Structural Heart

The Journal of the Heart Team

ISSN: 2474-8706 (Print) 2474-8714 (Online) Journal homepage: https://www.tandfonline.com/loi/ushj20

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To cite this article: Ioanna Kosmidou, Shmuel Chen, Bernard J. Gersh & Ori Ben-Yehuda (2019) Arrhythmia Endpoints in Interventional Cardiovascular Trials: A Missed Opportunity?, Structural Heart, 3:1, 20-23, DOI: 10.1080/24748706.2018.1536837

To link to this article: https://doi.org/10.1080/24748706.2018.1536837

Accepted author version posted online: 16 Oct 2018.
Published online: 25 Oct 2018.

STRUCTURAL HEART
2019, VOL. 3, NO. 1, 20–23
https://doi.org/10.1080/24748706.2018.1536837

OPINION

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Arrhythmia Endpoints in Interventional Cardiovascular Trials: A Missed Opportunity?

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Introduction

Randomized clinical trials are the cornerstone of the collective process evaluating novel technologic and pharmacologic discoveries. The commercial availability of breakthrough therapies is contingent upon the demonstration of an acceptable product safety and efficacy profile commensurate with the stringent regulatory approval process; this, in turn, has led to an explosive increase in randomized clinical trials that often enroll thousands of patients followed clinically for a number of years.[1] As a result, patient outcomes have improved dramatically over the past two decades, due in part to the rapid and safe implementation of life-saving therapeutic modalities through the well-orchestrated collaboration between innovators, industry, academia, and community physicians.[2] Nevertheless, one byproduct of this phenomenon has been the ever increasing specialization, which has inadvertently resulted in selective capture of clinical outcomes largely according to the investigators' expertise and the narrow scope or budget limitations of a regulatory-driven clinical investigation. Clinical trials in the field of interventional cardiology have focused on a restrictive number of clinical outcomes, such as death, myocardial infarction, reintervention, neurologic outcomes, and bleeding,[3–5] whereas capture and adjudication of arrhythmic events or arrhythmia-related hospitalization is notably absent.[6] Although electrocardiographic core laboratories are commonly employed in interventional cardiology trials, as end points (i.e. STEMI) optimally include electrocardiographic confirmation, core laboratory assessments have frequently omitted detailed rhythm analysis. In contrast, recent guidelines on endpoint assessment in aortic or mitral valve disease trials have included arrhythmic events and conduction system disturbances,[7–9] although these remain largely underreported. Arguably, this is an area that, once improved upon, could have a dramatic impact on our understanding of important disease processes that are either highly prevalent or associated with increased mortality and morbidity,[10] such as atrial fibrillation in surgically or percutaneously treated structural heart disease (SHD) or sudden cardiac death (SCD) and ventricular arrhythmias in the setting of SHD or ischemic heart disease (IHD). In the present review, we highlight the current status and future prospect of arrhythmic endpoint assessment in interventional cardiology trials.

Ischemic heart disease

Cardiovascular diseases are responsible for more than 17 million deaths every year in the world; of those, approximately 25% are identified as SCD,[11] and over half of SCDs are due to tachyarrhythmic mechanisms.[12] Causes of SCD vary with age,[10] but chronic degenerative diseases predominate in the older population, and while approximately 50% of cardiac arrests occur in individuals with previously identified cardiac disease, most suffer from concealed IHD.[13] Nevertheless, despite extensive research, the leading indicator consistently associated with the risk of SCD is left ventricular ejection fraction,[14] a frequently inaccurate and not consistently reproducible measure. Several other potential markers of risk for SCD, such as late potentials, T-wave alternans, and QT interval dispersion have not influenced clinical practice. Similarly, there are no specific clinical predictors differentiating between two modes of cardiac death, namely SCD or non-SCD.[15] As such, given their typically large sample size, interventional cardiology trials are a potentially useful source of risk stratification data for SCD, and although inclusion of specific monitoring parameters are too costly for entry into standard IHD trial protocols, well-described definitions of arrhythmic events and expert review by specialized committees might allow for the generation of improved risk stratification models of arrhythmic or SCD. To date, most trial protocols have largely included standardized definitions of death, assessing a cardiovascular versus non-cardiovascular origin without further discrimination. The recently implemented Academic Research Consortium definition of death has allowed capture of SCD,[5] but unless detailed identification of the cause of death is necessitated by the trial protocol and associated with a requirement for detailed documentation by the sites and clinical event committees, important information regarding the occurrence of an arrhythmic event is frequently not collected. This might be attributed to the expense involved in detailed data capture and adjudication of death, which frequently occurs out of hospital. Similarly, unless a specific approach to identification and categorization of SCD is implemented at the trial onset and included in the trial case report form, data on attendant arrhythmias will not be documented. Furthermore, significant discrepancies in investigator-reported versus adjudicated sudden death have been noted[16]; this currently limits the usefulness of large meta-analyses,

