Title: *FLOW-AF*: A Randomized Controlled Trial of Electrographic Flow-Guided Ablation in Redo Patients with Non-Paroxysmal Atrial Fibrillation

Authors
Vivek Reddy, MD; Petr Neuzil, MD, PhD; Moritoshi Funasako, MD, PhD; Anke Langbein, MD; Jan Petru, MD; Rohit Bhagwandien, MD; Sip Wijchers, MD; Leon Dinshaw, MD; Stefan G. Spitzer, MD; Andreas Rillig, MD; Melissa H. Kong, MD; Tamas Szili-Torok, MD, PhD

ABSTRACT:

Background
Electrographic Flow (EGF) mapping enables full spatiotemporal reconstruction of organized wavefront propagation, to both identify active atrial fibrillation (AF) sources and estimate the consistency of observed wavefront patterns. The dynamic detection of active extra-pulmonary vein (PV) sources offers a novel framework for phenotyping persistent AF.

Objectives
FLOW-AF is a multicenter, randomized, controlled study to evaluate if EGF mapping can 1) stratify a redo population of patients with non-paroxysmal AF by identifying extra-PV sources of AF, and 2) guide ablation of these sources.

Methods
FLOW-AF (NCT04473963) prospectively enrolled AF patients undergoing redo ablation at 4 centers. Serial EGF maps were obtained over 1-min recordings from multiple standardized basket positions in both atria. Patients with source activity ≥ 26.5% were randomized 1:1 to PVI + EGF-guided ablation *vs* control (PVI-only). If randomized to EGF-guided ablation, identified sources were ablated until below threshold. Patients with no sources > threshold were not randomized, and received standard ablation, primarily PVI-only. Clinical follow-up and EKG monitoring was performed at 3, 6 and 12 months.

Results
In total, 85 AF patients were enrolled: age 65.6±9.3 years; 37% female; mean LA diameter 4.4±0.6cm; mean AF duration 32.5±30.8 months. Thirty-four (40%) patients had no sources while 46 (60%) had at least 1 source > threshold. Patients with sources were older (62.6 v. 68.2 years, p=0.005) with higher CHA_2DS_2-VASc score (1.9 v. 2.8, p=0.001) compared with patients without sources. Primary safety endpoint (freedom from procedure-related serious adverse events at 7 days) was achieved in 97.2%. Primary efficacy endpoint was achieved with successful ablation (defined as eliminated upon post-ablation EGF-mapping) of 95% of identified sources randomized to EGF-guided ablation. Among randomized patients, freedom from AF at 12 months was 68% for EGF-guided ablation v. 17% for Control (p = 0.04); freedom from AF/AT/AFL at 12 months was 51% vs 14% (p=0.10), respectively.

Conclusions
In a difficult-to-treat redo population of non-paroxysmal AF patients: 1) EGF mapping identified sources in 60% of the cohort; and 2) PVI + source ablation improves AF free survival at 1 year v. PVI-alone. Larger studies are warranted to assess if EGF-based ablation improves freedom from AF/AT/AFL.
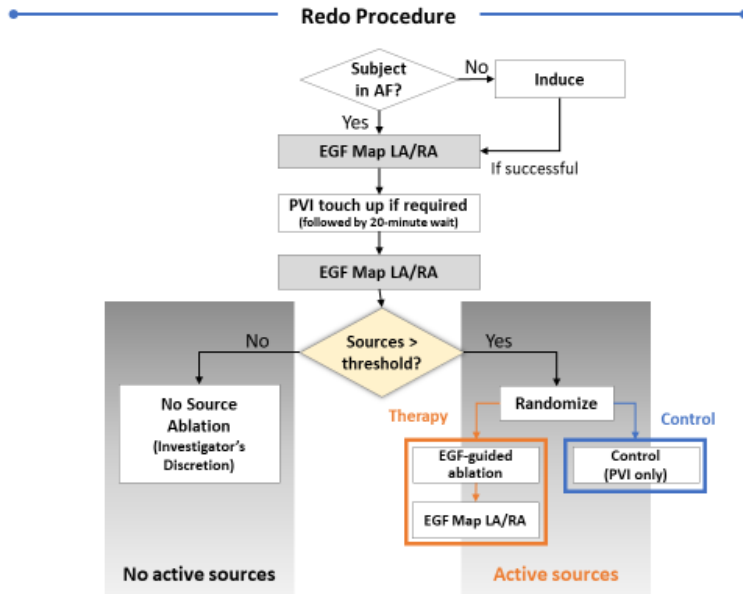
Table: Baseline Demographics for all enrolled patients (n=85)

