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The Current Landscape of Atrial Fibrillation and Atrial Flutter Clinical Trials

A Report of 348 Studies Registered With ClinicalTrials.gov

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ABSTRACT

OBJECTIVES This analysis sought to systematically characterize trial-level patterns in atrial fibrillation/atrial flutter (AF/AFL) by using the ClinicalTrials.gov database.

BACKGROUND Despite an abundance of clinical trials in this field, there is a lack of high-level evidence guiding management of AF/AFL.

METHODS We queried all closed, phase II to IV interventional trials registered in the ClinicalTrials.gov database through October 2016 that enrolled patients known to have AF/AFL. Published trials were evaluated for methodological quality, using the 3-item Jadad scale (range: 0 to 5, where 5 = highest quality).

RESULTS The initial search yielded 465 uniquely registered studies, of which 348 directly studied AF/AFL. Of those studies, 173 (50%) were published, enrolling a median of 190 patients from a median of 15 sites. The volume of published trials increased over time (7% prior to 2008 vs. 41% from 2014 to 2016; $p < 0.001$ for trend). Of the completed trials, 29% remain unpublished. Industry sources accounted for most funding (54%). Recurrence of AF/AFL was the most common endpoint (45%), whereas rates of primary clinical endpoints were low (13%). The mean Jadad score of published trials of pharmacological approaches ($n = 112$) was 4.0 ± 1.4. Of the 61 AF/AFL trials involving ablation or device therapies, 69% were randomized, 28% were single-arm studies, and patient, proceduralist, and event-ascertainment blinding was used in 16%, 4%, and 44%, respectively.

CONCLUSIONS Contemporary trials of AF/AFL are often multicenter and modest in size. The primary study endpoint is commonly recurrence of arrhythmia, even in high-quality and late-phase trials. Although methodological quality is high in trials of pharmacologic approaches, trials of AF/AFL ablation and device therapies variably employ randomization and blinding. (J Am Coll Cardiol EP 2018;■:■–■) © 2018 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF/AFL = atrial fibrillation/atrial flutter

LOE = level of evidence

QOL = quality of life

NME = new molecular entities

Atrial fibrillation/atrial flutter (AF/AFL) has evolved into a global epidemic, affecting more than 30 million individuals worldwide (1). Although the overall prevalence of AF/AFL is estimated to be 1%, its burden in older patients ranges from 5% to 9%, and its incidence is expected to double by 2030 (1-3). Furthermore, despite effective preventive therapies against stroke and systemic embolism, nearly half of all deaths in AF/AFL remain cardiovascular in nature (4-6). Although a number of AF/AFL devices and ablation are used in clinical practice, the quality of evidence supporting their use is uncertain. Recognition of the clinical and economic burden of AF/AFL has fueled research interest in management of this condition. Despite this growth in trial-level data, an analysis of the American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines of AF/AFL management revealed that 1) level of evidence (LOE) A accounted for a minority of all recommendations in the latest guidelines (7), and 2) the number of LOE A recommendations has not increased over a 13-year timespan (8).

There is limited understanding of the major factors that drive the lack of changes in these guidelines, including variability in study quality, inadequate blinding, lack of validated endpoints, and issues with publication and data transparency. Furthermore, whether similar adverse trends are apparent in the regulatory space with respect to new drugs and devices approved for clinical use is unclear. As such, we aimed to: 1) summarize contemporary trial-level patterns in AF/AFL by using publicly available data from the ClinicalTrials.gov registry; 2) systematically evaluate the methodological quality of these trials; and 3) identify AF/AFL drugs and devices recently approved by the U.S. Food and Drug Administration (FDA).

METHODS

ClinicalTrials.gov SEARCH STRATEGY. We identified uniquely registered AF/AFL studies updated prior to October 10, 2016 in the ClinicalTrials.gov database by using the following limits to the primary search strategy: interventional study design, closed enrollment, adult/senior population (≥18 years of age), and trial phases (II to IV). The terms "atrial fibrillation" and "atrial flutter" were searched as separate queries, and duplicate entries were subsequently deleted.

PUBLISHED REPORTS AND DATA EXTRACTION. Full-text publications of these studies were then identified by searching the title, principle investigator, and ClinicalTrials.gov unique identifier in PubMed and MEDLINE in duplicate by 2 independent authors (R.V.V. and A.S.). Trials were included if enrollment criteria required previously diagnosed AF/AFL. When available, the following data were abstracted from the full text of published trials: number of patients per trial, number of sites per trial, region of enrollment, year of publication, AF category of study, type of primary endpoint, and method of AF/AFL detection (only if AF/AFL recurrence or AF/AFL burden was a primary endpoint). Data regarding study design (phase of trial, patient allocation, presence of parallel study arm, blinding strategy, Data and Safety Monitoring Board oversight) were initially abstracted from ClinicalTrials.gov and subsequently verified in all full-text publications. Primary endpoints were classified as clinical (mortality, hospitalization, stroke/systemic embolism, myocardial infarction), intermediate (functional status, quality of life [QOL], length of hospital stay), safety, or surrogate. In the case of co-primary endpoints, both endpoints were tabulated. In addition, information regarding study design was abstracted from ClinicalTrials.gov for all studies that were identified as completed but unpublished as of October 10, 2016 (date of ClinicalTrials.gov query).

(Editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); and has served as site co-investigator for Biotronik, Boston Scientific, St. Jude Medical; and is a trustee of American College of Cardiology; and has received unfunded research support from FlowCo, PLx Pharma, and Takeda. Dr. Fonarow has relationships with, Novartis, Amgen, Bayer, Gambro, Medtronic, and Janssen; and holds the Eliot Corday Chair of Cardiovascular Medicine, UCLA, and is supported by the Ahmanson Foundation, Los Angeles, CA. Dr. Passman has received consulting/speaker fees for Medtronic and Biotronik and royalties from UpToDate. Dr. Javed Butler has received research support from U.S. National Institutes of Health and European Union; and has consulted for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CVRx, Janssen, Luitpold Pharmaceuticals, Medtronic, Merck, Novartis, Relypsa, Vifor Pharma, and ZS Pharma. Dr. Vaduganathan is supported by the U.S. National Heart Lung Blood Institute T32 postdoctoral training grant T32HL007604. All other authors have reported that they have no other relationships with industry relevant to the contents of this paper to disclose.

All authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Clinical Electrophysiology* author instructions page.

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