Canakinumab after Electrical Cardioversion in Patients with Persistent Atrial Fibrillation: A Pilot Randomized Trial

Running Title: *Krisai et al.:* Canakinumab after Electrical Cardioversion for AF

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Non-standard Abbreviations and Acronyms

AAD = antiarrhythmic drug

AF = atrial fibrillation

CONVERT-AF = Canakinumab for the Prevention of Recurrences After Electrical Cardioversion in Patients With Persistent Atrial Fibrillation

ECV = electrical cardioversion

HR = hazard ratio

hsCRP = high-sensitivity C-reactive protein

NLRP3 = NOD-, LRR- and pyrin-domain-containing protein-3

Nearly half of all patients with atrial fibrillation (AF) undergoing electrical cardioversion (ECV) experience AF recurrences within 6 months, even with antiarrhythmic drug (AAD) treatment.[1] As inflammatory biomarkers are associated with AF recurrences, anti-inflammatory treatment may improve long-term success rates after ECV.[2] In this pilot study we investigated the effects of canakinumab, a specific interleukin-1β antibody, on AF recurrence after ECV in patients with persistent AF and elevated high-sensitivity C-reactive protein (hsCRP) levels.

CONVERT-AF (Canakinumab for the Prevention of Recurrences After Electrical Cardioversion in Patients With Persistent Atrial Fibrillation) was a randomized, double-blind, placebo-controlled trial enrolling patients with persistent AF undergoing ECV. All patients scheduled for ECV were prospectively screened 2-10 days before ECV at five study centers. Inclusion criteria were ECG-documented AF prior to ECV, hsCRP levels ≥2mg/L, age ≥50 years (women needed to be postmenopausal) and ability to give informed consent. Main exclusion criteria were AF persistence after ECV or AF recurrence before randomization and use of amiodarone within the last 6 months. After inclusion of 11 patients, hsCRP for inclusion was decreased to ≥1.25mg/l (corresponding to the median hsCRP level of all previous screen) to facilitate recruitment. The study was approved by local ethics committees and patients provided informed written consent.

After sinus rhythm restoration, patients were randomly assigned within 60 minutes to a single subcutaneous injection of 150mg of canakinumab or matching placebo. The 150mg dose was chosen based on anticipated efficacy, safety and hsCRP lowering from a prior phase-2 study in diabetes.[3] Patients, health-care providers, data collectors, and outcome adjudicators were blinded to treatment allocation. Patients were followed at 1, 3 and 6 months after randomization by trained study personnel.

AF recurrence was ascertained at each study visit by 12-lead ECG and through medical record review. Patients were advised to obtain ECG documentation in case of arrhythmia symptoms.

The primary outcome was AF recurrence within 6 months. Secondary outcomes were time-to-first redo-ECV, hospitalization free survival, AAD use at 6 months and change in hsCRP from randomization to 6 months. The main safety outcomes were infections and infection-related hospitalizations. Cox proportional hazards models were used to compare the incidence of the primary and secondary endpoints across treatment groups. AAD use after 6 months was analyzed using a generalized linear model with binomial distribution and logit-link function. All hsCRP levels were log-transformed and analyzed using a linear model with baseline hsCRP levels as covariate. Statistical analyses were performed using R 3.2.2.

Eleven and 13 patients were randomized to canakinumab and placebo, respectively. Mean overall age was 66 years, 24% were women (Table S1). AF recurrence at 6 months occurred in 10 (77%) and 4 (36%) patients in the placebo and canakinumab groups, respectively (Figure), the hazard ratio (HR) (95% confidence interval (CI)) being 0.36 (0.11, 1.15; p=0.09). At 1 month AF recurred in 6 (46%) and 4 (36%) patients, at 3 months in 8 (62%) and 4 (36%) patients, respectively. The HRs (95% CIs) for time-to-first redo-ECV and hospitalization-free survival were 0.29 (0.03, 2.57; p=0.27) and 0.74 (0.12, 4.46; p=0.75), respectively. AADs at 6 months were used in 7 (54%) and 9 (82%) patients in the placebo and canakinumab group, respectively (odds ratio (95% CI) 3.86 (0.65, 32.36; p=0.16)) (Figure). Log-transformed hsCRP was 31% lower in the canakinumab group (95% CI -67, 40; p=0.27) at 6 months. Adverse events occurred in 3 (23%) and 3 (27%) patients in the placebo and canakinumab group, respectively (Table S2). Infections occurred in 2 (15%) and 2

(18%) patients in the placebo and canakinumab group, respectively. There was one infection-related hospital admission in the canakinumab group (supplementary appendix), and none in the placebo group.

Prior studies found a strong relationship of inflammatory biomarkers with incident AF. Patients with persistent AF had higher inflammatory biomarker levels than patients with paroxysmal AF, suggesting that anti-inflammatory treatment may be particularly effective in these patients.[2,4] Accordingly, a previous study using glucocorticoids showed a reduction in AF recurrence after cardioversion.[5] Recently, specific inflammatory pathways including the NLRP3 (NOD-, LRR- and pyrin-domain-containing protein-3) inflammasome activation with release of interleukin-1β were involved in AF pathogenesis (see supplementary appendix for detailed description).[2] Although we found a numerically lower incidence of AF recurrence at 6 months with a non-significant trend, no significant reductions were found. We believe that these data support further studies targeting this pathway and show the clinical feasibility of canakinumab use after ECV. Larger trials are needed to definitely assess the efficacy and safety of canakinumab to reduce AF recurrences after ECV, which remains an unmet clinical need. Potential limitations of our study include the small number of patients enrolled and the lack of long-term ECG monitoring during follow-up.

