂	*	*	*
-2.07(-0.69,-3.45)	-1.86(-0.42,-3.31)	-1.68(-0.28,-3.09)	-1.45(-0.01,-2.90)	-0.45(0.75,-1.65)	-0.22(1.18,-1.62)	GLP－1RAs	-0.15(-1.59,1.29)	*
-2.22(-0.23,-4.22)	-2.02(0.02,-4.05)	-1.84(0.17,-3.85)	-1.60(0.43,-3.64)	-0.60(1.27,-2.47)	-0.37(1.64,-2.38)	-0.15(1.29,-1.59)	二甲双胍	*
-2.67(-2.02,-3.33)	-2.47(-1.64,-3.29)	-2.29(-1.45,-3.13)	-2.05(-1.23,-2.88)	-1.05(-0.22,-1.89)	-0.82(-0.00,-1.64)	-0.60(0.86,-2.07)	-0.45(1.60,-2.50)	维格列汀

DPP－4i > PBO > GLP－1RAs > MET > SU。

3 讨论

本研究结果显示，所有 SGLT－2i 用于治疗 T2DM 均能明显改善血糖，减轻体质量，降低血压，其中以卡格列净 300 mg 的效果最好。但本研究中 SGLT－2i 在改善血糖、减轻体质量及降低血压方面的强度低于 ZACCARDI 等[46]的研究结果，其差异可能与纳入的研究及干预措施有关。首先，ZACCARDI 等[46]的研究主要纳入研究周期≥24 周的 RCT，其中 13 个 RCT 的研究周期不短于 75 周，甚至有 8 个 RCT 的研究周期不短于 102 周，而本研究中主要纳入研究周期约等于 1 年（约 52 周）的 RCT，故不排除治疗周期越长降糖效果越明显而导致本研究与其存在差异。其次，本研究中的干预措施包括 CANA 100 mg，CANA 300 mg，DAPA 5 mg，DAPA 10 mg，EMPA 10 mg，EMPA 25 mg，PBO，MET，SU，TZDs，DPP－4i，GLP－1RAs，而 ZACCARDI 等[46]的研究与本研究相比未涉及 TZDs 和 GLP－1RAs。而本研究结果显示，GLP－1RAs 的降糖效果优于 SGLT－2i，故不排除本研究中纳入 GLP－1RAs 而导致 SGLT－2i 在降糖强度方面弱于 ZACCARDI 等[46]的研究。但总的来说两项研究的结果基本一致。

本研究结果显示，二甲双胍的降糖效果优于 SGLT－2i，而 SGLT－2i 比二甲双胍具有更好的减轻体质量和降低血压作用。FERRANNINI 等[9]的“头对头”RCT 显示，二甲双胍的降糖效果强于恩格列净（HbA_{1C} 降低 0.42% ~ 0.47%，FBG 无明显差异），恩格列净减轻体质量方面优于二甲双胍（体质量减轻 1.04 ~ 1.17 kg），缺乏血压直接比较数据。虽然 FERRANNINI 等[9]的直接比较结果的绝对值大于本研究结果，但总体结果一致。本研究结果显示，GLP－1RAs 改善血糖强于 SGLT－2i，减轻体质量及降低血压方面弱于 SGLT－2i。但 TAIEB 等[47]的研究结果显示，卡格列净 300 mg 与 GLP－1RAs 相比有更好的降糖效果，卡格列净 100 mg 的降糖效果与 GLP－1RAs 相似；卡格列净 300 mg 和 100 mg 相较 GLP－1RAs 均能更有效地降低 SBP。LORENZI 等[48]的研究结果显示，利拉鲁肽相比 SGLT－2i 能更显著地降低 HbA_{1C} 水平；改善 FBG 方面，两者效果相似；减轻体质量方面，SGLT－2i 更有优势。总的来说，LORENZI 等的研究结果亦与本研究结果一致。目前尚无关于 SGLT－2i 与 GLP－1RAs 比较的“头对头”试验，无法对其结果进行直接评价，但间接比较结果倾向于 GLP－1RAs 比 SGLT－2i 更具降糖效果，而 SGLT－2i 减轻体质量和降低血压方面优于 GLP－1RAs。GORING 等[49]的研究结果显示，相比 DPP－4i，SGLT－2i（达格列净）可能有更好的降糖和减轻体质量效果及更低的致低血糖风险；SGLT－2i 降糖效果和致低血糖风险与 TZDs 相似；与 SU 相比具有相似的降糖效果和更好的减轻体质量效果，以及更低的致低血糖风险，与本研究结果基本一致。

本研究结果显示，SGLT－2i 间在疗效方面存在一些差异，且结果与 TAIEB 等[47]的研究相似。卡格列净 300 mg 相较于 100 mg 能更好地降低 HbA_{1C}、FBG、体质量和 SBP 水平；卡格列净 300 mg 相较于达格列净 5 mg 能更好地降低 FBG 水平；与卡格列净 100 mg 相比，达格列净 10 mg、卡格列净 300 mg 和任何剂量的恩格列净均能显著降低体质量；余 SGLT－2i 间及不同剂量组间的结果无显著差异。

因国内无相关的 RCT，本研究仅纳入了国外的 RCT，但研究人群中约有 18.6% 的亚洲人，其结果在一定程度上适用于中国人。本研究仅纳入药物治疗疗程约 1 年的 RCT，对于 SGLT－2i 治疗 T2DM 的长期疗效并不明确，考虑到 SGLT－2i 降低血糖的作用机制与胰岛素的分泌及其作用无关，SGLT－2i 的降糖效果可能不会随着糖尿病的进展而降低，因此接受 SGLT－2i 治疗的 T2DM 患者可长期获益。

本研究存在以下局限性：仅根据发表在期刊或临床试验注册网上的数据进行网状 Meta 分析，可能引入偏倚；在 RCT 中，受试者的种族、随访时间或结局指标的选择、定义及确认在某种程度上可能不同；尤其是缺乏“头对头”的试验。

综上所述，SGLT－2i 能显著降低患者的 HbA_{1C} 和 FBG 水平及体质量、血压，卡格列净 300 mg 的疗效可能是其中最好的。虽然 SGLT－2i 的降糖效果可能弱于 GLP－1RAs 和 MET，但与 DPP－4i，SU，TZDs 等相似。且在减轻体质量及降压方面，SGLT－2i 明显优于其他口服降糖药物。上述结论尚需开展更大样本、更高质量的多中心 RCT 予以证实。

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