Angiotensin Receptor Blockers Outperform angiotensin-converting enzyme Inhibitors in Preventing arthrofibrosis After Knee Arthroplasty

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INTRODUCTION: Arthrofibrosis is a debilitating complication following total knee arthroplasty (TKA), often manifesting as joint stiffness, reduced range of motion, and necessitating reintervention such as manipulation under anesthesia (MUA)or arthroscopic/open lysis of adhesions (LOA). Although the pathophysiology is multifactorial, excessive fibroblast activation and inflammatory cascades are central to the development of this fibrotic response. Strategies to mitigate arthrofibrosis remain limited.

Recent interest has emerged around the role of the renin-angiotensin-aldosterone system (RAAS) in modulating fibrosis. Both angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) have demonstrated anti-fibrotic effects across various organ systems. Despite their widespread use for cardiovascular and renal indications, their potential protective effects against postoperative fibrosis in orthopedic surgery remain understudied.

In this study, we evaluated whether perioperative exposure to ACEis or ARBs was associated with a lower risk of arthrofibrosis following TKA. We first analyzed the outcomes of patients who received either ACEis or ARBs around the time of surgery, comparing them to patients who were not on either medication. We then performed subgroup analyses separating ACEi users and ARB users to assess whether any differences existed between the two drug classes. Lastly, we directly compared outcomes between patients who received ACEis versus those who received ARBs to explore potential class-specific effects.

METHODS: We conducted a retrospective cohort study using the TriNetX Research Network, a large, federated database of deidentified electronic health records from healthcare organizations across the United States. Adult patients who underwent primary TKA between 2005 and 2025 were identified using standardized ICD-10 and CPT procedure codes.

Medication exposure was defined as active prescription of either an ACE inhibitor or an ARB during the perioperative period, which we defined as within 3 months before or after the date of surgery. Four primary comparisons were constructed: (1) patients prescribed either an ACEi or ARB vs. patients not prescribed either, (2) ACEi users vs. non-ACEi users, (3) ARB users vs. non-ARB users, and (4) ACEi users vs. ARB users.

For each comparison, cohorts were matched 1:1 using propensity score matching based on age, sex, race, body mass index (BMI), comorbidities (including diabetes and hypertension), and concurrent medications. This matching was conducted to reduce confounding and ensure comparability between groups.

We evaluated both short-term and long-term postoperative outcomes. Short-term outcomes, assessed at 90 days, and Long-term outcomes, assessed at 2 years, included clinically coded diagnoses of persistent knee stiffness and also arthrofibrosis which was defined as receipt of manipulation under anesthesia (MUA) or arthroscopic/open lysis of adhesions (LOA).

Comparative analyses were performed using chi-square tests for categorical outcomes and independent t-tests for continuous variables. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to compare event rates across groups. To reduce the risk of type I error due to multiple comparisons and the large sample size, a two-sided P-value < 0.01 was considered statistically significant.

RESULTS:

After propensity score matching, the cohorts included 105,072 patients for short-term follow-up and 75,277 for long-term follow-up, with balanced demographics across all comparisons. In the overall ACEi/ARB versus control analysis, the mean age was 66.6 ± 10.0 years in the treatment group and 67.0 ± 10.3 years in the control group. Female representation was 59% in both groups, and the mean BMI was similar (32.9), confirming successful matching ($P > 0.05$).

At 90-day follow-up, patients receiving ACEis or ARBs had significantly lower rates of knee stiffness ($P = 0.04$) and arthrofibrosis (1.8% vs. 2.1%; $P < 0.001$). At 2-year follow-up, the ACEi/ARB group continued to show significantly lower rates of arthrofibrosis (2.9% vs. 3.3%; $P < 0.001$) and knee stiffness ($P = 0.03$).

Subgroup analyses evaluating ACEis and ARBs separately revealed differential effects by medication class. ARB users (N = 81,900 per group) experienced the most consistent benefit, with significantly lower rates of arthrofibrosis and stiffness at both short- and long-term follow-up compared to controls. In contrast, among ACEi users (N = 84,933 per group), the differences in arthrofibrosis and stiffness rates compared to controls were not statistically significant at either time point. (Table 1)

In a direct comparison between ARBs and ACEis (N = 72,414 per group), ARBs were associated with significantly lower rates of arthrofibrosis at both short-term (1.8% vs. 2.1%; $P < 0.001$) and long-term follow-up (2.8% vs. 3.2%; $P = 0.005$).

These findings suggest a potential class-specific benefit of ARBs over ACE inhibitors in reducing postoperative fibrotic complications.

DISCUSSION AND CONCLUSION:

This study demonstrates a consistent association between perioperative ARB use and a reduced risk of arthrofibrosis and joint stiffness, both in the short and long term. While both ACE inhibitors and ARBs target the renin-angiotensin-aldosterone system, Direct comparisons confirmed that ARBs were more effective than ACE inhibitors in minimizing arthrofibrosis, underscoring a likely class-specific effect. Clinicians may consider favoring ARBs in the perioperative period for high-risk patients undergoing TKA. Further prospective studies and mechanistic investigations are warranted to validate these findings and determine whether ARBs could be repurposed as a strategy to prevent arthrofibrosis in orthopedic surgery.

Table 1. Arthrofibrosis and stiffness for ARB and ACEi groups in short- and long-term follow-ups

		ARTHROFIBROSIS			STIFFNESS		
FOLLOW-UP	**Comparison**	**(%)**	**OR (95% CI)**	**P value**	**(%)**	**OR (95% CI)**	**P value**
3M	ARB vs No ARB	1.7 vs 2.2	0.82 (0.77–0.88)	**<0.001**	3.9 vs 4.2	0.91 (0.87–0.96)	**0.0004**
	ACEi vs No ACEi	2.1 vs 2.1	0.98 (0.92–1.05)	0.63	4.1 vs 4.1	1.00 (0.96–1.05)	0.82
2Y	ARB vs No ARB	2.7 vs 3.2	0.88 (0.82–0.94)	**0.0001**	5.0 vs 5.5	0.91 (0.86–0.95)	**0.0002**
	ACEi vs No ACEi	3.2 vs 3.2	0.95 (0.90–1.01)	0.17	5.4 vs 5.4	0.99 (0.95–1.04)	0.92