

Initiation of SGLT2 Inhibitors and the Risk of Lower Extremity Minor and Major Amputation in Patients with Type 2 Diabetes and Peripheral Arterial Disease: A Health Claims Data Analysis

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WHAT THIS PAPER ADDS

Based on up to date nationwide real world data covering more than 100 000 patients over a period of eight years, it was found that patients with type 2 diabetes and peripheral arterial disease (PAD) initiating sodium glucose cotransporter 2 inhibitors (SGLT2i) face generally high risks of hospitalisation for heart failure and lower extremity minor and major amputation (LEA). Yet, in patients without a history of concomitant PAD an excess LEA risk was associated with new use of SGLT2i. The European Medicines Agency warning about the LEA risk likely affected SGLT2i prescription patterns attenuating relative safety risks.

Objective: To assess the association between long term risk of hospitalisation for heart failure (HHF) and lower extremity minor and major amputation (LEA) in patients initiating sodium glucose cotransporter 2 inhibitors (SGLT2i) suffering from type 2 diabetes and peripheral arterial disease (PAD). Outcomes were compared with patients without PAD and evaluated separately for the time periods before and after the official warning of the European Medicines Agency (EMA) in early 2017.

Methods: This study used BARMER German health claims data including all patients suffering from type 2 diabetes initiating SGLT2i therapy between 1 January 2013 and 31 December 2019 with follow up until the end of 2020. New users of glucagon like peptide 1 receptor agonists (GLP1-RAs) were used as active comparators. Inverse probability weighting with truncated stabilised weights was used to adjust for confounding, and five year risks of HHF and LEA were estimated using Cox regression. Periods before and after the EMA warning were analysed separately and stratified by presence of concomitant PAD.

Results: In total, 44 284 (13.6% PAD) and 56 878 (16.3% PAD) patients initiated SGLT2i or GLP1-RA, respectively. Before the EMA warning, initiation of SGLT2i was associated with a lower risk of HHF in patients with PAD (hazard ratio, HR, 0.85, 95% confidence interval, CI, 0.73 – 0.99) and a higher risk of LEA in patients without PAD (HR 1.79, 95% CI 1.04 – 2.92). After the EMA warning, the efficacy and safety endpoints were no longer statistically different between groups.

Conclusion: The results from this large nationwide real world study highlight that PAD patients exhibit generally high amputation risks. This study refutes the idea that the presence of PAD explains the excess LEA risk associated with initiation of SGLT2i. The fact that differentials among study groups diminished after the EMA warning in early 2017 emphasises that regulatory surveillance measures worked in everyday clinical practice.

Keywords: Outcomes, Health Services Research, Diabetes, Heart Failure, Peripheral arterial disease

Article history: Received 29 June 2021, Accepted 18 September 2021, Available online 12 November 2021

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<https://doi.org/10.1016/j.ejvs.2021.09.031>

INTRODUCTION

Comparative effectiveness and safety of sodium glucose cotransporter 2 inhibitors (SGLT2is) as second line therapy in diabetic patients have attracted increasing attention in recent years.^{1,2} While there is no doubt about the cardioprotective effects of SGLT2i therapy,³ publications of the CANVAS programme raised concerns about elevated risk of lower extremity minor and major amputation (LEA), ultimately leading to official box warnings by several regulators in the United States and Europe.⁴ The cause of the apparent amputation excess as a possible result of SGLT2i, however, remained unclear.

A larger number of clinical trials on the issue of safety has been carried out up until now. While one meta-analysis demonstrated a marginal association between SGLT2i use and increased risk of LEA,⁵ others failed to demonstrate any statistically significant association between SGLT2i and increased amputation risk.^{6–11}

Various arguments have been brought forward to explain the inconclusive evidence. A major issue concerns the failure to explicitly address the moderating role of a concomitant peripheral arterial disease (PAD).^{12,13} PAD is known as one of the most important LEA risk factors and both PAD and LEA rates in the general population have increased during past decades.^{12,14,15} Yet, observational studies on SGLT2i tailored to the PAD subgroup with large sample size and long term follow up are lacking until now. For example, the recently published DECLARE-TIMI 58 trial included only 6% participants with concomitant PAD.¹⁶

Disparate regulatory settings and prescription patterns contributed to the diversity in research findings among existing studies. While for many years empagliflozin and dapagliflozin were mostly prescribed in Europe, they replaced canagliflozin in the United States only after regulatory actions in 2017.^{17,18} At the same time, the European Medicines Agency (EMA) issued an official warning for the whole class of SGLT2i in February 2017, whereas the Drug Safety Communications of the US Food and Drug Administration (FDA) in May 2017 only concerned canagliflozin. The EMA warning contained information about a potential increased risk of LEA (mostly affecting the toes) in patients taking SGLT2i and recommended that patients are reminded to check their feet regularly and stop treatment in the presence of events preceding amputation.

To take advantage of the early European experience, a large, nationwide unselected database from Germany with up to date follow up until the end of 2020 was used. The aim was to assess the association of long term outcomes and initiation of SGLT2i use in PAD patients, while explicitly accounting for an effect of the official EMA warning.

