ISHNE Heart Failure World-Wide Internet Symposium

A Young Patient with Dilated Cardiomyopathy and Out-of-Hospital Sudden Death: From Randomized Trials and Guidelines to Real Life Patients.

Part II. Discussion: From Randomized Trials and Guidelines to Real Life Patients.

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PART II. DISCUSSION: FROM RANDOMIZED TRIALS AND GUIDELINES TO REAL LIFE PATIENTS.

Electrophysiologic evaluation after cardiac arrest?

Not very long ago, every patient surviving an episode of cardiac arrest would undergo electrophysiologic (EP) studies. During EP studies, arrhythmias were provoked by programmed ventricular stimulation. These induced arrhythmias were believed to represent the spontaneous (albeit undocumented) ventricular arrhythmia that caused the cardiac arrest. Patients with inducible arrhythmias would subsequently receive one or more antiarrhythmic medications and then undergo serial EP-studies until a therapeutic regimen suppressing the inducible arrhythmias was identified. The EP-guided therapy, i.e., the drug regimen that prevented the induction of arrhythmias or made them more hemodynamically-tolerable, was then recommended for long-term treatment (1). Indeed, 20 years ago, a large multicenter trial (the "Electrophysiologic Study Vs. Electrocardiographic Monitoring" or "ESVEM" trial) was conducted to demonstrate that EP-guided therapy is better than therapy chosen with serial Holter recordings for preventing arrhythmia recurrence (2). In fact, what ESVEM really showed was that only 40% of patients remain alive and free of arrhythmia-recurrence after 4 years of therapy, regardless of the therapeutic strategy (i.e., EP-guided or guided by serial Holter recordings). Post-hoc analyses of the ESVEM trial suggested that sotalol was the most effective drug. However, even with this medication arrhythmia recurrence was unacceptably high (3). Thus, ESVEM led to great disillusionment with EP-guided therapy or – for that matter – the use of any anti-arrhythmic drugs, with the exception of amiodarone. Since amiodarone was the only drug (available in those days) not tested in ESVEM, it remained the sole "ESVEM survivor" as a candidate for secondary prevention of ventricular tachyarrhythmias. This role for amiodarone gained support by the results of CASCADE trial (Cardiac Arrest in Seattle: Conventional Amiodarone Drug Evaluation), showing that empiric therapy with amiodarone is better than EP-guided therapy with other antiarrhythmic drugs for preventing recurrent arrhythmias among cardiac arrest survivors (4). Yet, even amiodarone failed to prevent to prevent death or arrhythmia recurrence in as many as 34% and 47% of patients by 4 and 6 years of follow-up, respectively (4). Similarly, in the Cardiac Arrhythmia Study in Hamburg (CASH) trial, amiodarone was no better than beta-blocker therapy for preventing death among cardiac arrest survivors (5). The "final nail in the coffin of EP-guided therapy" actually came from MUSTT (the Multicenter Un-Sustained Tachycardia Trial), a study evaluating the prognostic value of EP-evaluation in post-infarction patients with LVEF <40% and *non-sustained* VT (6). In MUSTT, long-term rates of arrhythmic death were actually *higher* among patients with inducible ventricular arrhythmias treated

with anti-arrhythmic medications deemed effective by EP-evaluation than among similar patients who were left untreated despite of having inducible arrhythmias at the EP-study (6).

When the ICD became available some 20 years ago, this device was initially reserved for cardiac arrest survivors for whom an “effective” antiarrhythmic therapy could not be identified with repeated EP-studies. Yet, physicians soon realized that the devices were very successful in preventing arrhythmic death and began recommending ICD implantation *instead of* EP-guided therapy for cardiac arrest survivors. As a result, fewer and fewer cardiac arrest survivors underwent EP-studies as part of their diagnostic work-up. As a matter of fact, ICD implantation for cardiac arrest survivors became common-practice even before prospective randomized trials (i.e., AVID and CIDS) (7,8) demonstrated the superiority of ICDs (in comparison to amiodarone or EP-guided sotalol) in prolonging long-term survival after cardiac arrest.

In the ICD era, there is little role for EP-evaluation of cardiac arrest survivors. This is because of the following: 1) Patients with inducible arrhythmias that are easy to cure with radiofrequency ablation (like patients with bundle branch reentry VT) usually have additional inducible arrhythmias (less amenable to catheter ablation), and are therefore likely to receive an ICD regardless of the radiofrequency-ablation results. 2) Inducing VT to select the ICD antitachycardia-pacing parameters that are more likely to terminate spontaneous VT with overdrive pacing (instead of painful shocks), is no longer advocated. This is because selection of “standard” antitachycardia-pacing parameters works just as well during long-term follow-up (9). 3) Even negative EP-studies are of questionable significance for cardiac arrest survivors. This is because roughly one third of patients presenting with cardiac arrest have no inducible arrhythmias; yet, the prognostic value of this finding is highly controversial (10). 4) Supraventricular tachyarrhythmias are the most common reason for inappropriate ICD shocks after device implantation. Thus, performance of EP-studies can be recommended to identify and treat such arrhythmias (with radiofrequency ablation) before ICD implantation. However, such supraventricular tachycardias are inducible in less than 10% of cardiac arrest survivors (10).

