Can Amiodarone Prevent Sudden Cardiac Death in Patients with Hemodynamically-Tolerated Sustained Ventricular Tachycardia and Coronary Artery Disease?

Arash Arya MD, Mohammad Ali Sadr-Ameli MD, Majid Haghjoo MD, Babak Kazemi MD and Zahra Emkanjoo MD

Abstract

One of the most important challenges in today's practice of cardiology is prevention of sudden cardiac death (SCD) in high risk patients with coronary heart disease (CAD). Hemodynamically-tolerated sustained ventricular tachycardia (HTVT) comprises up to 30% of all cases of monomorphic ventricular tachycardia (MMVT) in patients with CAD. While there is a consensus on treatment of hemodynamically-unstable sustained VT in patients with CAD, some controversies regarding the proper treatment of HTVT exist. We re-examined existing clinical evidence, controversies and current guidelines on the treatment of HTVT in patients with CAD and demonstrated that compared to implantable cardioverter-defibrillators, amiodarone is not an acceptable therapeutic option in patients with ischemic heart disease who suffer from HTVT ***(Iranian Heart Journal 2006; 7 (1): 47-55)***.

Key words*:* coronary artery disease■ ventricular tachycardia■ implantable defibrillators■ amiodarone

One of the most important challenges facing cardiologists today is prevention of sudden cardiac death in high risk patients with CAD.[1] There is some evidence in favour of amiodarone's potential benefit in prevention of SCD in high-risk post-myocardial infarction (MI) patients.[2]

The development of ICDs has been a dramatic advancement in the management of patients with ventricular tachycardia (VT).

Several reviews have assessed the current evidence on the superiority of ICD in prevention of SCD in various patient populations with spontaneous sustained MMVT compared to amiodarone, which is beyond the scope of this article; and based on these studies, AHA/ACC guidelines have given ICD a class I indication with level of evidence:

B in patients with spontaneous sustained VT (irrespective of hemodynamic status during arrhythmia) in association with structural heart disease.[3, 4]

While there is a consensus on the treatment of hemodynamically-unstable sustained VT in patients with CAD, some controversies exist regarding the proper treatment of HTVT.[1, 4]

This review intends to re-examine existing

Received Apr 19, 2005; Accepted for publication Oct 1, 2005.
From the Department of Pacemaker and Electrophysiology, Shaheed Rajaie Cardiovascular Medical Center, Mellat Park, Vali-Asr Avenue, Tehran, 1996911151, Iran.
Correspondence to: Arash Arya MD, Department of Pacemaker and Electrophysiology, Shaheed Rajaie Cardiovascular Medical Center, Mellat Park, Vali-Asr Avenue, Tehran, Iran.

clinical evidence, controversies and current guidelines on the treatment of HTVT in patients with CAD.

Prevalence of MMVT and HTVT in patients with CAD and its impact on survival

Late sustained MMVT occurs in 3-5%[5] of patients after an acute myocardial infarction (MI) and has been associated with a poor prognosis (relative risk of mortality: 2.6 to 9.1 according to different studies compared to those with no VT).[41] Several studies have assessed the effect of MMVT on the survival of patients with CAD.[6-10, 41] The reported annual mortality of these patients varied from 5% (in those with EF>50%)[8] to more than 40%[9] in patients with LV dysfunction.