MATERIALS AND METHODS

Study population

This retrospective observational study was based on longitudinally linked patient level data of Germany's second largest insurance fund, BARMER, covering 9 million persons

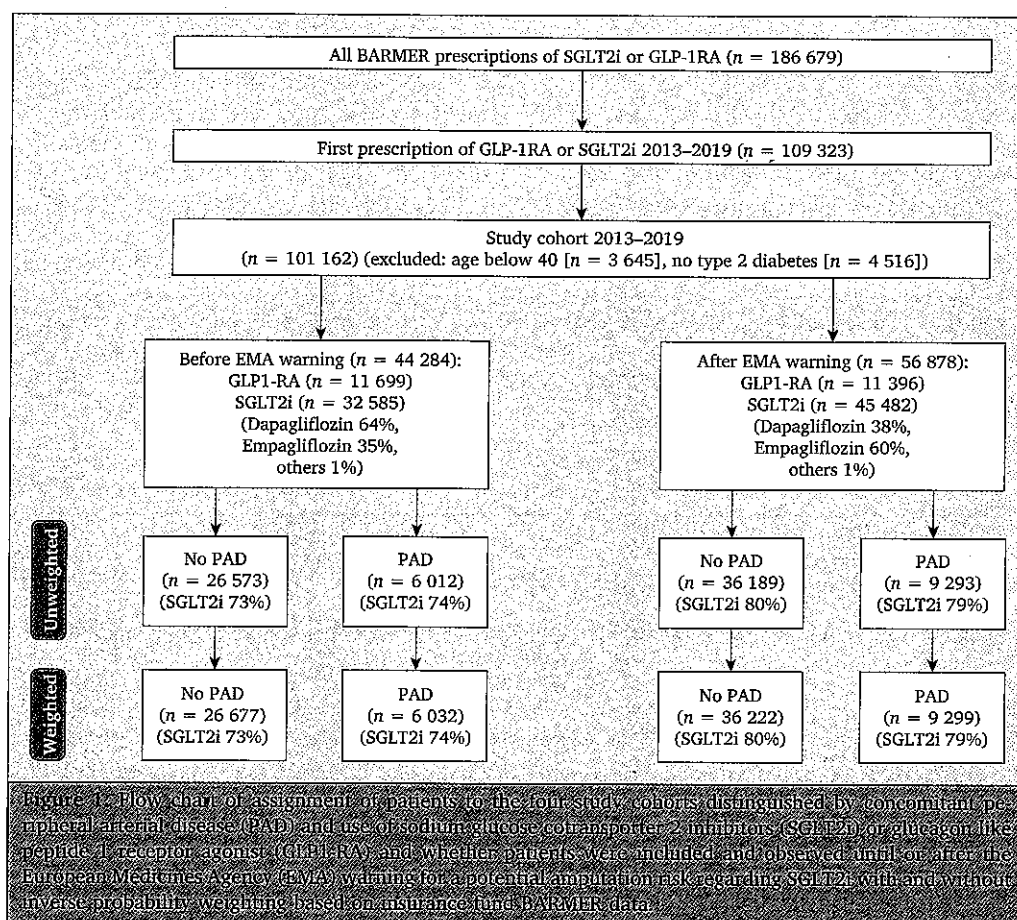
representing an unselected 10.7% of Germany's entire population. Details concerning the database, including peculiarities of the German healthcare system, have been described previously.^{19,20} Prescriptions (study drugs and other drugs), inpatient and outpatient diagnoses (for comorbidities), and in hospital procedures (for comorbidities and endpoints) were identified following the International Classification of Diseases in its 10th revision of the German Modification (ICD-10-GM), the Operations and Procedures Codes (OPS), and the German version of the international Anatomical Therapeutic Chemical (ATC) classification. A regular random sample validation of internal and external validity was performed by the Medical Service of the Health Funds in Germany.

Study design

Applying an active comparator new user study design, patients suffering from type 2 diabetes initiating therapy with either a SGLT2i or a GLP1-RA were compared (Fig. 1). Since SGLT2is first became available in 2013, the study cohorts included patients between 2013 and 2019 with follow up until the end of 2020. The first cohort comprised index cases between 2013 and the EMA warning on the 24 February 2017, whereby follow up was ended (censoring) at that date ensuring that both inclusion and minor and major LEA were unaffected by the warning. The second cohort comprised index cases identified after the date of the warning up to the end of 2019 with follow up until the end of 2020. Patients ≤ 40 years and without an earlier diagnosis of type 2 diabetes were excluded. Few cases with missing information on age, sex, or follow up ($\sim 0.5\%$) were removed using complete case deletion. Exposure was defined using an intention to treat approach so that long term minor and major LEA events could be attributed to the initial decision for assigning patients to one of the study drugs. Censoring occurred at the end of the study period, death or change of the insurance provider. All analyses were performed separately for patients with or without an outpatient or inpatient diagnosis of PAD up until index.

Study variables

Primary safety outcome was any minor and major LEA while HHF was applied for assessing effectiveness (for coding of study variables see Supplementary Table S1). PAD was defined based on either any outpatient diagnosis of PAD or primary inpatient PAD diagnosis (main diagnosis driving the reimbursement costs for the actual hospital stay). PAD was also defined if a primary diagnosis of diabetic foot syndrome, other peripheral vascular diseases, arterial embolism and thrombosis, cellulitis of finger and toe, including acute lymphangitis, or chronic ulcer of skin, and gangrene was registered together with a secondary inpatient PAD diagnosis.²¹ Inpatient PAD was further categorised into intermittent claudication (IC) and chronic limb threatening ischaemia (CLTI) based on the Fontaine classification, which were used as adjustment variables in the models focusing on PAD patients.



