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# **Empagliflozin and Risk of Lower Respiratory Tract Infection in Heart Failure with Mildly Reduced and Preserved Ejection Fraction: an EMPEROR-Preserved analysis**

## **Short title: Empagliflozin and lower respiratory infection in HFmrEF/HFpEF**

João Pedro Ferreira<sup>1,2,3</sup>; Faiez Zannad<sup>3</sup>; Milton Packer<sup>4</sup>; Gerasimos Filippatos<sup>5</sup>; Stuart J Pocock<sup>6</sup>; Francisco Vasques-Nóvoa<sup>1,7</sup>; Michael Böhm<sup>8</sup>; Javed Butler<sup>9</sup>; Stefan Anker<sup>10</sup>

### Affiliations:

<sup>1</sup> UnIC@RISE, Cardiovascular Research and Development Center, Department of Surgery and Physiology, Faculty of Medicine of the University of Porto, Portugal.

<sup>2</sup> Heart Failure Clinic, Internal Medicine Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, Portugal.

<sup>3</sup> Université de Lorraine, INSERM, Centre d'Investigations Cliniques Plurithématique 1433, and INSERM U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France

<sup>4</sup> Baylor Heart and Vascular Institute, Dallas, TX, USA & Imperial College, London, UK.

<sup>5</sup> National and Kapodistrian University of Athens School of Medicine, Athens, Greece.

<sup>6</sup> London School of Hygiene and Tropical Medicine, London, UK.

<sup>7</sup> Internal Medicine Department, Centro Hospitalar Universitário de São João, Porto, Portugal.

<sup>8</sup> Department of Internal Medicine III, Cardiology, Angiology, Intensive Care Medicine, Universitätsklinikum des Saarlandes and Saarland University, Homburg, Germany.

<sup>9</sup> Baylor Scott and White Research Institute, Dallas, TX, USA & University of Mississippi, Jackson, MS, USA.

<sup>10</sup> Department of Cardiology (CVK) and Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin Berlin, Berlin, Germany & Institute of Heart Diseases, Wrocław Medical University, Wrocław, Poland.

### Contact to:

Prof. João Pedro Ferreira

Faculty of Medicine of the University of Porto, Portugal

Alameda Prof. Hernâni Monteiro, 4200-319 Porto

Phone: +351225513600

Mail: [jpferreira@med.up.pt](mailto:jpferreira@med.up.pt)

Twitter handle: @unic\_cardiovasc

## **Abstract**

*Background:* Lower respiratory tract infections (LRTI) are common worldwide. Patients with heart failure and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) have a high risk of developing LRTI. Prior studies were able to show that SGLT2 inhibitors may reduce the incidence of LRTI in patients with type 2 diabetes (T2D).

*Aims:* To study the patient's characteristics and prognosis according to LRTI status and assess the effect of empagliflozin on LRTI in 5988 patients with HFmrEF/HFpEF enrolled in the EMPEROR-Preserved trial randomized to either empagliflozin or placebo over a median follow-up of 26 months.

*Methods:* Time-updated models were used to study the mortality risk after a LRTI. Cox regression was used to study the effect of empagliflozin on incident LRTI.

*Results:* Throughout the follow-up, 699 of 5988 (11.7%) patients developed LRTI: these were older, were more frequently hospitalized within the previous year, had T2D, chronic kidney disease (CKD), and had higher NTproBNP levels than patients without incident LRTI. Patients who developed LRTI had a 2.7-fold higher risk of subsequent mortality compared to patients without LRTI. The incidence of LRTI was 5.2 [95%CI 4.6-5.8] events per 100 person-years in empagliflozin group and 6.2 [95%CI 5.6-6.9] events per 100 person-years in placebo group, HR=0.83, 95%CI=0.71-0.96, P=0.014. The total number of LRTI was reduced with empagliflozin group IRR=0.80, 95%CI=0.68-0.94, P=0.008. No effect of empagliflozin was observed on COVID-19 incidence.

*Conclusion:* In EMPEROR-Preserved, LRTI was frequent and associated with a poor prognosis. Empagliflozin was associated with a reduced the risk of LRTI compared to placebo.

