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Clinical Study Synopsis for Public Disclosure

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Jardiance® (Empagliflozin)			
Name of active ingredient: Empagliflozin ("EMPA") (ATC code: A10BK03) Dipeptidyl peptidase 4 inhibitors ("DPP-4i") (A10BH) ➢ Sitagliptin ("SITA") (A10BH01) ➢ Glucagon-like peptide-1 receptor agonists ("GLP-1-RA") (A10BJ)			
Report date: 11 March 2022	**Study number:** 1245-0221	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	Healthcare costs in new users of empagliflozin versus DPP-4 inhibitors and GLP-1 agonists: A retrospective cohort study based on Real-World data from German sickness funds		
Keywords:	Type 2 diabetes mellitus, empagliflozin, DPP-4 inhibitors, GLP-1 receptor agonists, healthcare costs		
Rationale and background:	For most of the available SGLT-2 inhibitors (SGLT-2i), DPP-4 inhibitors (DPP-4i) and GLP-1 receptor agonists (GLP-1-RA), cardiovascular outcome studies have been conducted in recent years. However, much less is known about cost associated with therapy of type 2 diabetes mellitus (T2DM) patients with SGLT-2i, DPP-4i and GLP-1-RA. Accordingly, the objective of this study was to collect these data.		
Research question and objectives:	Achieving good glycemic control in T2DM may require individualized pharmacological approaches. We aimed to compare direct healthcare costs in patients treated with empagliflozin (EMPA) compared to DPP-4i (specifically sitagliptin (SITA)) or GLP-1-RA.).		
Study design:	This retrospective study of German claims data included continuously		

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	insured persons with at least two outpatient diagnoses and/or one inpatient diagnosis of T2DM if they started EMPA, DPP-4i (specifically SITA) or GLP-1-RA in 2015 – 2018. Costs were assessed from therapy initiation until the end of data availability, death, or therapy discontinuation and compared among propensity score-matched cohorts.		
Setting:	[redacted] The analysis sample included all adult persons, who were continuously insured between 01/01/2014 until 31/12/2018 (except for death) and received at least one outpatient prescription with EMPA, DPP-4i, or GLP-1-RA between 01/01/2015 and 31/12/2018 (= index date), excluding all patients already receiving one of the respective agents in 2014 (12-month treatment-free period ensuring the identification of therapy starters). Patients starting more than one of the drugs of interest (e.g., EMPA and SITA) at the same time are also excluded. All patients included in the analysis were identified as having T2DM by observing at least one inpatient diagnosis or at least two outpatient diagnoses in two different quarters within one year before the treatment		

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	initiation (index date). Finally, patients were excluded if another form of diabetes (type 1, gestational, or secondary diabetes), neoplasms (identified by diagnosis or prescriptions of cancer-related drugs), or one of the top three most cost-intensive diseases as defined by the German Federal Insurance Office (sepsis, human immunodeficiency virus [HIV], or opportunistic infections) have been diagnosed in the 12 months before the start of treatment with EMPA, DPP-4i, or GLP-1-RA. Patients were observed starting from the first day of treatment initiation until the date of death, the end of data availability (31/12/2018), or the date of therapy discontinuation. Discontinuation of therapy was assumed if there was a gap in drug availability of at least 90 days, with approximating the drug supply based on the quantity and the daily defined dose (DDD) of prescribed medication. If a gap in drug availability was observed, the end of the respective gap was considered the end of the treatment.		
Subjects and study size, including dropouts:	Overall, 24,465 T2DM patients newly treated with EMPA, DPP-4i, or GLP-1-RA were retrospectively observed.		
Variables and data sources:	The data source for this study was provided [redacted]. Baseline variables: Age (at index date), gender, binary indicators for the		

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	level of care at index date, the Charlson Comorbidity Index (CCI), binary indicators for the use of prespecified antidiabetic and cardiovascular therapies (insulin, metformin, sulfonylurea, other antidiabetics, anti-thrombotic agents, beta blockers [BBs], calcium channel blockers [CCBs], renin-angiotensin-aldosterone system [RAAS]-inhibitors, lipid-lowering therapy [LLT]), binary indicators for prevalent cardiovascular disease (ischemic stroke, myocardial infarction, coronary heart disease, or heart failure), documented alcohol abuse, documented nicotine dependence, the top ten most frequently diagnosed comorbidities (any outpatient or inpatient diagnosis), as well as T2DM-associated and non-T2DM-associated costs for outpatient physician visits, inpatient stays, and drug prescriptions. Exposure variables: Empagliflozin Comparator variables: DPP-4 inhibitor, SITA only, and any GLP-1-RA. Outcome variables: Direct healthcare costs in Euros (inpatient, outpatient, medication, total)		
Results:	Of 24,465 patients included, 3,285 received EMPA, 19,443 DPP-4i (thereof 18,382 Sitagliptin), and 1,747 GLP-1-RA. Matched cohorts were balanced on baseline characteristics (EMPA vs. DPP-4i: n1/n2 =		

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	3,100/3,100; and EMPA vs. GLP-1-RA: n3/n4 = 1,346/1,346). The median follow-up time in the EMPA group was 242 days when matched to DPP-4i (vs. 458 days), and 259 days when matched to GLP-1-RA (vs. 302 days). After adjustment for differences in length of follow-up, significantly higher expenses for healthcare were observed among patients initiating DPP-4i (mean: € 7,009 vs. € 4,274; p<0.001) and GLP-1-RA (mean: € 6,851 vs. € 4,895; p<0.001) in comparison with EMPA. The highest differences between EMPA and DPP-4i were observed in terms of inpatient care (€ 1,455 vs. € 3,040; p<0.001) and pharmacy sales for prescribed drugs (€ 1,966 vs. € 2,689; p<0.001), whereas incremental cost differences vs. GLP-1-RA were mainly driven by medication costs alone (€ 2,433 vs. € 3,575; p<0.001).). Significantly higher healthcare expenses were also observed among patients initiating SITA (mean: € 6,535 vs. € 4,319; p<0.001) in comparison with EMPA. The highest cost differences between EMPA and SITA were observed in terms of inpatient care (€ 1,486 vs. € 2,806; p<0.001) and medication (€ 1,970 vs. € 2,516; p<0.001).		
Discussion:	This retrospective analysis of a nationwide German claims dataset, covering the years 2015 – 2018, showed substantially higher costs for		

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	patients starting DPP-4i compared with EMPA, driven by a 2-fold increase in cost for inpatient care, whereas the cost differences between EMPA and GLP-1-RA were mainly due to the higher drug price and the intensified dosing of the latter, resulting in higher medication costs. While previous database analyses from the US already highlighted that SGLT-2i are associated with longer treatment persistence resulting in reduced healthcare utilization as well cost savings relative to DPP-4i and GLP-1, this study reinforces previous findings with novel data for the German statutory health insurance (SHI) context. In particular, patients newly treated with EMPA were found to have lower inpatient costs compared with DPP-4i users. The cost advantage for EMPA over GLP-RA-1 was mainly due to the difference in direct medication costs. Further studies are recommended to confirm these results, particularly with regard to the real-world efficacy of SLGT-2 inhibition in heart failure.		
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Names and affiliations of principal investigators:	[redacted]		