Inverse probability weighting with truncated stabilised weights was used to adjust for confounding using 35 variables measured up to baseline containing information about demographics (age and sex), comorbidities (prior minor or major amputation, history of stroke/transient ischaemic attack, TIA, coronary artery disease, history of myocardial infarction, congestive heart failure, cardiac dysrhythmias, chronic renal failure, dyslipidaemia, history of bone fractures, malignancy, hypovolaemia), obesity (according to the World Health Organization definition), alcohol abuse (any alcohol related behavioural disorder), smoking (any smoking related behavioural disorder), and concomitant medications (insulin, metformin, sulphonylurea, inhibitors of dipeptidyl peptidase 4, lipid lowering drugs, antiplatelets, anticoagulants, antihypertensives, non-steroidal anti-inflammatory drugs, analgesics, and antidepressants). The variables were selected after a discussion of their clinical relevance and after reviewing the baseline characteristics of the cohorts. The van Walraven comorbidity risk score summarising 30 broad disease groups, the GermanVasc risk score (<https://score.germanvasc.de>) tailored for minor and major LEA risk in PAD patients, and the logarithmically transformed frailty score summarising 109 diseases were used to cover a broad range of patient risk at baseline.^{14,22,23} To account for the intensity and duration of prior treatment, the years on diabetic drugs, the number of medical prescriptions during the

year before index, and the number of hospital stays during the year before index were added to the model.

Statistical analysis

The probability of initiating either SGLT2i or GLP1-RA was estimated via logistic regression using the 35 variables explained above as explanatory variables. Then, the propensity distribution was trimmed at the first and 99th percentiles and inversely transformed resulting in truncated stabilised weights. The balance of the study groups after weighting was assessed through standardised mean differences. For predicting the outcome, Cox regression models with binary treatment variable as predictor were estimated and the validity of assuming proportional hazards was assessed using tests and plot diagnostics. Based on the model estimates, the five year incidence for each outcome was extrapolated. Confidence intervals (CI) for absolute differences, expressed as risk difference, relative differences, and hazard ratio (HR) between weighted study groups were constructed using bootstrapping with 1000 replications. SAS version 9.04 (SAS Institute, Cary, NC, USA) was used for data management. Descriptives, plots, penalised and unpenalised Cox regressions, and model diagnostics were performed in R version 4.0.3 (ggplot2, survival, glmnet, Hmisc, tableone package; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

First historical cohort before the warning (pre-warning period)

Up until the official EMA warning, 2 099 patients with concomitant PAD initiated GLP1-RA and 6 012 SGLT2i (Table 1). Thereby, new users of GLP1-RA were younger

(65.8 vs. 68.8 years) and empagliflozin accounted for 38.4% and dapagliflozin for 60.3% of SGLT2i cases. After weighting, no sizable differences among measured characteristics between the study groups remained. SGLT2i initiation was not associated with a higher risk of minor and major LEA compared with initiation of GLP1-RA (HR 1.31, 95% CI 0.89 – 1.87) (Table 2). The five year incidence of both groups

Table 1. Pre-warning baseline characteristics of the unweighted and weighted cohort of patients with peripheral arterial disease in retrospective analysis of health insurance claims on glucagon-like peptide 1 receptor agonists (GLP1-RA) and sodium glucose cotransporter 2 inhibitors (SGLT2i)

