Angiotensin Converting Enzyme Inhibition as a Potential Risk Factor for Periprosthetic Joint Infection

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Introduction:
There is growing evidence suggesting that the angiotensin-converting enzyme (ACE) has an immunomodulatory role. Prior *in-vitro* studies and *in-vivo* surgical animal models from our study group have shown that ACE inhibitors (ACEi) may have an immunosuppressive effect[1]. As such, ACE inhibition may represent an unappreciated risk factor for periprosthetic joint infection (PJI). In addition to intra-operative techniques to mitigate PJI such as antibiotic eluting beads, antimicrobial coated implants and vancomycin powder, optimizing the perioperative patient immunoprofile is of paramount importance. Given ACEis and angiotensin receptor blockers (ARB) have similar clinical indications, this study aims to determine whether a difference in infectious burden exists in patients taking ACEis versus ARBs prior to a total knee arthroplasty (TKA).

Methods:
A retrospective review of the PearlDiver database was performed. Patients were divided into two groups; those taking an ACEi or an ARB for at least 1 year prior to primary TKA. Current Procedural Terminology codes were used to identify which patients underwent an irrigation and debridement procedure as a surrogate for infection following surgery after 6 months, 1 year, 5 year, and 10 years. Propensity matching controlled for age, gender, insurance plan, Charlson Comorbidity Index (CCI), and medical comorbidities. Kaplan Meier survival (KMS) curves and log-rank tests calculated survival differences. Odds ratios (ORs) and 95% confidence intervals (CI) were analyzed with significance defined as a p-value of <0.05.

Results:
A total of 77831 patients in the ACEi group and 39105 in ARB group were identified. Mean CCI score in the ACEi and ARB group was 1.95 and 2.06, respectively. After propensity score matching, 39105 patients were included in each group. Patients in the ACEi group had statistically significant higher rates of infection in the KMS compared to the ARB group, p <.0001. At 6 months ACEi had a 95% CI of [2.10, 3.57], 1 year [2.06, 3.36], 2 year [2.06, 3.26], and 5 year [2.12, 3.19] with all p-values < .0001.

Discussion:
The sequelae of periprosthetic joint infection are devastating, thus any strategy to optimize the host immune system to mitigate infection is paramount. Prior studies have demonstrated that ACEi, but not ARB, treatment resulted in increased bacterial burden and impaired immune response in a preclinical model of implant infection[1]. Further studies are warranted, however, given the relative interchangeability of ACEis and ARB, the current study suggests that if a patient can switch from an ACEi to an ARB perioperatively, it may potentially decrease their postoperative infectious burden.

Significance/Clinical Relevance:
This is the first study of its kind to investigate the potential clinical immunomodulatory effect of ACE inhibition. By expanding on our prior animal model, this translational study indicates that ACEi treatment may represent an under-appreciated, modifiable perioperative infectious risk factor.

References:
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Figure 1: Kaplan Meier Survival Curve ACEi relative to ARB periprosthetic joint infection at 6 months, 1 year, 2 year, 5 year, 10 year following index surgery. Dotted lines represent 95% confidence intervals.