Newby et al.[6] have examined the incidence and impact of MMVT on the survival of 40,895 post-MI patients in the "Global Use of Streptokinase t-PA for Occluded Coronary Arteries" (GUSTO)-I trial. In GUSTO-I, the incidence of late sustained MMVT was 3.5%. The overall one-year mortality in 30-day survivors in the late VT group was 24.7% (mean EF=46%) compared to 2.7% in patients with no VT (mean EF=52%). Al-Khatib et al.[11] has recently assessed the effect of late MMVT on survival of 15,042 post-MI patients participating in GUSTO-III trial, which confirmed the above-mentioned findings of GUSTO-I. These results were confirmed also by a study on 26,416 patients with acute coronary syndrome.[12] The prevalence of late MMVT in these patients was 2.1% (lower than post-MI patients in GUSTO-I and III), but the hazard ratio (HR) was comparable (HR = 5, 95% confidence interval=3.8-6.5) to GUSTO-I and III studies, compared to patients with no VT. It is worth mentioning that in GUSTO I and III, the mortality of patients with late sustained MMVT was higher compared to patients with late VF. This is in accordance to CARE group results,[40] which showed that the probability of appropriate ICD discharge is two times higher in patients with sustained MMVT compared to those with aborted SCD and VF. A recently published guideline by the European Society of Cardiology[1] has recommended amiodarone and beta blockers as a class IIa and ICD, along with ablation and surgery, as class IIb recommendation for the treatment of patients with HTVT. The above-mentioned statement could only be accepted if one assumes that the mortality in HTVT is significantly lower than more severely symptomatic VTs and that amiodarone therapy is equal or superior to ICD with respect to prevention of SCD in these patients. HTVT comprises up to 30% of all cases of MMVT in patients with CAD.[13, 14] Several studies have examined the effect of HTVT on survival compared to more severely symptomatic VT. Although Sarter et al. have suggested a better prognosis for HTVT,[15] some debate exists on their data[16] as 64% of deaths in their study were non-sudden either due to perioperative death, recurrent infarction or progressive heart failure. Thirty-seven percent of the patients were treated with VT surgery, with a perioperative mortality of 20%. This surgery improved the outcome in patients who survived the operation and gave an inaccurate estimate of the risk of SCD in those who survived. They also found that longer VT cycle length, which one could expect to be associated with more benign symptoms, is associated with higher mortality and showed that the risk is similar to patients with more severely symptomatic VT. Raitt et al. performed a retrospective subgroup analysis of AVID registry [16] and showed that the absence of symptoms with sustained VT does not predict a benign prognosis (see below). Olson et al. assessed the predictors of SCD in 122 patients followed for an average of 19.5 months [17] and showed that the rate of SCD is not affected by presence or absence of symptoms during MMVT. Multiple VTs (including very rapid, poorly tolerated VTs) are commonly induced during electrophysiological (EP) testing in patients with stable VT.[18] Having these in mind, HTVT actually is a marker of the substrate for re-entrant VA, which may cause more

malignant VA during long-term follow-up. Based on available data, ICD therapy decreases all-cause mortality in CAD patients with sustained VT, and with respect to the above-mentioned findings, could also decrease the mortality in patients with HTVT. Patients with HTVT are at high risk for sudden arrhythmic death, and presumably it is not the recurrence of the stable VT, but a more malignant VT, that leads to SCD. Bocker et al. studied the natural course of 50 patients (82%, CAD) with HTVT who received ICD.[19] They showed that during a mean follow-up of 17 months, 33 patients (66%) had 3861 episodes of ventricular tachycardia, which is comparable to other studies on patients with sustained MMVT.[20,21,40] Ninety-one percent of these episodes were terminated by antitachycardia pacing. Eleven patients (22%) had episodes of potentially life-threatening fast VT (CL<250 ms) during the follow-up period. In the AVID registry, [16] (mean follow-up of 16.9 months) the mortality rate for patients with syncopal VT was 21.2% and for asymptomatic VT was 19.7% (P=NS). Had the ICD not been implanted in the Bocker study, their patients would have had at least the same mortality as in the AVID registry. It is worth mentioning that in Bocker's study (like Electrophysiologic Study vs. Electromagnetic Monitoring trial),[22] EP study failed to predict which patient would have more rapid VT in the follow-up. In conclusion, currently available data depict that HTVT negatively affects the survival of post-MI patients as more severely symptomatic VT does.

Role of amiodarone in the treatment of patients with Sustained VT

A: Empiric Amiodarone therapy

Secondary Prevention: Amiodarone suppresses premature ventricular depolarisations and episodes of non-sustained VT, but there have not been any placebo-controlled trials on its effectiveness on sustained VT and VF.[2] All available articles only report the outcomes of patients with resuscitated cardiac arrest or recurrent VT treated with amiodarone alone or versus other antiarrhythmic agents. Some reports conclude that amiodarone is effective, and some suggest that amiodarone is not as effective as it was shown by early promising reports. Cardiac Arrest in Seattle: Conventional versus Amiodarone Drug Evaluation study, as the only randomized clinical trial, showed that amiodarone is superior to other conventional antiarrhythmic drugs, which we know today increase cardiac mortality.[23] The largest follow-up of amiodarone-treated patients[24] (589 patients with supraventricular tachycardia, 83% of whom had VT or VF), showed that 5-year cumulative risk of sudden death was 22% and of total death, 46%. The cumulative risk of drug failure (defined as SCD, VA recurrence or drug discontinuation) at 5 years was 50%. In conclusion, it is hard to reach any definite conclusion as to the efficacy of amiodarone based on these uncontrolled reports.