	Unweighted sample			Weighted sample		
	GLP1-RA (n = 2 099)	SGLT2i (n = 6 012)	SMD	GLP1-RA (n = 2 074)	SGLT2i (n = 6 032)	SMD
Demographics						
Female sex	962 (45.8)	2 478 (41.2)	0.093	863.4 (41.6)	2 551.3 (42.3)	0.014
Age at index – y	65.82 ± 9.10	68.79 ± 8.92	0.329*	67.90 ± 8.96	67.97 ± 9.09	0.007
General						
Year of prescription	2 014.84 ± 1.18	2 015.18 ± 1.11	0.292*	2 015.05 ± 1.16	2 015.08 ± 1.14	0.024
Empagliflozin	—	2 306 (38.4)	—	—	2 225.1 (36.9)	—
Dapagliflozin	—	3 624 (60.3)	—	—	3 713.6 (61.6)	—
Prior lower limb amputation	107 (5.1)	199 (3.3)	0.089	74.6 (3.6)	227.8 (3.8)	0.010
Prior hospital stays – n	3.57 ± 3.96	2.89 ± 3.43	0.183*	3.08 ± 3.59	3.06 ± 3.61	0.004
Different medications at prior year – n	9.48 ± 3.30	8.43 ± 3.08	0.328*	8.75 ± 3.20	8.72 ± 3.18	0.010
Comorbidities, 5 years before index						
van Walraven score	12.07 ± 11.08	11.23 ± 10.63	0.078	11.36 ± 10.75	11.42 ± 10.73	0.005
GermanVasc score	16.75 ± 6.23	17.53 ± 6.46	0.123*	17.30 ± 6.31	17.31 ± 6.45	0.001
Log frailty	1.14 ± 1.09	0.92 ± 1.03	0.205*	0.97 ± 1.05	0.97 ± 1.04	0.008
Inpatient diagnosis IC	182 (8.7)	579 (9.6)	0.033	217.4 (10.5)	569.7 (9.4)	0.035
Inpatient diagnosis CLTI	142 (6.8)	293 (4.9)	0.081	105.2 (5.1)	322.3 (5.3)	0.012
History of stroke or TIA	314 (15.0)	858 (14.3)	0.019	310.7 (15.0)	875.6 (14.5)	0.013
Coronary artery disease	1 116 (53.2)	3 170 (52.7)	0.009	1 091.2 (52.6)	3 189.7 (52.9)	0.006
History of myocardial infarction	393 (18.7)	1 004 (16.7)	0.053	347.0 (16.7)	1 036.9 (17.2)	0.012
Congestive heart failure	892 (42.5)	2 182 (36.3)	0.127*	785.6 (37.9)	2 287.1 (37.9)	0.001
Cardiac dysrhythmias	785 (37.4)	2 239 (37.2)	0.003	758.6 (36.6)	2 241.6 (37.2)	0.012
Chronic renal failure	863 (41.1)	1 768 (29.4)	0.247*	663.1 (32.0)	1 951.2 (32.3)	0.008
Hypovolaemia	134 (6.4)	347 (5.8)	0.026	127.1 (6.1)	357.4 (5.9)	0.008
Dyslipidaemia	318 (15.2)	986 (16.4)	0.034	340.4 (16.4)	963.7 (16.0)	0.012
Fractures	129 (6.1)	353 (5.9)	0.012	119.1 (5.7)	357.6 (5.9)	0.008
History of cancer	320 (15.2)	935 (15.6)	0.009	332.8 (16.0)	935.3 (15.5)	0.015
Lifestyle, 5 years before index						
Obesity	1 721 (82.0)	3 834 (63.8)	0.419*	1 410.2 (68.0)	4 135.9 (68.6)	0.013
Alcohol abuse	147 (7.0)	399 (6.6)	0.015	148.1 (7.1)	407.8 (6.8)	0.015
Smoking	446 (21.2)	1 238 (20.6)	0.016	434.3 (20.9)	1 247.8 (20.7)	0.006
Diabetes drugs up until index, prior year						
Time on diabetes drugs – y	7.84 ± 3.21	7.91 ± 3.30	0.021	7.93 ± 3.25	7.90 ± 3.26	0.009
Insulin	1 345 (64.1)	2 604 (43.3)	0.426*	1 048.9 (50.6)	2 964.9 (49.2)	0.028
Metformin	1 468 (69.9)	4 767 (79.3)	0.216*	1 584.5 (76.4)	4 628.3 (76.7)	0.008
Sulphonylurea	367 (17.5)	1 196 (19.9)	0.062	380.2 (18.3)	1 152.7 (19.1)	0.020
DPP4	1 088 (51.8)	3 409 (56.7)	0.098	1 168.4 (56.3)	3 344.2 (55.4)	0.018
Other drugs up until index, prior year						
Lipid lowering drugs	1450 (69.1)	4025 (66.9)	0.046	1 418.2 (68.4)	4 084.5 (67.7)	0.014
Antiplatelets	627 (29.9)	1871 (31.1)	0.027	634.1 (30.6)	1 851.7 (30.7)	0.003
Anticoagulation	339 (16.2)	889 (14.8)	0.038	305.2 (14.7)	914.2 (15.2)	0.012
Antihypertensives	1 999 (95.2)	5 543 (92.2)	0.125*	1 918.2 (92.5)	5 608.8 (93.0)	0.020
NSAID	850 (40.5)	2 329 (38.7)	0.036	814.2 (39.3)	2 363.9 (39.2)	0.001
Analgesics	832 (39.6)	1 889 (31.4)	0.172*	696.0 (33.6)	2 029.5 (33.6)	0.002
Antidepressants	433 (20.6)	993 (16.5)	0.106*	362.0 (17.5)	1 060.1 (17.6)	0.003
Diuretics	1 056 (50.3)	2 346 (39.0)	0.229*	855.5 (41.2)	2 534.7 (42.0)	0.016

Data are presented as n (%) or mean ± standard deviation. TIA = transient ischaemic attack; SMD = standardised mean difference; NSAID = non-steroidal anti-inflammatory drug; DPP4 = dipeptidylpeptidase inhibitor 4.

* SMD's above 0.1 were deemed as clinically relevant.

Table 2 Hazard ratio of lower-extremity amputation and hospitalisation for heart failure in patients with peripheral arterial disease treated with glucagon like peptide 1 receptor agonist (GLP1-RA) and sodium dependent glucose co-transporter 2 inhibitor (SGLT2i)

Outcome	Study groups	<i>n</i>	Events	Median follow up – y	Hazard ratio (95% CI)*
<i>Pre-warning period</i>					
Lower extremity amputation	GLP1-RA	2 099	48	1.52	1.31 (0.89–1.87)
	SGLT2i	6 012	104	1.12	
Hospitalisation for heart failure	GLP1-RA	2 099	296	1.40	0.85 (0.73–0.99)
	SGLT2i	6 012	522	1.05	
<i>Post-warning period</i>					
Lower extremity amputation	GLP1-RA	2 436	77	1.95	1.24 (0.84–1.77)
	SGLT2i	9 293	267	2.09	
Hospitalisation for heart failure	GLP1-RA	2 436	552	1.79	0.95 (0.84–1.08)
	SGLT2i	9 293	1 595	1.92	

CI = confidence interval.

* GLP1-RA is the reference for hazard ratio.

was 58 and 45 minor and major amputations per 1 000 patients (risk difference 14, 95% CI –5 – 31) (Fig. 2). HHF occurred less often among new users of SGLT2i than in new users of GLP1-RA (HR 0.85, 95% CI 0.73 – 0.99, five year incidence: 232 vs. 266, risk difference: –34, 95% CI –68 – –2).