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despite the fact that the combination of SCD data is likely the most useful approach to assessing this uncommon endpoint. Novel schemes of identification and detailed assessment of the mode of mortality events have been described to address this issue; however, utilization in clinical trials has been limited.[17,18]

In addition to SCD, any arrhythmic event, particularly sustained ventricular arrhythmias, is of importance in outcomes analysis and risk stratification of patients with IHD; however, despite recent efforts to signify the impact of such events,[19] most recent randomized trials capture only periprocedural tachy- and bradyarrhythmias,[20,21] largely omitting the long-term occurrence of such events and associated consequences, including device implantation, ablations, bleeding, and stroke. Subsequently, underreporting of arrhythmic events or associated hospitalizations reduces the clinician's ability to optimally implement relevant therapies in patients with IHD. Capture of arrhythmias is further limited by lack of consensus regarding clinically meaningful duration, especially as it pertains to atrial fibrillation,[22,23] and inconsistent patient reporting, which renders identification of such arrhythmias dependent on frequent clinical or electrocardiographic follow-up. Similarly, capture of conduction system abnormalities is commonly omitted, though even limited effects of an evolving cardiomyopathic substrate on the atrioventricular conduction system have adverse prognostic impact.[24] Further, outside the realm of electrophysiology-specific trials, there is surprising underutilization of data from cardiac implantable devices. These limitations can be addressed with the addition of detailed instructions on capture of arrhythmic events in relevant guidance documents, operational implementation in clinical trial protocols and utilization of data derived from cardiac implantable devices. As an example, implementation of a rigorous and detailed process for capture of atrial arrhythmic events in the EXCEL trial[25] led to important insights on the prevalence and prognostic significance of atrial fibrillation on long-term cardiovascular outcomes in patients with left main coronary artery disease,[26] indicating the need for long-term surveillance of patients with atrial fibrillation following revascularization. In contrast, review of the EXCEL trial case report forms revealed that ventricular arrhythmic events were not consistently collected following discharge from the index hospitalization, though information regarding the variable presentation of adverse events, such as left main stent thrombosis or graft occlusion would have significantly added to our current understanding of percutaneously or surgically treated left main disease. Consequently, standardization of data capture forms and addition of arrhythmic parameters of interest is critical.

Structural heart disease

SHD has been identified as the "next cardiac epidemic"[27] largely because of the strong association between valvular heart disease and aging; this, in turn, has resulted in explosive development of novel device therapies targeting SHD. Given the rigorous scientific and regulatory oversight of these therapies, the established association between SHD-related arrhythmias and adverse outcomes,[28–30] and the varying degrees of insult on the conduction system incurred during surgical or percutaneous valve implantations,[31] arrhythmic endpoints have been incorporated in SHD trials more consistently compared with IHD trials. However, examination of the case report forms of the PARTNER I and II trials revealed that while conduction disturbances and the need for permanent pacing were captured consistently, collection of major tachyarrhythmic events was limited and did not include a detailed documentation of the event. Such information could have allowed us to learn about the relative effectiveness of the treatment modality (conservative vs. transcatheter aortic valve replacement (TAVR) vs. surgical aortic valve replacement (SAVR)) on the incidence of major tachyarrhythmias in patients with relatively high prevalence of ventricular hypertrophy and SCD. Ongoing large randomized trials, such as PARTNER 3 (NCT02675114) and EARLY TAVR (NCT03042104), include arrhythmic endpoints in their respective protocols and are expected to provide significant insight into the short- and long-term incidence and impact of electrophysiological disturbances in patients with SHD. Similarly, investigations of device therapies for structural or functional abnormalities that may halt or reverse deterioration of a cardiomyopathic process —such as ventricular assist devices or implants for mitral valve disease—may provide ample evidence on the temporal relationship between cardiomyopathy and arrhythmias. Trials addressing valvular abnormalities in the setting of cardiomyopathy, such as COAPT (NCT01626079), include rehospitalization for heart failure or cardiovascular rehospitalization as efficacy endpoints; given the frequent association between arrhythmia development and rehospitalization, specific consideration should be given to inclusion of such events in trial protocols. A similar focus on device therapies is anticipated in patients with heart failure with preserved ejection fraction, and identification of arrhythmic events will play a prominent role in defining long-term outcomes.