In conclusion, anti-inflammatory treatment with canakinumab did not reduce AF recurrences after ECV in patients with persistent AF, although we observed a promising trend in this pilot trial.

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Disclosures

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Data statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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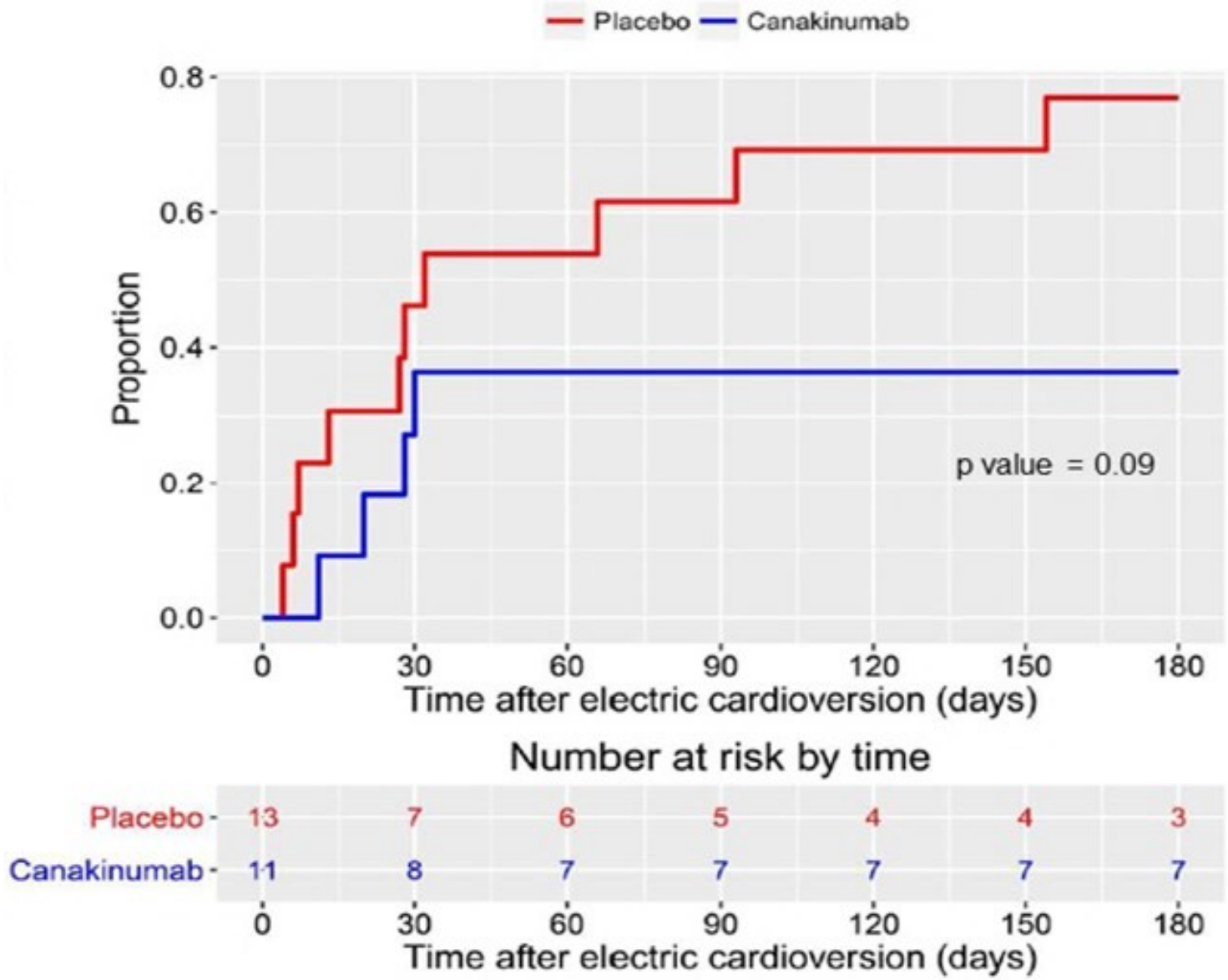
Figure legend

(A) Cumulative incidence of atrial fibrillation recurrence up to 6 months of follow-up. Y-axis indicates proportion of patients with documented atrial fibrillation recurrence. (B) Estimates for the primary and secondary outcomes. *indicates truncated upper confidence interval. AAD = anti-arrhythmic drug; AF = atrial fibrillation; CI = confidence interval; HR = hazard ratio; OR = odds ratio.



Outcome, n		Estimate (95% CI)		p-value
AF recurrence at 6 months		HR	0.36 (0.11; 1.15)	0.09
Placebo	10 (76.9)			
Canakinumab	4 (36.4)			
Time to first redo ECV		HR	0.29 (0.03; 2.57)	0.27
Placebo	4 (30.8)			
Canakinumab	1 (9.1)			
Any hospitalization		HR	0.74 (0.12; 4.46)	0.75
Placebo	3 (23.1)			
Canakinumab	2 (18.2)			
AAD use at 6 months		OR	3.86 (0.65; 32.36)	0.16
Placebo	7 (53.8)			
Canakinumab	9 (81.8)