There were 9 600 and 26 573 patients without PAD who initiated GLP1-RA and SGLT2i up until the EMA warning, respectively (Supplementary Table S2). Thereby, new users of GLP1-RA were more often female (53.9% vs. 48.1%) and younger (60.3 vs. 63.7 years). After weighting, no sizable differences among measured characteristics between the study groups remained. SGLT2i initiation in the subgroup without PAD was associated with a higher risk of minor and major LEA as compared with initiation of GLP1-RA (HR 1.79, 95% CI 1.03 – 3.02) (Table 3). The five year incidence of both groups was 10 and 6 minor and major amputations per 1 000 patients (risk difference: 5, 95% CI 1 – 8) (Fig. 2). HHF did not differ among new users of SGLT2i and GLP1-RA (HR 1.03, 95% CI 0.93 – 1.15, five year incidence: 123 vs. 120, risk difference: 4, 95% CI –8 – 16).

Second cohort after the warning (post-warning period)

After the official EMA warning, 2 436 patients with PAD initiated GLP1-RA and 9 393 SGLT2i (Table 4). Thereby, new users of GLP1-RA were more often female (47% vs. 37%) and younger (69.3 vs. 70.4 years) and empagliflozin accounted for 68.2% and dapagliflozin for 30.5% of SGLT2i cases. After weighting, no sizable differences among measured characteristics between the study groups remained. SGLT2i initiation was not associated with a higher risk of minor and major LEA as compared with initiation of GLP1-RA (HR 1.24, 95% CI 0.84 – 1.77) (Table 2). The five year incidence of both groups was 47 and 38 minor and major amputations per 1 000 patients (risk difference 9,

95% CI –5 – 23) (Fig. 2). HHF did not differ among new users of SGLT2i and GLP1-RA (HR 0.95, 95% CI 0.84 – 1.08, five year incidence: 260 vs. 270, risk difference: –11, 95% CI –40 – 17).

There were 8 960 and 36 189 patients without PAD who initiated GLP1-RA and SGLT2i after the EMA warning (Supplementary Table S3). Thereby, new users of GLP1-RA were more often female (55.9% vs. 45.0%) and younger (52.5 vs. 65.2 years). After weighting, no sizable differences among measured characteristics between the study groups remained. In the subgroup without PAD, SGLT2i initiation was not associated with a different risk of minor and major LEA as compared with initiation of GLP1-RA (HR 0.89, 95% CI 0.57 – 1.33) (Table 3). The five year incidence of both groups was 12 and 11 minor and major amputations per 1 000 patients (risk difference –1, 95% CI –6 – 4) (Fig. 2). HHF did not differ among new users of SGLT2i and GLP1-RA (HR 0.94, 95% CI 0.85 – 1.05, five year incidence: 126 vs. 132, risk difference –7, 95% CI –19 – 6).

DISCUSSION

In this nationwide real world analysis including more than 100 000 patients with type 2 diabetes, the association between initiation of SGLT2i compared with GLP1-RA and long term outcomes was determined. Thereby, the study groups differed up until the EMA warning in early 2017. Initiation of SGLT2i was associated with a 15% lower risk of HHF in patients with concomitant PAD and with a 79% higher risk of minor and major LEA in patients without PAD. There were no significant differences among the study groups during the period after the EMA warning. Over the whole study period, PAD patients exhibited an approximately five times higher five year incidence of minor and major LEA and two time higher five year incidence of HHF compared with patients without PAD.

