



# Cigarette Smoking as a Predictor of Sodium–Glucose Cotransporter 2 Inhibitor–Associated Genital Infections: A Retrospective Cohort Study

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The most frequent adverse events associated with sodium–glucose cotransporter 2 (SGLT2) inhibitors are genital infections, with an incidence ranging from 3.7% to 11.4% in clinical trials (1,2). Treatment with SGLT2 inhibitors has also been associated with a modest increase in the risk of urinary tract infections (3). Genito-urinary infections are more frequent in women, particularly those reporting previous recurrent episodes of such events (4).

To identify further predictors of genital infections, a retrospective cohort study was performed. We enrolled all patients with type 2 diabetes aged  $\geq 18$  years and referred to the Diabetes Outpatient Clinic of Careggi University Hospital, Florence, between 1 October and 30 November 2020 who had received a prescription of an SGLT2 inhibitor before 1 October 2018 and who provided their informed consent, with no other exclusion criteria. Demographic and clinical characteristics of patients at the date of prescription were retrieved from patients' clinical records. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration algorithm and used for categorization of renal function (for eGFR below or above the median value). Information on treatment discontinuation and on genital infections, as recorded by the physician in charge, in the 2 years after the first SGLT2 inhibitor

prescription was also retrieved from clinical records. Patients were categorized as current smokers, former smokers, and nonsmokers on the basis of their smoking status at the date of the first prescription of SGLT2 inhibitors, as reported in clinical records. After excluding cases with missing data, characteristics of patients with and without genital infections during the 2-year follow-up were compared using two-tailed *t* tests and  $\chi^2$  tests for continuous and categorical variables, respectively. In addition, a Cox regression analysis was performed, with genital infections as time-dependent outcome and sex, age, and patient characteristics significantly associated with events in univariate analysis as covariates. Statistical analysis was performed with IBM SPSS Statistics 27.0. The study protocol was approved by the local Ethical Board of Florence (Ref. 18526\_oss/2020), and it was performed as part of the institutional activity of the investigators, with no specific funding. Out of 508 enrolled patients, 53 (10.4%) reported at least one episode of genital infection during the follow-up period.

The proportion of patients reporting a genital infection after the initiation of SGLT2 inhibitor therapy was 18.3%, 9.4%, and 7.1% in current smokers, former smokers, and nonsmokers, respectively ( $P < 0.01$ ). The difference in incidence of genital infection between

patients with eGFR above or below median values (88 mL/min/1.73 m<sup>2</sup>) was not statistically significant (11.7% vs. 7.3%, respectively,  $P = 0.09$ ). No other parameter was significantly different between patients with or without infections. The results of Cox regression are summarized in Fig. 1. Current smoking was associated with a significant increase in the risk of genital infection even after adjusting for age, sex, and renal function.

To our knowledge, this is the first report of an association between smoking status and genital infections associated with the use of SGLT2 inhibitors. Mechanisms underlying this association are hypothetical: smoking may alter resident microbial flora in the genital tract or increase the susceptibility to infections (5).

