Introduction:
In preclinical models of sepsis, we have previously demonstrated that activation of AMP activated protein kinase (AMPK) using metformin, improves survival and organ function. Thus, AMPK activation is a potential therapeutic target in sepsis, and we hypothesize that exposure to metformin during sepsis is associated with decreased AKI and mortality.

Methods:
Retrospective analysis of a 13-hospital cohort of adult ICU patients with type 2 diabetes mellitus (T2DM) who presented sepsis. We investigated if exposure to metformin during the hospitalization was associated with reduced 90-day mortality and AKI. We used 1:4 Propensity Score Matching (PSM), Propensity Score Stratification (PSS) and Propensity Score Weighting (PSW) based on the probability to be exposed to metformin using 55 covariates. For PSM an exact match for insulin, amputation, cardiovascular diseases, retinopathy, Charlson Index, eGFR, HbA1C, and APACHE III, were used. Sepsis was defined using sepsis 3 criteria, and AKI as KDIGO stage 2 or 3.

Results:
From 164,910 patients, we found 673 diabetic adults exposed to metformin during hospitalization and 14,174 who were not. PSM included 523 treated vs 1,680 no treated patients and resulted in an OR of 0.54 (95%CI 0.41-0.71, p<0.001) for 90-day mortality favoring metformin exposure (Figure 1). PSS: (OR: 0.49, 95%CI 0.34-0.63, p<0.001) and PSW (OR: 0.58, 95%CI 0.55-0.61, p<0.001) confirmed this protective effect. Metformin exposure also had a protective effect on stage 2-3 AKI (PSM: OR 0.82, 95%CI 0.67-0.99, p=0.04; PSS: OR 0.83, 95%CI: 0.71-0.98, p=0.02; PSW: OR 0.72, 95%CI 0.69-0.76 p<0.001)

Conclusion:
Metformin exposure during hospitalization is associated with decreased 90-day mortality and AKI in septic adult patients with T2DM. These findings suggest that metformin may constitute a potential therapeutic strategy in sepsis, and the potential role of AMPK activation as a protective mechanism. However, studies are needed to confirm this association and the specific mechanisms of action.
Survival estimates (90 days) by Metformin exposure

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Events/Total</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposed</td>
<td>80/673</td>
<td>0.29 (0.24-0.37)</td>
</tr>
<tr>
<td>Not Exposed</td>
<td>4889/14174</td>
<td>Reference</td>
</tr>
</tbody>
</table>

Logrank P-value < 0.0001

Censor

No at Risk
Exposed       673
Not Exposed   14174

Survival Estimates (90 days) by Metformin Exposure