*Key-words:* Lower respiratory tract infection; Empagliflozin; Heart failure and a preserved ejection fraction

## **Abbreviations**

LRTI, lower respiratory tract infection

SGLT2i, sodium glucose co-transporter 2 inhibitor

HFmrEF, heart failure with mildly reduced ejection fraction

HFpEF, heart failure with preserved ejection fraction

T2D, type 2 diabetes

CKD, chronic kidney disease

## **Introduction**

Lower respiratory tract infections (LRTI) are important causes of morbidity and mortality worldwide.<sup>1</sup> LRTI include pneumonia, atypical pneumonia, infectious exacerbation of chronic obstructive pulmonary disease (COPD), or bronchitis/tracheobronchitis which are conditions difficult to differentiate clinically, with a similar diagnostic and treatment approach.<sup>2</sup> The incidence of LRTI in adults increases among the elderly and along with the accumulation of comorbid conditions, such as heart failure (HF).<sup>3</sup>

Patients with heart failure and mildly reduced or preserved ejection fraction (HFmrEF/HFpEF) are frequently elderly with multiple comorbidities. Consequently, they present a higher risk of LRTI and experience a poorer prognosis compared to age- and sex-matched populations without HFmrEF/HFpEF.<sup>4</sup> LRTI is also a clinically important factor precipitating HF decompensations and hospitalizations.<sup>5,6</sup>

Beyond pneumococcal and influenza vaccinations, whose uptake is poor, no strategies have proven to reduce the incidence of LRTI in HF.<sup>7,8</sup> An electronic health record study matching new SGLT2 inhibitor with DPP4 inhibitor users, suggested that the use of SGLT2 inhibitors was associated with a lower risk of pneumonia and pneumonia-related mortality compared with DPP4 inhibitors.<sup>9</sup> A meta-analysis of randomized trials including 59,264 patients with type 2 diabetes treated with a SGLT2 inhibitor or placebo showed that SGLT2 inhibitors reduced the relative risk of pneumonia by 13%.<sup>10</sup>

Using the EMPEROR-Preserved (EMPagliflozin outcome tRial in Patients With chrOnic heaRt Failure With Preserved Ejection Fraction; NCT03057951) data,<sup>11</sup> we aimed to study the incidence of LRTI throughout the follow-up, patient's characteristics according to LRTI status, the risk of mortality after the occurrence of LRTI, and the effect of empagliflozin on incident LRTI. Reported symptomatic COVID-19 cases are also explored.

## **Methods**

### **Study design and patient population**

The design and primary results of the EMPEROR-Preserved trial have been published previously.<sup>12,13</sup> In brief, the EMPEROR-Preserved trial was a Phase III international, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial that enrolled adult patients who had chronic HF with New York Heart Association (NYHA) class II-IV symptoms for at least 3 months and a left ventricular ejection fraction (LVEF) >40% with no

prior measurement  $\leq 40\%$  under stable conditions. Patients were required to have elevated N-terminal pro-hormone B-type natriuretic peptide (NT-pro BNP) levels ( $>900$  pg/mL or  $>300$  pg/mL in patients with or without atrial fibrillation, respectively) and have evidence of structural heart disease (left ventricular hypertrophy or left atrial size) or a documented HF hospitalization within 12 months. The protocol was approved by the Ethical Committee of each of the 622 participating sites in 23 countries, and all patients gave written informed consent to participate in the study.

### **Randomization**

Patients were randomized in a double-blind manner (in a 1:1 ratio) to receive placebo or empagliflozin 10 mg daily, in addition to their usual therapy. Following entry into the trial, all appropriate treatments for HF or other medical conditions could be initiated, discontinued, or altered at the clinical discretion of the investigator.

### **Endpoints**

The primary endpoint in the EMPEROR-Preserved trial was a composite of adjudicated cardiovascular death and hospitalization for HF, analyzed as the time to first event. The main outcome of interest in the present analysis was LRTI, which included lung infections defined as “pneumonia”, “atypical pneumonia”, “infectious pleural effusion”, infective exacerbation of COPD”, “bronchitis”, or “tracheobronchitis”. *Supplementary Table 1.*

LRTI and COVID-19 were investigator-reported diagnoses, as adverse events or serious adverse events i.e., adverse events of special interest, defined following the Medical Dictionary for Regulatory Activities (MedDRA), based on the reporting of the preferred term “LRTI” and “COVID-19”.