Primary prevention: Two meta-analyses assessed fifteen randomized clinical trials (5864 patients), including six in post-MI patients,[25-30] which were performed on amiodarone as a prophylaxis against SCD in moderate- to-high-risk patients for SCD. The medical regimens used in "usual care" controls were not reported clearly and active control therapies included propranolol, sotalol and treatment with predominantly type I antiarrhythmic agents.[2]

Two meta-analyses[30,31] of these trials showed a 13% to 19% reduction in total mortality, but the odds ratio was different based on the control group: the odds ratio for total mortality was lower in trials with "usual care" controls (odds ratio, 0.58; 95% CI, 0.41 to 0.83; *P*=.003) and in trials with active controls (odds ratio, 0.73; 95% CI, 0.43 to 1.25; *P*=.25) than in trials with placebo controls (odds ratio, 0.90; 95% CI, 0.76 to 1.06; *P*=.20). These two meta-analyses suggested that amiodarone therapy reduces

total mortality by between 10% (placebo-controlled trials only, P=NS) and 13-19% (all trials, P=0.03 and P<0.01, respectively) in patients with moderate-to-high risk of sudden cardiac death. There has been no placebo-controlled trial so far to assess amiodarone's effect in patients with HTVT. Finally, the preliminary results of The Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) has recently been presented (March 8, 2004) by Bardly. Among patients with NYHA class II and III congestive heart failure and EF ≤ 35% (23% with history of NSVT) who were on optimum medical therapy, amiodarone (compared to placebo) did not show a beneficial effect on total mortality by intention to treat analysis (hazard ratio=1.06, 97.5% confidence interval=0.86-1.30, P=0.529).

B: EP-Guided Amiodarone therapy

Amiodarone is usually prescribed (as it is recommended by ESC taskforce on SCD) empirically. Several studies have suggested that EP-guided therapy can increase the success rate of therapy with amiodarone.[32-39] In these studies, lack of inducible VA after amiodarone therapy was associated with a better outcome. Lack of suppression of VA, increased VT cycle length and unchanged ventricular effective refractory period were all associated with higher long-term recurrence of VA and mortality. There are three major setbacks in EP-guided amiodarone therapy. First, the success rate for complete VT suppression rate during EP study varies between 10-40% in these studies. Second, there is no standard and widely accepted ventricular stimulation protocol for the assessment of its usefulness, and different protocols have been used so far. Third, it has not been tested against ICD (as the most effective treatment against arrhythmic SCD) in the above-mentioned trials. Schläpfer et al. conducted the first study aiming at a comparison between EP-guided amiodarone and ICD therapy in 84 consecutive post-MI patients with sustained MMVT.[14] Aborted SCD and syncope were clinical presentations of index arrhythmia in 40% of cases, and 77% of their patients were in NYHA class ≤ II. They showed that the outcome of the patients (including 55% with EF≥ 35%) in their study was better with ICD than EP - guided amiodarone therapy. During follow-up of 63 ± 30 months, total mortality (and SCD) was 42% (21%) in the EP-guided group and 15% (2%) in the ICD group. It is noteworthy that their data showed even *complete* suppression of VT by EP-guided amiodarone therapy was not protective against risk of future SCD (Schläpfer J: Personal communication).