For all of aforementioned reasons, most electrophysiologists now reserve EP-studies for cardiac arrest survivors who have no organic heart disease, mainly to identify the very rare patient who had cardiac arrest due to a curable supraventricular arrhythmia (11) and we would argue that it is worth identifying patients with idiopathic VF or Brugada syndrome who may benefit from quinidine therapy (12,13).

Our patient has dilated cardiomyopathy and therefore is very unlikely to benefit from EP-studies. Therapeutic decisions can be taken without subjecting him to EP-evaluation.

ICD implantation or "amiodarone and hope for the best"?

"Cardiac arrest due to VF or VT, which is not due to a transient or reversible causes" is a "class I indication" for ICD implantation according to AHA/ACC/NASPE guidelines (14). Our patient presented with VF in the setting of dilated cardiomyopathy and therefore has a class I indication for ICD implantation. Nonetheless, in regard to the applicability of this indication to the case at hand, it is noteworthy that the survival benefit derived from ICDs differs in the settings of primary vs. secondary prevention of cardiac arrest (15). In fact, compared with medical management, the absolute survival benefit afforded by an ICD is *smaller* among patients with AVID-indications (7) (i.e., secondary prevention) than among patients with MADIT-I indications (16) (i.e., primary prevention in patients with ischemic cardiomyopathy). In other words, patients receiving an ICD for *prevention of recurrence* after they already experienced one episode of sustained VT or VF derive less benefit (in terms of actual survival) than patients who receive a prophylactic ICD for having old infarction, impaired left ventricular function and inducible VT (17). It is also noteworthy that our patient is young, has relatively well-preserved left ventricular function (estimated LVEF 40%) and has no clinical evidence of heart failure. Post-hoc analyses of randomized ICD trials suggest that the survival of patients with such characteristics is similar when either ICD implantation or a combination of amiodarone and beta-blockers are used (15,18). Thus, while current practice guidelines strongly endorse ICD therapy in this case (14), abundant published data sheds doubts on its superiority over optimal medical therapy (15,18).

Two additional points must be taken into consideration. The first is the concept of "competing risks." The ideal candidate for ICD implantation is the patient at high risk for arrhythmic death whose concomitant risk of death *from other causes* is low. In contrast, patients with severe cardiac or non-cardiac illness will derive less benefit from ICD implantation *regardless of their arrhythmic risk* because they are likely to die soon from non-arrhythmic causes. Notwithstanding the tremendous improvement in long-term prognosis of patients with AIDS, achieved with the newer antiretroviral medications, the fact that our patient has HIV-infection ought to be counted as a "competing risk." The second point is the issue of compliance with medications. One could argue that in view of the poor compliance with HIV-medications, this patient is likely to discontinue amiodarone. However, using the same argument, it is clear that a poor compliance with HIV-medications will affect his prognosis adversely even if an ICD is implanted. Following a lengthy debate, ICD therapy was recommended.

Which ICD: A single chamber, double chamber or biventricular device?

The patient has dilated cardiomyopathy but has *no* clinical evidence of heart failure, has a relatively preserved left ventricular function (LVEF 40%), and his QRS complex is not very wide. Therefore, the data from randomized trials demonstrating that cardiac resynchronization therapy (CRT) with biventricular pacing improves functional capacity and survival (19,20) are not relevant for him. Given the relatively preserved LVEF, this patient would not even be eligible for enrollment in ongoing trials examining the role of CRT in preventing clinical heart failure (e.g., the MADIT-CRT trial) (21). Therefore, CRT was not considered in this case and the options are ICD with single-chamber or double-chamber pacing capabilities.

Our patient has a sinus rate of 72 beats/min, a normal PR interval and a slightly prolonged (114 msec) QRS complex. Since these parameters were recorded during therapy with carvedilol and amiodarone, and considering that amiodarone will be discontinued after ICD implantation, it is reasonable to assume that our patient will not require atrial or atrio-ventricular pacing in the near future. There is sufficient evidence that unnecessary right ventricular pacing should be avoided because it leads to over heart failure in many patients. In a randomized study, patients with dual-chamber defibrillators were hospitalized for heart failure more frequently than similar patients with single chamber (VVI) defibrillators (22). Therefore we opted for implanting an ICD with single chamber (VVI) pacing capabilities. A Medtronic Marquis VR (Model 7230Cx) was implanted and the lower rate limit was programmed to 40 beats/min to avoid pacing. The pacing and defibrillation thresholds were good and the peri-procedural course was uneventful. The patient was discharged several days later with the non-cardiac therapeutic regimen mentioned above, with only carvedilol and aspirin given for cardiac indications.