	All (n=85)	Not Randomized (n=34)	Randomized (n=46)	P-value*
Female sex, n (%)	31/85 (36.5%)	10/34 (29.4%)	18/46 (39.1%)	0.368
Age (years), mean±SD	65.6 ± 9.3	62.6 ± 7.3	68.2 ± 10.0	0.005
Body mass index (kg/m2), mean±SD	29.1 ± 4.6	30.3 ± 4.2	28.3 ± 4.8	0.051
Left atrial diameter (cm), mean±SD	4.4 ± 0.6	4.4 ± 0.5	4.5 ± 0.6	0.681
Left ventricular ejection fraction (%) mean±SD	57.2 ± 6.4	56.2 ± 6.8	57.2 ± 5.9	0.508
AF duration (months), mean±SD	32.5 ± 30.8	29.3 ± 22.7	36.5 ± 36.7	0.297
Number of failed AADs (n), mean±SD	1.0 ± 0.7	1.1 ± 0.6	1.0 ± 0.8	0.721
History of atrial flutter, n(%)	15/85 (17.6%)	5/34 (14.7%)	10/46 (21.7%)	0.426
History of congestive heart failure, n (%)	6/85 (7.1%)	2/34 (5.9%)	4/46 (8.7%)	0.637
Hypertension, n (%)	63/85 (74.1%)	24/34 (70.6%)	36/46 (78.3%)	0.433
Diabetes mellitus, n (%)	15/85 (17.6%)	6/34 (17.6%)	8/46 (17.4%)	0.976
Prior stroke/transient ischemic attack, n (%)	4/85 (4.7%)	1/34 (2.9%)	3/46 (6.5%)	0.468
Coronary artery disease, n (%)	14/85 (16.5%)	5/34 (14.7%)	9/46 (19.6%)	0.572
Previous myocardial infarction, n (%)	0/85 (0.0%)	0/34 (0.0%)	0/46 (0.0%)	N/A
Dyslipidemia	16/85 (18.8%)	2/34 (5.9%)	11/46 (23.9%)	0.031
Peripheral Vascular Disease	6/85 (7.1%)	3/34 (8.8%)	3/46 (6.5%)	0.699
CHA_2DS_2-VASc score, mean±SD	2.4 ± 1.3	1.9 ± 1.0	2.8 ± 1.4	0.001
CAAP-AF score, mean±SD	7.1 ± 1.3	6.9 ± 1.2	7.2 ± 1.3	0.176

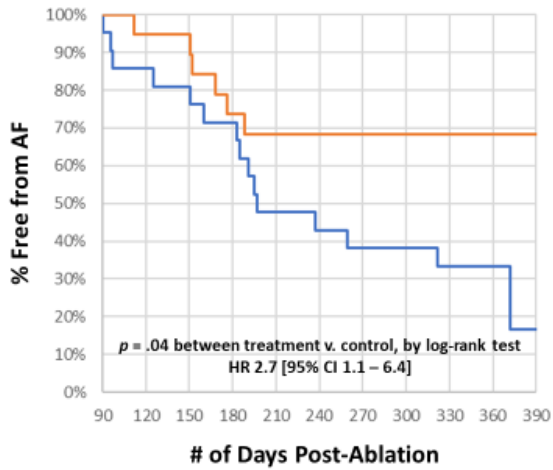*P-value from two-sided two-sample t-test for continuous variables and Chi-squared test for proportions.

Figure

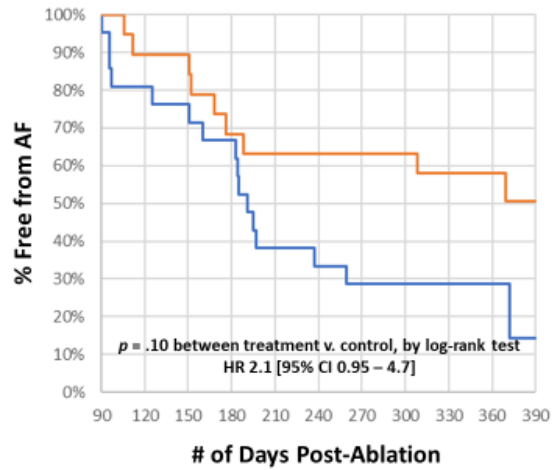## *FLOW-AF* Randomized Controlled Trial Design

Redo Procedure

Subject in AF? — No → Induce

Yes ↓

EGF Map LA/RA ← If successful

PVI touch up if required
(followed by 20-minute wait)

EGF Map LA/RA

Sources > threshold?

No → No Source Ablation (Investigator's Discretion)

Yes → Randomize

Therapy → EGF-guided ablation → EGF Map LA/RA

Control → Control (PVI only)

No active sources | Active sources

12-Month Freedom from AF for EGF-Guided Ablation v. Control (PVI-only)

A. Kaplan-Meier Plot for Freedom from AF

p = .04 between treatment v. control, by log-rank test
HR 2.7 [95% CI 1.1 – 6.4]

% Free from AF

# of Days Post-Ablation

B. Kaplan-Meier Plot for Freedom from AF/AT/AFL

p = .10 between treatment v. control, by log-rank test
HR 2.1 [95% CI 0.95 – 4.7]

% Free from AF

# of Days Post-Ablation

—— Control (PVI-only)   —— EGF-Guided Treatment