Analyses were conducted until the end of planned treatment in concordance with efficacy analyses in EMPEROR-Preserved.

### **Statistical analysis**

Baseline characteristics were compared between patients who developed LRTI and those who did not, using the appropriate descriptive statistics tests. The association between the occurrence of LRTI and hospitalizations and treatment interruption or withdrawal was based on descriptive statistics as reported by the investigators in the case record form (CRF). Time-updated survival models were used to study the association between the occurrence of LRTI and subsequent HF hospitalization or cardiovascular death, HF hospitalization and cardiovascular death alone, non-cardiovascular death, and all-cause death, with follow-up

time set to 0, in both the treatment and placebo groups, at the time of LRTI occurrence. The effect of empagliflozin on incident LRTI was assessed using a Cox model and the effect of empagliflozin on total LRTI was studied with a negative binomial regression model accounting for follow-up time. Similar analyses were performed to study COVID-19. P values and 95% confidence intervals presented in this report have not been adjusted for multiplicity, given the exploratory nature of this work. All analyses were performed using Stata®, version 18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

All analysis here presented were performed within the Vivli® (<https://vivli.org/>) platform, and the trial sponsor was not involved in this analysis.

## **Results**

### **Patient's characteristics by incident LRTI status**

Throughout the follow-up 699 of 5988 (11.7%) patients developed LRTI, these were older, had been more frequently hospitalized within the previous 12 months, had longer HF duration, and presented more frequently diabetes *mellitus*, atrial fibrillation, COPD, and chronic kidney disease (CKD). Patients who developed LRTI were also more frequently smokers or former smokers, were more often treated with loop diuretics, and had higher NTproBNP levels and poorer health related quality of life than patients who did not develop LRTI. No significant between-group difference in ejection fraction was found. *Table 1*.

The description of LRTI is presented in the *Supplementary Table 1*.

### **Association of incident LRTI with subsequent events**

As described by the investigators in the CRF, a total of 198 of 699 (28.3%) LRTI required hospitalization, 103 in the empagliflozin group and 95 in the placebo group (P =0.46). LRTI prolonged hospitalization in 61 (8.7%) patients, 36 in the empagliflozin group and 25 in the placebo group (P =0.43). LRTI was causally linked to death in 32 (4.5%) patients, 17 in the empagliflozin group and 16 in the placebo group (P =0.22). LRTI led to treatment interruption or withdrawal in 69 (9.9%) patients, 36 in the empagliflozin group and 33 in the placebo group (P =0.88).

Only 43 of 699 (6.2%) LRTI occurred within  $\pm 7$  days of a HF hospitalization.



In time-updated models, the occurrence of LRTI was associated with a 2 to 4-fold higher risk of subsequent cardiovascular mortality or HF hospitalization, cardiovascular and non-cardiovascular mortality, and all-cause mortality. *Table 2 and Figure 1.*

### **Empagliflozin effect on incident LRTI**

LRTI incidence was 5.2, 95%CI 4.6-5.8 events per 100 person-years in the empagliflozin group and 6.2, 95%CI 5.6-6.9 events per 100 person-years in placebo group, with a corresponding HR =0.83, 95%CI 0.71-0.96, P =0.014. The total number of LRTI was reduced with empagliflozin vs placebo: IRR =0.80, 95%CI 0.68-0.94, P =0.008. *Table 3 and Figure 2.*

Patients with HFmrEF (n =1967) and HFpEF (n =3979) experienced a similar benefit with empagliflozin regarding the reduction of LRTI events (interaction P =0.11).

### **COVID-19**

Throughout the follow-up 299 of 5988 (5.0%) patients developed COVID-19, these had higher BMI and lower eGFR than those without COVID-19, otherwise they were similar. *Supplementary Table 2.* A total of 92 (30.9%) COVID-19 infections required hospitalization, 12 (4.0%) prolonged hospitalization, and 40 (13.4%) were fatal. Having COVID-19 increased the risk of dying by 1.5-fold but did not increase the risk of HF hospitalization.