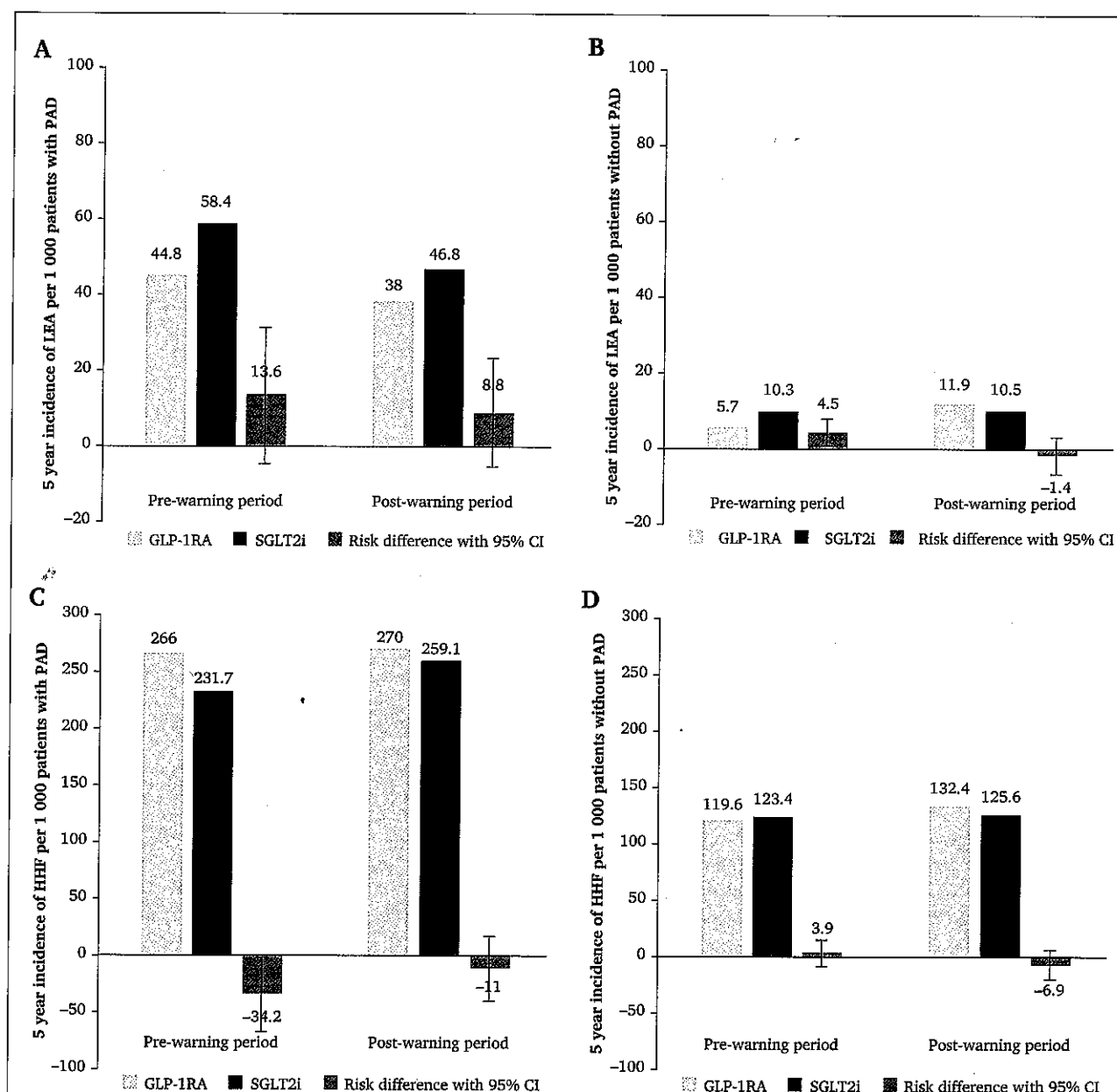


Figure 2. Changes in the five year incidence of (A, B) lower extremity amputation (LEA) and (C, D) hospitalisation for heart failure (HHF) in patients with (A, C) or without (B, D) peripheral artery disease (PAD) after initiation of sodium glucose cotransporter 2 inhibitor (SGLT2i) and glucagon like peptide 1 receptor agonist (GLP-1RA) medications before (pre-warning period between 2013 and 2017) and after (post-warning period between 2017 and 2020) the official warning about a potential amputation risk regarding SGLT2i were issued by the European Medicines Agency on 24 February 2017. Both periods were analysed separately using inverse probability weighting and Cox proportional hazard models. CI = confidence interval.

This analysis provides long term evidence on benefits and risks associated with SGLT2i initiation in PAD patients based on up to date data from a European real world cohort with predominant use of empagliflozin and dapagliflozin. The large study size and long observational time frame allowed the period before and after the EMA warning to be clearly distinguished. Rather than solely focusing on relative risks, estimates of five year incidence were provided. For this purpose, a rigorous intent to treat like study design was

used allowing tracing of all long term events associated with the initial patient selection irrespective of patient compliance.

In Germany, canagliflozin was already removed from the market in 2014. Hence, it appears surprising that the findings from the current study – mainly based on dapagliflozin and empagliflozin – were in line with the initial study results from the CANVAS programme both for HHF and LEA.⁴ Also similar to the results from the CANVAS program,

Table 3 Hazard ratio of lower extremity amputation and hospitalisation for heart failure in patients without peripheral arterial disease treated with glucagon-like peptide 1 receptor agonist (GLP1-RA) and sodium-dependent glucose co-transporter 2 inhibitor (SGLT2i)

Outcome	Study groups	n	Events	Median years of follow up	Hazard ratio, 95% CI*
Pre-warning period					
Lower extremity amputation	GLP1-RA	9 600	23	1.69	1.79 (1.03–3.02)
	SGLT2i	26 573	74	1.21	
Hospitalisation for heart failure	GLP1-RA	9 600	595	1.62	1.03 (0.93–1.15)
	SGLT2i	26 573	1 126	1.17	
Post-warning period					
Lower extremity amputation	GLP1-RA	8 960	51	2.21	0.89 (0.57–1.33)
	SGLT2i	36 189	178	2.22	
Hospitalisation for heart failure	GLP1-RA	8 960	822	2.05	0.94 (0.85–1.05)
	SGLT2i	36 189	2 942	2.12	

CI = confidence intervals.

* GLP1-RA is the reference for hazard ratio.

patients with PAD exhibited a generally higher absolute risk of minor and major LEA but the relative risk associated with SGLT2i use was seen only in those without PAD.⁴ Interestingly, more recent clinical trials specifically focusing on empagliflozin via the EMPA-REG OUTCOME trial and dapagliflozin via the DECLARE-TIMI 58 trial did not confirm the presence of a higher LEA risk.^{16,24} Of note, the prospective measurement of amputation events was neither initially included in the EMPA-REG OUTCOME trial nor the DECLARE-TIMI 58. These studies identified LEA fully or partially retrospectively or amended their study protocols and instructed the site specific investigators casting doubt on the validity of the measurement of this endpoint. Although clearly suffering from selection bias due to non-randomisation, the claims data used in the current study might be viewed as somewhat more objectifiable since both patients and providers were not aware of the LEA specific safety risk until the publication of CANVAS and the subsequent box warnings. It is therefore no coincidence that the only other real world study within Europe also using data before the EMA warning and applying the same study design and study groups reported similar findings.¹⁸ While a couple of older claims studies received critical acclaim due to methodological flaws,²⁵ two recent statistically robust studies from the United States confirmed the safety signal in real world data reporting a HR of 1.44 (95% CI 1.06 – 1.96) and 1.73 (95% CI 1.30 – 2.29), respectively.^{2,26}

Unlike for LEA, there is less doubt about the benefits of SGLT2i use regarding HHF. Based on 149 clinical trials, the meta-analysis of Palmer et al. reported an odds ratio of 0.74 (95% CI 0.65 – 0.85) comparing SGLT2i to GLP1-RA for this efficacy outcome.¹⁰ Interestingly, in the current analysis this association was present only in patients with PAD but not in those without PAD at baseline. Although it appears plausible that patients with a higher disease burden and

subsequently higher odds of exhibiting heart failure will benefit more from the cardioprotective effects of SGLT2i, it cannot be ruled out that this reflects differences in patient selection. If confirmed in further studies, the duality of evidence for harm and no evidence for benefits might sound a note of caution for the use of SGLT2i in low risk patients.