Three months later, the patient was found dead in his home. His body was found seated in the leaving room in front of the television. The television was still on.

Part III to follow: What went wrong?

References.

1. Ruskin JN, DiMarco JP, Garan H. Out-of-hospital cardiac arrest: electrophysiologic observations and selection of long-term antiarrhythmic therapy. N Engl J Med 1980;303:607-13.
2. Mason JW. The ESVEM investigators. A comparison of electrophysiologic testing with Holter monitoring to predict arrhythmic drug efficacy for ventricular tachyarrhythmias. N Engl J Med 1993;329:445-451.
3. Mason JW. A comparison of seven antiarrhythmic drugs in patients with ventricular tachyarrhythmias. Electrophysiologic Study versus Electrocardiographic Monitoring Investigators. N Engl J Med 1993;329:452-8.
4. Greene HL. The CASCADE Study: randomized antiarrhythmic drug therapy in survivors of cardiac arrest in Seattle. CASCADE Investigators. Am J Cardiol 1993;72:70F-74F.
5. Cappato R. Secondary prevention of sudden death: the Dutch study, the Antiarrhythmics Versus Implantable Defibrillator trial, the Cardiac Arrest Study Hamburg, and the Canadian Implantable Defibrillator Study. Am J Cardiol 1999;83:68D-73D.
6. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. for the Multicenter Unsustained Tachycardia Trial investigators. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999;341:1882-1890.
7. The Antiarrhythmic Versus Implantable Defibrillators (AVID) Investigators. The Antiarrhythmic Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 1997;337:1576-1583.
8. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297-302.
9. Schaumann A, von zur Muhlen F, Herse B, Gonska BD, Kreuzer H. Empirical versus tested antitachycardia pacing in implantable cardioverter defibrillators: a prospective study including 200 patients. Circulation 1998;97:66-74.
10. Brodsky MA, Mitchell LB, Halperin BD, Raitt MH, Hallstrom AP. Prognostic value of baseline electrophysiology studies in patients with sustained ventricular tachyarrhythmia: the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. Am Heart J 2002;144:478-84.

11. Wang YS, Scheinman MM, Chien WW, Cohen TJ, Lesh MD, Griffin JC. Patients with supraventricular tachycardia presenting with aborted sudden death: incidence, mechanism and long-term follow-up. J Am Coll Cardiol 1991;18:1711-9.
12. Belhassen B, Glick A, Viskin S. Efficacy of quinidine in high-risk patients with Brugada syndrome. Circulation 2004;110:1731-7.
13. Belhassen B, Viskin S, Fish R, Glick A, Setbon I, Eldar M. Effects of electrophysiologic-guided therapy with Class IA antiarrhythmic drugs on the long-term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol 1999;10:1301-1312.
14. Gregoratos G, Cheitlin MD, Conill A, et al. ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices: Executive Summary-a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 1998;97:1325-1335.
15. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. Eur Heart J 2000;21:2071-8.
16. Moss AJ, Hall WJ, Cannom DS, et al. for the Multicenter Automatic Defibrillator Implantation Trial Investigators. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmias. N Engl J Med 1996;335:1933-1940.
17. Halkin A, Rosenschein U, Barron HV, Viskin S. Prevention of cardiac arrest: risk assessment after myocardial infarction. Card Electrophysiol Rev 2002;6:9-14.
18. Sheldon R, Connolly S, Krahn A, Roberts R, Gent M, Gardner M. on behalf of the CIDS investigators. Identification of patients most likely to benefit from ICD therapy: the Canadian Implantable Defibrillator Study. Circulation 2000;101:1660–1664.
19. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004;350:2140-50.
20. Cleland JG, Daubert JC, Erdmann E, et al. The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 2005;352:1539-49.
21. Moss AJ, Brown MW, Cannom DS, et al. Multicenter automatic defibrillator implantation trial-cardiac resynchronization therapy (MADIT-CRT): design and clinical protocol. Ann Noninvasive Electrocardiol 2005;10:34-43.

22. Wilkoff BL, Cook JR, Epstein AE, et al. Dual-chamber pacing or ventricular backup pacing in patients with an implantable defibrillator: the Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. Jama 2002;288:3115-23.