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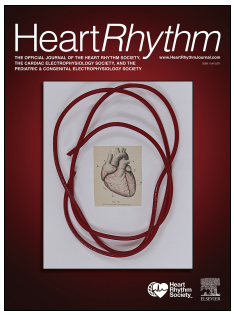

Flecainide use before and after CAST: A systematic review

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Flecainide use before and after CAST: A systematic review

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The 1989 Cardiac Arrhythmia Suppression Trial (CAST) remains a defining moment in modern cardiology. It dismantled the hypothesis that arrhythmia suppression was synonymous with improved survival after it demonstrated that ventricular ectopy suppression with class IC antiarrhythmics, including flecainide, paradoxically increased mortality in patients with prior myocardial infarction (MI).[1] Since then, flecainide acetate has evolved from a broad-spectrum suppressor of ventricular ectopy to a targeted therapy for atrial fibrillation (AF) and inherited arrhythmia syndromes in structurally normal hearts.[2] While the clinical implications of CAST are well-known, the extent to which this landmark trial reshaped the research landscape itself has not been quantified. We performed a systematic review of 60 years of literature to describe this evolution.

A literature search was conducted in Web of Science, MEDLINE, EMBASE, and CINAHL electronic databases for English-language human studies (minimum of 5 patients) involving flecainide published between January 1965 and June 2025. Data were extracted on study design, population demographics, indications, dosing regimens, and adverse events. Studies were stratified into pre-CAST (≤1989) and post-CAST (>1989) eras (Figure 1). Of 7,518 studies identified, 453 met inclusion criteria, encompassing 1,472,310 patients (8,322 pre-CAST; 1,463,988 post-CAST).

The primary finding of this review is a decisive change in study indications. In the post-CAST era, studies investigating flecainide use in AF increased four-fold from 11.6% pre-CAST to 49.6% ($p<0.001$). Conversely, ventricular tachycardia-focused studies fell sharply (23.3% to 5.6%; $p<0.001$), and investigations in post-MI cohorts declined (6.2% to 1.2%; $p=0.006$). This realignment reflects the acceptance of the fundamental CAST findings: that the combination of sodium channel blockade and ischemic substrate facilitates malignant re-entrant ventricular arrhythmias. Consequently, modern guidelines strictly reserve flecainide for rhythm control in patients without structural heart disease or ischemic pathology, aligning with the mortality risks established by the CAST investigators and recently reappraised by Echt.[2, 3]

A diversification in study populations was also observed. Pre-CAST studies were overwhelmingly adult-focused (92.6%). Pediatric cohort studies increased post-CAST (7.4% to 11.2%; $p=0.009$), and fetal cohort studies only appeared after CAST publication (4.1% of post-CAST studies). Furthermore, studies involving genetic arrhythmia syndromes—specifically Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and Long QT Syndrome (LQTS)—appeared exclusively after 1989. Among these, CPVT has generated the largest body of evidence, consistently demonstrating that flecainide reduces exercise-induced ventricular arrhythmias when used adjunctively with beta-blockers.[4] Similarly, arrhythmogenic cardiomyopathy may represent an evolving rare exception to the restriction of class IC

agents to structurally normal hearts, with growing evidence supporting the safety and efficacy of flecainide combined with beta-blockers in this population.[5]

By publication geography, Europe contributed the largest share of studies overall and increased its proportion post-CAST (53.9% to 63.2%; p<0.001), while North America decreased (40.6% to 19.7%; p<0.001). This shift was accompanied by a sustained interest in intravenous dosing regimens in Europe that virtually disappeared from North American practice.

Methodologically, prospective interventional study designs predominated overall (44.8%) but declined post-CAST (74.4% to 33.0%; p<0.001). Prospective observational studies increased after 1989 (7.0% to 16.0%; p=0.01). Notably, the proportion of randomized controlled trials (RCTs) remained remarkably stable (13.2% pre-CAST vs 15.1% post-CAST; p=0.61) (Figure 1).

Safety reporting patterns persisted across eras, with life-threatening adverse events reported in 29.6% of pre-CAST and 21.5% of post-CAST studies (p=0.089). However, interpreting these rates requires caution to avoid false equivalence. Pre-CAST studies typically enrolled high-risk, post-MI populations where proarrhythmia and sudden death were primary mortality drivers. Conversely, post-CAST studies largely involved lower-risk AF populations with structurally normal hearts, where adverse events are less common. The fact that adverse event reporting remained prominent in the modern era despite the shift to lower-risk populations likely reflects evolved standards in clinical research that now prioritize rigorous safety monitoring and adjudication compared to the 1980s.

This study has limitations. First, as a bibliometric analysis, it treats each study as an equivalent statistical unit regardless of sample size or design quality; thus, a small retrospective series carries the same weight as a large RCT in frequency analyses. There is also a substantial lack of uniformity in what was studied and how it was reported across decades, and a substantial number of studies were missing data thus limiting precision. Second, the post-CAST era spans 35 years compared to the 10-year pre-CAST period, creating an unavoidable era imbalance. Finally, geography was assigned by senior author affiliation, which may misclassify multi-national trials.

In conclusion, the publication of CAST fundamentally redirected the trajectory of flecainide research. The field moved decisively away from ischemic and ventricular arrhythmia pathology toward atrial fibrillation and niche pediatric and genetic indications. Contemporary guidelines restricting the use of class IC antiarrhythmic agents to patients without structural heart disease remain aligned with these trends, and the emergence of genetic arrhythmia indications reflects flecainide's evolving, targeted therapy role.

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None

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Figure 1 Legend

(*Left panel*) Number of flecainide studies published by year. Blue indicates before CAST, red indicates after CAST. (*Right panel*) Number of flecainide studies published by year broken down by study design.

Legend: *UNCLEAR* – studies with unclear methodology. *MIXED* – studies with both retrospective and prospective design elements. *CASE* – studies reporting detailed patient case series. *RET* – studies with retrospective design including reviews, cohort studies, and registry analyses. *PROS-O* – prospective studies without flecainide as the active intervention. *PROS-I* – prospective studies with flecainide as the active intervention that do not include randomization. *RCT* – randomized control trial study design.