Drawing on latest data, this study is the first systematic comparison of SGLT2i and GLP1-RA therapy after the EMA warning was issued. While differences in relative risks between the study groups diminished the absolute risks for five year incidence of minor and major LEA or HHF remained stable in the second period. This indicates that health providers reacted to the warnings and allocated high risk patients to another drug with a more favourable safety profile. By making use of risk scores developed for predicting LEA risks for patients with indication for SGLT2i use, therapy decisions will probably be further optimised in the future.²⁷

The similarity of effects in this European cohort mainly including dapagliflozin and US cohorts mainly including canagliflozin provides further input into the debate about a class effect of SGLT2i as it was also presumed in the 2017 EMA warning.²⁸ Along with accumulating evidence of excess LEA risk beyond canagliflozin this should encourage research targeted at identifying the causal pathway, e.g., through hypovolaemia or a diuretic effect.^{29,30} Apart from that, the study sheds light on the issue of long term outcomes of the predominantly used SGLT2i in the US after the decline of canagliflozin after the FDA box warning.¹⁷ Unfortunately, the current study was not able to illuminate a class effect of the respective SGLT2i on the market. Future studies involving data on the different available drugs will hopefully address this interesting aspect.

Table 4 Post-warbling baseline characteristics of the unweighted and weighted cohort of patients with peripheral arterial disease in retrospective analysis of health insurance claims on glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium glucose cotransporter 2 inhibitors (SGLT2i)

	Unweighted sample			Weighted sample		
	GLP1-RA (n = 2 436)	SGLT2i (n = 9 293)	SMD	GLP1-RA (n = 2 453)	SGLT2i (n = 9 299)	SMD
<i>Demographics</i>						
Female sex	1 136 (46.6)	3 431 (36.9)	0.198*	932.6 (38.0)	3 624.1 (39.0)	0.020
Age at index – y	69.28 ± 9.46	70.38 ± 9.05	0.119*	69.89 ± 9.37	70.11 ± 9.14	0.024
<i>General</i>						
Year of prescription	2018.25 ± 0.78	2018.15 ± 0.81	0.134*	2018.15 ± 0.80	2018.17 ± 0.80	0.019
Empagliflozin	–	6 342 (68.2)	–	–	6 390.3 (68.7)	–
Dapagliflozin	–	2 833 (30.5)	–	–	2 787.6 (30.0)	–
Prior lower limb amputation	150 (6.2)	364 (3.9)	0.103*	109.8 (4.5)	406.4 (4.4)	0.005
Prior hospital stays – n	4.00 ± 4.06	3.19 ± 3.50	0.214*	3.42 ± 3.64	3.37 ± 3.67	0.014
Different medications at prior year – n	9.62 ± 3.14	8.41 ± 3.05	0.390*	8.68 ± 2.99	8.67 ± 3.16	0.003
<i>Comorbidities, 5 years before index</i>						
Van Walraven score	14.63 ± 11.67	13.03 ± 11.10	0.141*	13.27 ± 11.09	13.35 ± 11.26	0.007
GermanVasc score	18.95 ± 7.02	18.91 ± 6.94	0.006	18.87 ± 6.93	18.90 ± 6.98	0.004
Log frailty	1.44 ± 1.18	1.14 ± 1.11	0.261*	1.22 ± 1.13	1.20 ± 1.14	0.013
Inpatient diagnosis IC	227 (9.3)	957 (10.3)	0.033	252.2 (10.3)	942.2 (10.1)	0.005
Inpatient diagnosis CLTI	194 (8.0)	499 (5.4)	0.104*	138.4 (5.6)	549.1 (5.9)	0.011
History of stroke or TIA	421 (17.3)	1 524 (16.4)	0.024	426.9 (17.4)	1 554.2 (16.7)	0.018
Coronary artery disease	1 387 (56.9)	5 442 (58.6)	0.033	1 429.0 (58.3)	5 415.1 (58.2)	<0.001
History of myocardial infarction	477 (19.6)	2 004 (21.6)	0.049	515.0 (21.0)	1 967.9 (21.2)	0.004
Congestive heart failure	1 181 (48.5)	3 909 (42.1)	0.129*	1 035.3 (42.2)	4 020.5 (43.2)	0.021
Cardiac dysrhythmias	1 070 (43.9)	4 027 (43.3)	0.012	1 074.9 (43.8)	4 044.8 (43.5)	0.006
Chronic renal failure	1 381 (56.7)	3 377 (36.3)	0.417*	962.7 (39.2)	3 768.4 (40.5)	0.026
Hypovolaemia	289 (11.9)	720 (7.7)	0.139*	217.0 (8.8)	802.1 (8.6)	0.008
Dyslipidaemia	367 (15.1)	1 423 (15.3)	0.007	372.8 (15.2)	1 425.0 (15.3)	0.004
Fractures	196 (8.0)	601 (6.5)	0.061	181.8 (7.4)	634.7 (6.8)	0.023
History of cancer	435 (17.9)	1 544 (16.6)	0.033	395.1 (16.1)	1 558.8 (16.8)	0.018
<i>Lifestyle, 5 years before index</i>						
Obesity	1 946 (79.9)	5 360 (57.7)	0.494*	1 487.4 (60.6)	5 790.3 (62.3)	0.034
Alcohol abuse	178 (7.3)	624 (6.7)	0.023	197.7 (8.1)	637.0 (6.9)	0.046
Smoking	532 (21.8)	2 223 (23.9)	0.050	581.1 (23.7)	2 182.4 (23.5)	0.005
<i>Diabetes drugs up until index, prior year</i>						
Time on diabetes drugs – y	9.92 ± (4.38)	8.93 ± (4.54)	0.222*	9.12 ± (4.49)	9.13 ± (4.53)	0.002
Insulin	1 629 (66.9)	3 424 (36.8)	0.630*	1 044.1 (42.6)	4 009.5 (43.1)	0.011
Metformin	1 596 (65.5)	7 384 (79.5)	0.316*	1 899.0 (77.4)	7 120.0 (76.6)	0.020
Sulfonylurea	248 (10.2)	1 351 (14.5)	0.133*	341.3 (13.9)	1 270.8 (13.7)	0.007
DPP4	1 190 (48.9)	4 761 (51.2)	0.048	1 349.4 (55.0)	4 746.0 (51.0)	0.080
<i>Other drugs up until index, prior year</i>						
Lipid lowering drugs	1 699 (69.7)	6 785 (73.0)	0.072	1 778.7 (72.5)	6 716.5 (72.2)	0.006
Antiplatelets	814 (33.4)	3 409 (36.7)	0.069	873.3 (35.6)	3 347.9 (36.0)	0.008
Anticoagulation	551 (22.6)	1 960 (21.1)	0.037	506.0 (20.6)	1 988.1 (21.4)	0.019
Antihypertensives	2 311 (94.9)	8 629 (92.9)	0.084	2 292.3 (93.4)	8 670.3 (93.2)	0.008
NSAID	774 (31.8)	3 070 (33.0)	0.027	824.9 (33.6)	3 051.6 (32.8)	0.017
Analgesics	1 124 (46.1)	3 253 (35.0)	0.228*	903.5 (36.8)	3 472.9 (37.3)	0.011
Antidepressants	546 (22.4)	1 460 (15.7)	0.171*	432.3 (17.6)	1 595.5 (17.2)	0.012
Diuretics	1 426 (58.5)	4 008 (43.1)	0.312*	1 119.1 (45.6)	4 307.0 (46.3)	0.014