*Supplementary Table 3.* Empagliflozin did not influence the incidence of COVID-19.

*Supplementary Table 4.*

### **Discussion**

This study shows that LRTI is a frequent complication among patients with HFmrEF/HFpEF and increases the risk of subsequent HF hospitalizations and mortality. Remarkably, empagliflozin reduced the incidence of LRTI in HFmrEF/HFpEF, extending the evidence of a benefit of SGLT2 inhibitors reported in observational studies and meta-analysis in patients with type 2 diabetes.<sup>9,10,14</sup>

In EMPEROR-Preserved, patients who had LRTI were older, and had T2D, CKD, and prior hospitalizations more frequently, characteristics aligned with epidemiological data showing that patients who develop LRTI are more likely to have multiple comorbidities, poorer quality of life and prior hospitalizations.<sup>15</sup> In the placebo group of EMPEROR-Preserved the incidence rate of LRTI (6.4 events per 100 person years) was 6-fold higher than among elderly people of the general population participating in the Cardiovascular Health Study, and

1.6-fold higher than the incidence observed in patients with HFmrEF/HFpEF enrolled in the PARAGON-HF (NCT01920711) trial.<sup>4,16</sup> While HF *per se* may explain the higher risk of patients enrolled in EMPEROR-Preserved compared to the general population, the higher risk observed in EMPEROR-Preserved compared to PARAGON-HF may be related to a higher prevalence of diabetes, a well-established risk factor for pneumonia,<sup>17</sup> in EMPEROR-Preserved compared to PARAGON-HF (49% vs. 43%), and by the inclusion of bronchial and lung infections not classified by the investigators as pneumonia in EMPEROR-Preserved.

SGLT2 inhibitors reduce systemic inflammation, oxidative stress, promote mitochondrial and cellular homeostasis, which are key mechanisms postulated to improve cardiorenal outcomes and health status.<sup>18,19</sup> Conversely, an increase in systemic inflammation, oxidative stress, and immunological dysfunction increase the risk of LRTI.<sup>20</sup> Furthermore, it has been postulated that increased BNP levels may suppress neutrophil function, whereas lung congestion may impair bacterial clearance and local defence mechanisms in patients with HF.<sup>21,22</sup> Therefore, it is mechanistically plausible that SGLT2 inhibitors reduce the risk of LRTI by counterbalancing inflammation and oxidative stress, and by improving congestion, health status and HF outcomes.<sup>11,18,19,23,24</sup> Thus, a general health status improvement may play a major role in the reduction of LRTI, an hypothesis that is aligned with the reduction in hospitalizations from all causes seen with SGLT2i.<sup>25</sup> Notwithstanding, it is possible that SGLT2 inhibitors improve host defense by enhancing xenophagy, i.e., the use of autophagy to surround and dispose of microbial invaders, particularly those acting intracellularly, such as *Streptococcus pneumoniae*.<sup>26</sup> It is worth noting that autophagy may be one of the major mechanisms of action mediating the beneficial effects of SGLT2 inhibitors.<sup>18,27-29</sup>

The risk reduction of LRTI seen with SGLT2 inhibitors in HF may be specific of these agents. A study of pneumonia in HF in trials testing the effect of sacubitril/valsartan, also found that HF patients have a high risk of pneumonia and a poor prognosis after having had a pneumonia, but did not find any association between the use of sacubitril/valsartan and a reduction in the incidence of pneumonia.<sup>4,30</sup> In EMPEROR-Preserved only a few (n =43) LRTI occurred within a week of a HF hospitalization, suggesting that a differentiation between LRTI and HF hospitalization was thoroughly performed by the independent adjudication committee. Furthermore, the reduction in the incidence of pneumonia was also documented in patients with T2D without HF, in whom congestion and worsening HF are less central to the disease course.<sup>10</sup>

In EMPEROR-Preserved, most (>70%) LRTI were treated outside the hospital and few (<5%) resulted directly in death. However, the risk of death was high and increased steadily in the months/years after a LRTI, reaching ~50% at 3 years. Epidemiological studies showed a sustained risk subsequent to an acute pneumonia, possibly due to a persistence of systemic inflammation and a procoagulant state.<sup>31</sup> These findings support the overall high-risk profile of patients who had a LRTI, who are patients approaching the end of their lives when the lung infection develops.<sup>32</sup> Still, LRTI furtherly aggravates the health status of these already fragile patients; thus, preventing LRTI in HFmrEF/HFpEF may represent another important reason to use SGLT2 inhibitors.