Despite increasing awareness of the clinical significance of arrhythmic events in SHD, known limitations to accurate data capture still hinder the ability to accurately define the incidence and impact of arrhythmic phenomena. In this instance, utilization of monitoring data available via cardiac implantable devices or short-term monitoring devices may provide additional information regarding electrophysiological events. Implantable loop recorders may be of particular use in patients with unknown propensity to arrhythmia recurrence or at high risk for significant conduction abnormalities.[32,33] Careful review of monitoring data should not, however, diminish the role of independent review by clinicians with expertise on electrophysiological monitoring, since monitoring devices, similar to electrocardiograms, provide inaccurate arrhythmia or conduction system disease interpretations. This can be best achieved through centralized interpretation of arrhythmic events by expert physicians.

Future directions and conclusions

Interventional cardiology trials have largely underreported arrhythmic events and arrhythmia-related hospitalizations and data from cardiac implantable devices or monitoring devices. Inclusion of arrhythmic endpoints in trial protocols

and centralized review by clinical experts or specialized core labs will allow for a fruitful interaction between cardiovascular disciplines and improved insight into the interplay between structural heart disease and electrophysiologic disturbances

Disclosure statement

No potential conflicts of interest have been reported by the authors.

References

1. Krall R. *The State of Clinical Research in the United States: An Overview*. National Academies Press (US); 2010.
2. Mensah GA, Wei GS, Sorlie PD, et al. Decline in cardiovascular mortality: possible causes and implications. *Circ Res*. 2017;120 (2):366–380. doi:10.1161/CIRCRESAHA.116.309115.
3. Lansky AJ, Messe SR, Brickman AM, et al. Proposed standardized neurological endpoints for cardiovascular clinical trials: an academic research consortium initiative. *J Am Coll Cardiol*. 2017;69 (6):679–691. doi:10.1016/j.jacc.2016.11.045.
4. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123 (23):2736–2747. doi:10.1161/CIRCULATIONAHA.110.009449.
5. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation*. 2007;115(17):2344–2351. doi:10.1161/CIRCULATIONAHA.106.685313.
6. Hicks KA, Tcheng JE, Bozkurt B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association task force on clinical data standards (writing committee to develop cardiovascular endpoints data standards). *J Am Coll Cardiol*. 2015;66(4):403–469. doi:10.1016/j.jacc.2014.12.018.
7. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Am Coll Cardiol*. 2012;60(15):1438–1454. doi:10.1016/j.jacc.2012.09.001.
8. Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the mitral valve academic research consortium. *J Am Coll Cardiol*. 2015;66(3):308–321. doi:10.1016/j.jacc.2015.05.049.
9. Stone GW, Vahanian AS, Adams DH, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 1: clinical trial design principles: a consensus document from the mitral valve academic research consortium. *J Am Coll Cardiol*. 2015;66(3):278–307. doi:10.1016/j.jacc.2015.05.046.
10. John RM, Tedrow UB, Koplan BA, et al. Ventricular arrhythmias and sudden cardiac death. *Lancet*. 2012;380(9852):1520–1529. doi:10.1016/S0140-6736(12)61413-5.
11. Mendis SPPNB. *Global Atlas on Cardiovascular Disease Prevention and Control*. Geneva: World Health Organization; 2011.
12. Goldberger JJ, Cain ME, Hohnloser SH, et al. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society scientific statement on noninvasive risk stratification techniques for identifying patients at risk for sudden cardiac death: a scientific statement from the American Heart Association Council on clinical cardiology committee on electrocardiography and arrhythmias and council on epidemiology and prevention. *Circulation*. 2008;118(14):1497–1518.
13. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death. Structure, function, and time-dependence of risk. *Circulation*. 1992;85:I2–10.
14. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346(12):877–883. doi:10.1056/NEJMoa013474.
15. Every N, Hallstrom A, McDonald KM, et al. Risk of sudden versus nonsudden cardiac death in patients with coronary artery disease. *Am Heart J*. 2002;144(3):390–396.
16. Wise RA, Kowey PR, Austen G, et al. Discordance in investigator-reported and adjudicated sudden death in TIOSPIR. *ERJ Open Res*. 2017;3:1. doi:10.1183/23120541.00073-2016.