C: Adjunctive Amiodarone in Patients with ICD

No empiric antiarrhythmic therapy is currently indicated in patients who have received an ICD. Up to 40% of patients receiving an ICD ultimately develop "electrical storm," defined as two or more episodes of VT and/or VF in a one day period.[51, 52] These patients frequently receive multiple ICD shocks, which severely impair quality of life. Intravenous followed by oral amiodarone results in successful management and possibly a long-term effect similar to patients who do not have electrical storm.[51, 52]

The OPTIC (Optimal Pharmacological Therapy in Implantable Cardioverter) study currently assesses the potential benefit of antiarrhythmic medications in the reduction of ICD therapy and electrical storm. In OPTIC, the patients are randomized to β-blocker, amiodarone plus β-blocker or sotalol. A sub-study of the OPTIC study will also assess defibrillation threshold before and after drug therapy in patients randomized to the above-mentioned drugs.

Although the role of amiodarone in ICD recipients is not completely clear, amiodarone may have some other potential benefits in patients with ICDs including the prevention of supraventricular tachyarrhythmias, which could cause inappropriate ICD shocks; the slowing of ventricular tachycardia, which makes the VT more hemodynamically well-

tolerated and/or more amenable to pace termination; and the prevention of non-sustained but symptomatic ventricular arrhythmias. Further studies are warranted to clarify this issue. [53]

Do the Benefits of Amiodarone (and ICD) Change Over Time?

Meta-analysis [42] of CASH, CIDS and AVID trials have shown a significant reduction in death from any cause with ICD, and a summary hazard ratio (ICD:amiodarone) of 0.72 (95% CI, 0.60 to 0.87; P: 0.0006). However, neither the CIDS nor CASH trials have demonstrated a significant benefit of ICD over amiodarone. Bokhari et al. [43] have recently published an 11-year follow-up in a subset of patients of the CIDS trial. After a mean follow-up of 5.6 ± 2.6 years in 120 patients, there were 28 deaths (47%) in the amiodarone group, compared with 16 deaths (27%) in the ICD group (P=0.0213). Total mortality was 5.5% per year in the amiodarone group versus 2.8% per year in the ICD group (hazard ratio of amiodarone: ICD, 2.011; 95% confidence interval, 1.087 to 3.721; P=0.0261).

In the amiodarone group, 49 patients (82% of all patients) had side effects related to amiodarone, of which 30 patients (50% of all patients) required discontinuation or dose reduction; and 19 patients crossed over to ICD because of amiodarone failure (n=7) or side effects (n=12).[43]

They showed that during long term follow-up, the benefit of the ICD over amiodarone increases and that most amiodarone-treated patients eventually develop side effects, have arrhythmia recurrences or die.

This finding was also confirmed recently by Salukhe et al.[44] They estimated, from published data of 8 major ICD trials, the cumulative benefit of life-years gained and calculated the dependency of the benefit on the duration of follow-up.

They found that the number of life-years gained from 1-device implantation increases with the length of follow-up. Importantly, this increase is markedly *non-linear*.

Within the 3-year span addressable, the benefit rises with the square of time (gain α $t^{1.94}$, R2=0.998, P=0.001).

They concluded that the expected benefit in life span (life-years gained) for a patient who has an ICD is dramatically dependent on the time window over which the benefit is assessed. It is important to consider the effect of follow-up duration while interpreting the results and outcome in ICD trials.[44]

Concerns have recently been raised about the role of ICD therapy in apparently stable patients with left ventricular dysfunction several years after MI.[49]

It is widely believed that among patients with CAD as the time passes from MI, the risk of SCD, and hence, the potential benefit of ICD over amiodarone is diminishing.[53-57]

Long-term follow-up of MI survivors conducted in the 1970s and 1980s indicated that the greatest risk of sudden death was in the initial 6 to 12 months after infarction, particularly in high-risk subgroups such as those with impaired ventricular function. [45–48]

Wilber and his colleagues analyzed the time dependence of mortality risk after MI in the MADIT II cohort and evaluated whether long-term survival benefit diminished as a function of elapsed time from infarction to ICD implantation.[50] They found that in contrast to early reports, mortality risk in the MADIT II cohort did not diminish as a function of time from MI; instead, it actually increased.

In addition the survival benefit associated with ICDs appears to be greater for remote MI and remains substantial for up to ≥15 years after MI.

They also found a trend toward increasing device benefit with remote MI, although it did not reach statistical significance. [50]

In conclusion, the aforementioned studies have shown that the benefit of ICD over amiodarone increases over time (Fig. 1).

This effect is observed in both primary and secondary prevention trials.