The EMPEROR-Preserved trial was conducted during the COVID-19 pandemic; the trial staff had to adapt to different policies and lockdown periods across the participating countries, but the pandemic did not have major impact on trial adherence and event reporting.<sup>11</sup> In EMPEROR-Preserved 5.0% of patients developed COVID-19 disease, these patients had higher BMI and lower eGFR, consistently with the epidemiology of the disease.<sup>33</sup> Empagliflozin did not affect the incidence of COVID-19, a finding that was concordance with evidence from populational studies and the DELIVER (NCT03619213) trial with dapagliflozin.<sup>34-36</sup> In addition, SGLT2 inhibitors also did not improve outcomes among people hospitalized with severe COVID-19 infection.<sup>37</sup>

### **Limitations**

This study has some limitations. LRTI was an investigator-reported diagnosis, and we do not have detail on the use of antibiotics nor agent isolation. Although LRTI increased the risk of HF hospitalizations, the latter were independently adjudicated and clearly separated from pneumonia as the principal diagnosis of hospitalization (with only 43 LRTI occurring within 7 days of a HF hospitalization). Pneumococcal and influenza vaccination status was unknown, and we cannot ascertain if vaccination could change the risk of pneumonia in this setting. We included bronchial and lung infections not classified as pneumonia by the study investigator, because such infections are also clinically important and difficult to distinguish from pneumonia in clinical practice.

### **Conclusion**

LRTI was frequent and associated with a poor prognosis in patients with HFmrEF/HFpEF. Empagliflozin allocation was associated with a lower risk of LRTI compared to placebo. These findings should be regarded as hypothesis-generating and require further replication.



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## **Disclosures**

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## **Data sharing agreement**

Researchers should use the <https://vivli.org/> link to request access to study data and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

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Table 1. Comparison of patient's characteristics with and without LRTI

<b>Characteristic</b>	<b>No LRTI</b> n =5289	<b>LRTI</b> n =699	<b>P-value</b>
Total N =5988			
Age, yr	71.7 ± 9.4	72.8 ± 9.3	0.006
Age >75 yr	2011 (38.0%)	306 (43.8%)	0.003
Women	2355 (44.5%)	321 (45.9%)	0.48
Race			0.027
White	3990 (75.4%)	552 (79.0%)	
Asian	751 (14.2%)	73 (10.4%)	
Black	222 (4.2%)	36 (5.1%)	
Other	326 (6.2%)	38 (5.3%)	
Region			<0.001
Asia	621 (11.7%)	65 (9.3%)	
Europe	2426 (45.9%)	263 (37.6%)	
Latin America	1314 (24.8%)	201 (28.8%)	
North America	593 (11.2%)	126 (18.0%)	
Other	335 (6.3%)	44 (6.3%)	
Hosp. prev. 12 mo	1715 (32.4%)	287 (41.1%)	<0.001
Prior HF hosp.	1113 (21.0%)	193 (27.6%)	<0.001
HF duration			0.002
≤1 year	1363 (25.8%)	149 (21.3%)	
>1 to 5 years	2388 (45.1%)	305 (43.6%)	
>5 years	1538 (29.1%)	245 (35.0%)	
Smoking status			0.008
Current smoker	376 (7.1%)	60 (8.6%)	
Former smoker	2094 (39.6%)	309 (44.3%)	
Never smoked	2816 (53.3%)	329 (47.1%)	
COPD	624 (11.8%)	171 (24.5%)	<0.001
Diabetes	2552 (48.3%)	386 (55.2%)	0.002
BMI, Kg/m <sup>2</sup>	29.8 ± 5.8	30.3 ± 6.2	0.023
SBP, mmHg	131.9 ± 15.6	131.4 ± 16.1	0.49
Heart rate, bpm	70.3 ± 11.9	70.9 ± 11.8	0.18
AFib/Flutter	1810 (34.2%)	270 (38.6%)	0.022
NYHA III/IV	904 (17.1%)	197 (28.2%)	<0.001
LVEF, %	54.3 ± 8.8	54.3 ± 8.8	0.82
eGFR, ml/min	61.1 ± 19.8	56.8 ± 19.7	<0.001
eGFR <60 ml/min	2580 (48.8%)	408 (58.4%)	<0.001
Hemoglobin, g/dL	13.8 ± 1.5	13.5 ± 1.6	<0.001
Potassium, mmol/L	4.6 ± 0.5	4.6 ± 0.5	0.78
ACEi/ARB	4331 (81.9%)	545 (78.0%)	0.012
ARNi	119 (2.3%)	21 (3.0%)	0.22
MRA	2013 (38.1%)	278 (39.8%)	0.38
Beta-blocker	4596 (86.9%)	593 (84.4%)	0.13
Loop diuretic	3560 (67.3%)	541 (77.4%)	<0.001
Statin	3681 (69.6%)	493 (70.5%)	0.61
UACR, mg/g	20 (7-66)	30 (11-127)	<0.001
NTproBNP, pg/mL	946 (485-1691)	1182 (634-2047)	<0.001
KCCQ-OSS	70 ± 21	63 ± 22	<0.001