17. Boehmer JP, Carlson MD, De Marco T, et al. Adjudication of mortality events in a heart failure-arrhythmia trial by a multiparameter descriptive method: comparison with methods used in heart failure trials and methods used in arrhythmia trials. *J Interv Card Electrophysiol*. 2008;23(2):101–110. doi:10.1007/s10840-008-9277-3.
18. Epstein AE, Carlson MD, Fogoros RN, Higgins SL, Venditti FJ Jr. Classification of death in antiarrhythmia trials. *J Am Coll Cardiol*. 1996;27:433–442. doi:10.1016/0735-1097(95)00482-3.
19. Cannon CP, Brindis RG, Chaitman BR, et al. ACCF/AHA key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes and coronary artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on clinical data standards (writing committee to develop acute coronary syndromes and coronary artery disease clinical data standards). *J Am Coll Cardiol*. 2013;61(9):992–1025. doi:10.1016/j.jacc.2012.10.005.
20. Mehta RH, Starr AZ, Lopes RD, et al. Incidence of and outcomes associated with ventricular tachycardia or fibrillation in patients undergoing primary percutaneous coronary intervention. *JAMA*. 2009;301(17):1779–1789. doi:10.1001/jama.2009.600.
21. Kosmidou I, Redfors B, Dordi R, et al. Incidence, predictors, and outcomes of high-grade atrioventricular block in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the HORIZONS-AMI Trial). *Am J Cardiol*. 2017;119(9):1295–1301. doi:10.1016/j.amjcard.2017.01.019.
22. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med*. 2012;366(2):120–129. doi:10.1056/NEJMoa1105575.
23. Darkner S, Chen X, Hansen J, et al. Recurrence of arrhythmia following short-term oral AMIOdarone after CATheter ablation for atrial fibrillation: a double-blind, randomized, placebo-controlled study (AMIO-CAT trial). *Eur Heart J*. 2014;35(47):3356–3364. doi:10.1093/eurheartj/ehu354.
24. Kosmidou I, Redfors B, McAndrew T, et al. Worsening atrioventricular conduction after hospital discharge in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention: the HORIZONS-AMI trial. *Coron Artery Dis*. 2017;28(7):550–556. doi:10.1097/MCA.0000000000000525.
25. Xu B, Gao R, Yang Y, et al. Biodegradable polymer-based sirolimus-eluting stents with differing elution and absorption kinetics: the PANDA III trial. *J Am Coll Cardiol*. 2016;67 (19):2249–2258. doi:10.1016/j.jacc.2016.03.475.
26. Ioanna Kosmidou SC, Pieter Kappetein A, Serruys PW, et al. New-onset atrial fibrillation after PCI and CABG for left main disease: analysis from the EXCEL trial. *J Am Coll Cardiol*. 2017;71 (7):739–748. doi:10.1016/j.jacc.2017.12.012.
27. d'Arcy JL, Prendergast BD, Chambers JB, Ray SG, Bridgewater B. Valvular heart disease: the next cardiac epidemic. *Heart*. 2011;97 (2):91–93. doi:10.1136/hrt.2010.205096.
28. Biviano AB, Nazif T, Dizon J, et al. Atrial fibrillation is associated with increased mortality in patients undergoing transcatheter aortic valve replacement: insights from the placement of aortic transcatheter valve (PARTNER) trial. *Circ Cardiovasc Interv*. 2016;9(1): e002766. doi:10.1161/CIRCINTERVENTIONS.115.002766.
29. Regueiro A, Abdul-Jawad Altisent O, Del Trigo M, et al. Impact of new-onset left bundle branch block and periprocedural permanent pacemaker implantation on clinical outcomes in patients undergoing transcatheter aortic valve replacement: a systematic review and meta-analysis. *Circ Cardiovasc Interv*. 2016;9(5): e003635. doi:10.1161/CIRCINTERVENTIONS.115.003635.

30. Steinberg BA, Harrison JK, Frazier-Mills C, Hughes GC, Piccini JP. Cardiac conduction system disease after transcatheter aortic valve replacement. *Am Heart J*. 2012;164(5):664–671. doi:10.1016/j.ahj.2012.07.028.
31. Krasopoulos G, Falconieri F, Benedetto U, et al. European real world trans-catheter aortic valve implantation: systematic review and meta-analysis of European national registries. *J Cardiothorac Surg*. 2016;11(1):159. doi:10.1186/s13019-016-0552-6.
32. El-Chami MF, Merchant FM, Smith P, et al. Management of new-onset postoperative atrial fibrillation utilizing insertable cardiac monitor technology to observe recurrence of AF (MONITOR-AF). *Pacing Clin Electrophysiol*. 2016;39(10):1083–1089. doi:10.1111/pace.12949.
33. Jorgensen TH, Thyregod HG, Tarp JB, Svendsen JH, Sondergaard L. Temporal changes of new-onset atrial fibrillation in patients randomized to surgical or transcatheter aortic valve replacement. *Int J Cardiol*. 2017;234:16–21. doi:10.1016/j.ijcard.2017.02.098.