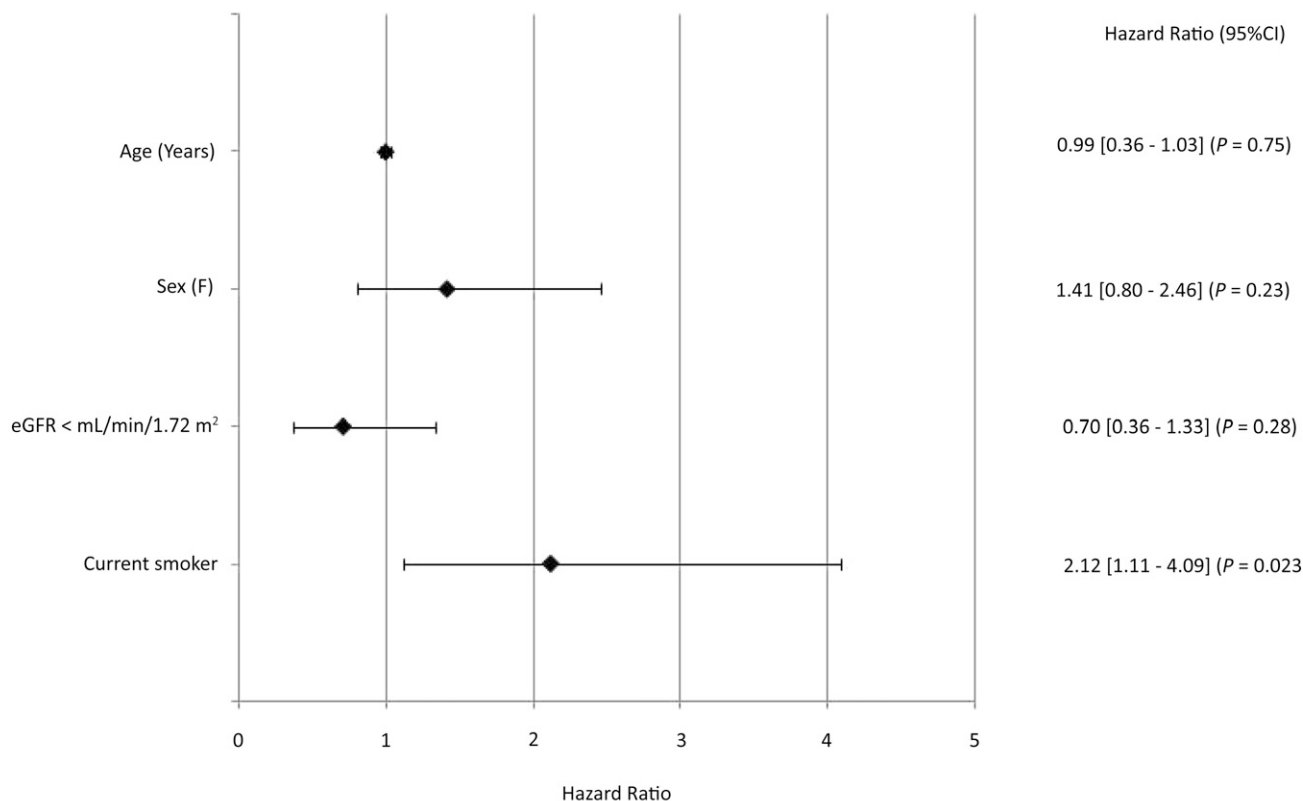
The current study is intended to be a preliminary exploration of factors associated with genital infection in patients with type 2 diabetes treated with SGLT2 inhibitors. The relatively small sample size could have prevented the observation of other relevant associations. In addition, the association of smoking with infections could have been determined by undetected confounders. Furthermore, the diagnosis of genital infection and the determination of smoking status were based on clinical records, with possible misclassifications and/or incomplete reporting. The

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**Figure 1**—Cox regression analysis for predictors of infection. Hazard ratios (with 95% CI) are given for incident genital infections. F, female.

retrospective nature of the study, based on annotations of adverse events reported in clinical records, prevented a reliable distinction between genital and urinary tract infections. For the same reason, it was not possible to retrieve reliable information on prior genital infections, which are a known risk factor for this adverse event. In addition, the sample studied, which was enrolled in a single diabetes outpatient clinic of a university hospital, cannot be considered representative of the whole population of patients with diabetes receiving treatment with SGLT2 inhibitors; furthermore, the moderators of SGLT2 inhibitor-associated genital infections may vary on a different genetic and cultural background. The higher prevalence of genital infection compared with that in most trials (1,2) could have been determined by differences in case mix.

In conclusion, cigarette smoking appears to be a relevant predictor of genital infections associated with SGLT2 inhibitor treatment, deserving further investigation with specific, larger-scale observational studies and with analyses of data from randomized trials.

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responsibility for the integrity of the data and the accuracy of the data analysis.

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