Legend: LRTI, lower respiratory tract infection; HF, heart failure; COPD, chronic obstructive pulmonary disease; BMI, body mass index; SBP, systolic blood pressure; AFib, atrial fibrillation; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; ACEi/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; UACR, urinary albumin-to-creatinine ratio; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire – Overall Symptom Score.

Table 2. Event risk after LRTI

<b>Outcome</b>	<b>No LRTI</b>	<b>LRTI</b>	<b>HR (95%CI)</b>	<b>P-value</b>
CV death or HFH	689/5289 (13.0%)	211/673 (31.3%)	2.62 (2.24-3.01)	<0.001
HFH	420/5289 (7.9%)	166/674 (24.6%)	3.37 (2.82-4.04)	<0.001
CV death	365/5289 (6.9%)	98/699 (14.0%)	2.00 (1.60-2.50)	<0.001
Non CV death	255/5289 (4.8%)	131/699 (18.7%)	3.76 (3.05-4.65)	<0.001
ACM	620/5289 (11.7%)	229/699 (32.8%)	2.73 (2.35-3.18)	<0.001

Legend: LRTI, lower respiratory tract infection; CV, cardiovascular; HFH, heart failure hospitalization; ACM, all-cause mortality.

Notes: Of the 211 patients who had a pneumonia before a CV death or HFH event, 86 (41%) had such event within 3 months after the pneumonia. Of the 229 patients who had a pneumonia and died, 131 (57%) died within 3 months after the pneumonia.