Data are presented as n (%) or mean ± standard deviation. TIA = transient ischaemic attack; SMD = standardised mean difference; NSAID = non-steroidal anti-inflammatory drug; DPP4 = dipeptidylpeptidase inhibitor 4.

* SMDs above 0.1 were deemed as clinically relevant.

Besides several strengths, the current study also has limitations. In line with previous studies, the issue of confounding through non-random assignment remains unsolved in observational research. To minimise this risk, a large range of variables and risk scores was used for balancing study characteristics among study groups along with robust weighting. A new user active comparator design was applied to prevent prevalent and healthy user bias.

Thus, the central conclusions are valid to the extent that patients initiating SGLT2i are comparable with those initiating GLP1-RA. The fact that GLP1-RA patients were older, more often female, obese and on insulins may signal more fundamental differentials among study groups. Of note, contrasting results were reported depending on what the control group was. For example, Yang and colleagues demonstrated that the use of SGLT2 inhibitors was

associated with increased risk of lower extremity amputation when compared with the use of dipeptidyl-peptidase-4 inhibitors (DPP-4i), but not when compared with sulphonylureas.³¹ Interestingly, there are also data showing that the risk of amputation is lower in patients taking SGLT2i comparing to sulphonylureas³² or comparing to DPP-4i.¹² However, a recent systematic review and network meta-analysis clearly suggested that SGLT2i and GLP1-RA exhibit an excellent comparability for a broad range of relevant outcomes, assuring the choice for the specific study design.¹⁰ It has to be emphasised that the current study included both minor amputations below and major amputations above ankle level as one common primary endpoint. Although this was in line with the results derived from the CANVAS program and corresponding boxed warnings by regulators, a possible inverse relationship between major and minor amputations, particular among diabetics, may introduce uncertainty to some degree.

Furthermore, although a good validity was shown in peer reviewed and external validation studies for the primary endpoints, some data was not validly available to improve the models. For instance, information on medication relies on filled prescriptions, which does not guarantee drug ingestion.

Conclusion

The results from this large nationwide real world study highlight that PAD patients exhibit generally high amputation risks. Yet, this study refutes the idea that the presence of PAD explains the excess LEA risk associated with initiation of SGLT2i. The fact that differentials among study groups diminished after the EMA warning in early 2017 emphasises that regulatory surveillance measures worked in everyday clinical practice.

CONFLICT OF INTEREST

None.

FUNDING

This work was supported by the German Federal Joint Committee (grant number 01VSF18035 to C.A.B.).

ACKNOWLEDGEMENTS

We thank Thea Kreutzburg and Jenny Kuchenbecker to their statistical advice and valuable comments on earlier versions of this manuscript.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2021.09.031>.

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