Table 3. Effect of empagliflozin on incident LRTI

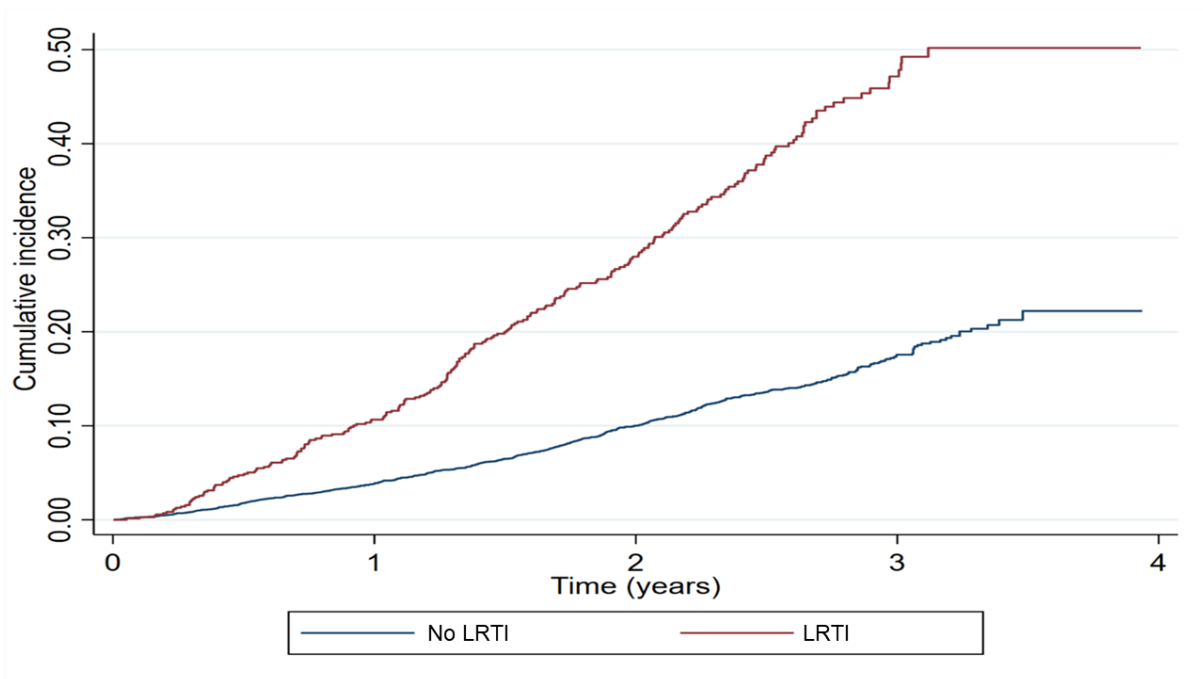
<b>Event</b>	<b>Empagliflozin</b>	<b>Placebo</b>	<b>HR (95%CI)</b>	<b>P-value</b>
LRTI	320/2997 (10.7%)	379/2991 (12.7%)	0.83 (0.72-0.97)	0.016
Total LRTI *	391/2997	493/2991	0.80 (0.68-0.94)	0.008

Legend: LRTI, lower respiratory tract infection.

\*Negative binomial model results expressed as incidence rate ratio.

Median follow-up time to pneumonia =764 (528-996) days.

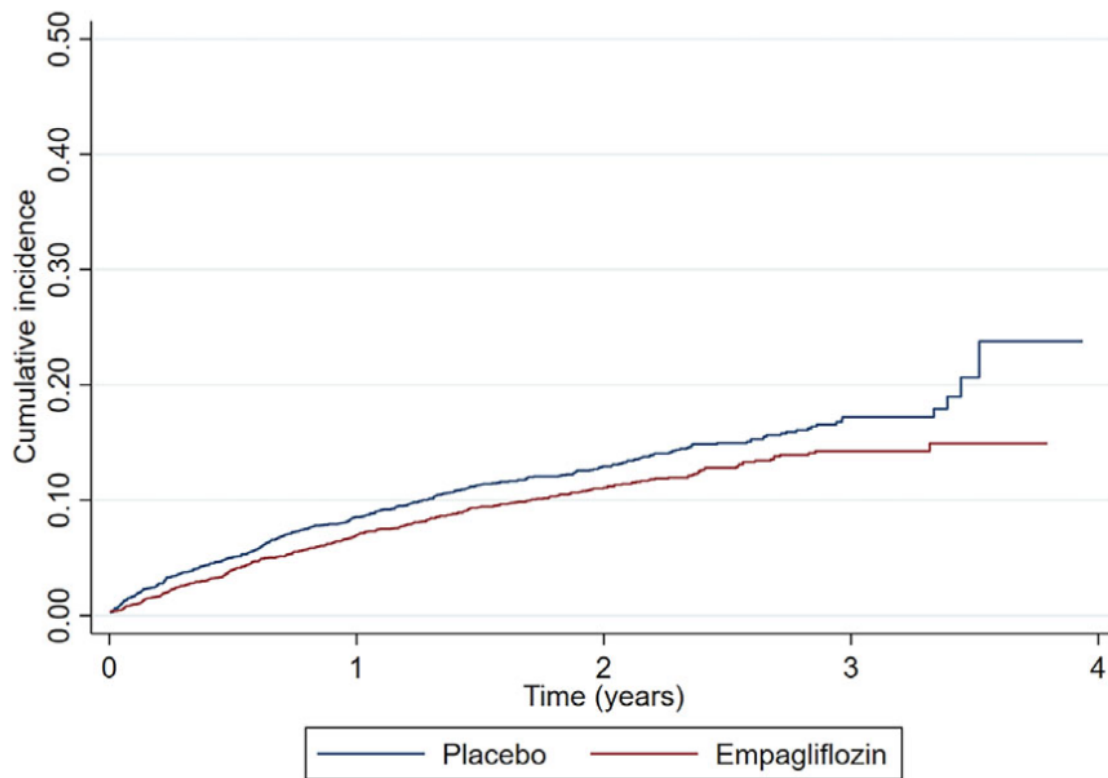
Figure 1. Mortality risk after LRTI



Legend: Time-updated mortality risk after a LRTI event.

Caption: The cumulative incidence of death is nearly 50% at 3 years after a LRTI.

Figure 2. Empagliflozin impact on incident LRTI

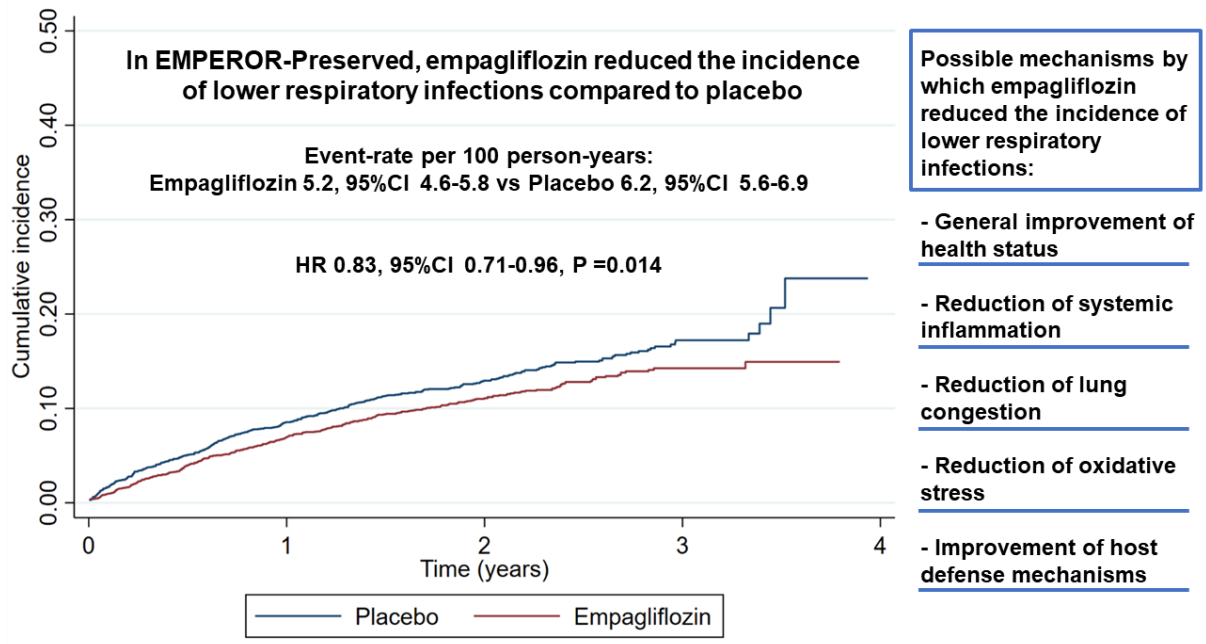


Legend: Empagliflozin reduced the risk of LRTI in EMPEROR-Preserved.

Caption: Event-rate per 100 person-years =5.2, 95%CI 4.6-5.8 in empagliflozin group and =6.2, 95%CI 5.6-6.9 in placebo group.



Graphical abstract. Empagliflozin reduced the risk of lower respiratory infections



Legend: HR, hazard ratio; CI, confidence interval.