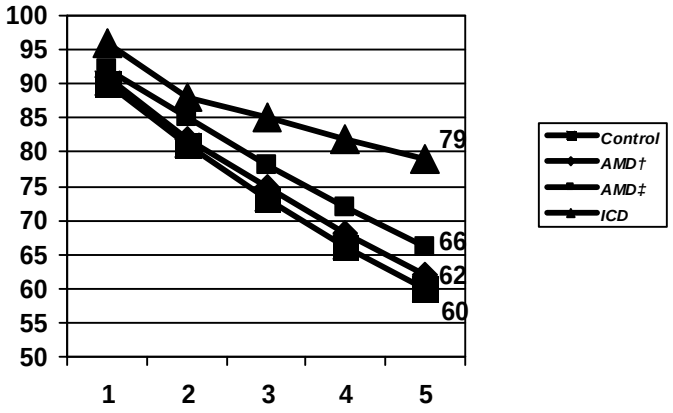

Fig. 1. Survival curves¶ during hypothetical 5 year follow up of patients with HTVT treated with ICD vs. amiodarone and control group*.

FIGURE LEGEND:
* The annual all cause mortality is assumed to be 10% in control group.
† The calculated survival is based on 10% reduction in mortality by AMD.
‡ The calculated survival is based on 20% reduction in mortality by AMD.
¶ Note that survival curves diverge dramatically after 2 years of follow up which signifies the effect of follow up duration on assessment of treatment options in these patients (see also: Do the Benefits of Amiodarone (and ICD) Change Over Time?).
AMD: Amiodarone.

Conclusion

Despite current controversies and differences in guidelines, the currently available data show that CAD patients with HTVT have a similar prognosis to more severely symptomatic VT patients and, therefore, amiodarone is not an acceptable treatment in the ICD era in these patients and that ICD is the preferred mode of treatment in this setting. Thus, we suggest that in CAD patients who have HTVT, ICD should be considered as a class IIa (level of evidence: B) treatment and that amiodarone should also be reclassified from class IIa to class IIb indication in these patients.

References

1. Priori SG, Aliot E, Lundqvist C, Bossaert L, Breithardt G, Brughada P, Camm AJ, Cappato R, Cobbe SM, Di Mario C, Maron BJ, McKenna WJ, Pedersen AK. Task Force on Sudden Cardiac Death of the European Society of Cardiology. European Heart Journal 2001; 22: 1374–1450.

2. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. Circulation 1999; 100: 2025-2034.

3. Ezekowitz JA, Armstrong PW, McAlister A. Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. Ann Intern Med 2003; 138: 445-452.

4. Gregoratos G Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV. ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices: Summary Article. Circulation 2002; 106: 2145.

5. Stevenson WG, Brugada P, Waldecker B, Zehender M, Wellens HJ. Clinical, angiographic, and electrophysiologic findings in patients with aborted sudden cardiac death as compared with patients with sustained ventricular tachycardia after myocardial infarction. Circulation 1985; 71: 1146-1152.

6. Newby KH, Thompson T, Stebbins A, Topol EJ, Califf RM, Natale A. Sustained ventricular arrhythmias in patients receiving thrombolytic therapy incidence and outcomes. Circulation 1998; 98: 2567-2573.

7. Bigger JT Jr, Fleiss JL, Rolnitzky LM. Prevalence, characteristics and significance of ventricular tachycardia detected by 24-hour continuous electrocardiographic recordings in the late hospital phase of acute myocardial infarction. Am J Cardiol 1986; 58: 1151-60.

8. Bodegas A, Arana J, Rumoroso JR, Rodrigo D, Barrenetxea JI. Prognosis of patients with a first episode of sustained monomorphic ventricular tachycardia. Int J Cardiol 1998; 65: 181-5.

9. Willems AR, Tijssen JG, Van Capelle FJ, Kingma JH, Hauer RN, Vermeulen EF, Brugada P, Van Hoogenhuyze DC, Janse MJ. Determinants of prognosis in symptomatic ventricular tachycardia or ventricular fibrillation late after myocardial infarction. The Dutch Ventricular Tachycardia Study Group of the Interuniversity Cardiology Institute of The Netherlands. J Am Coll Cardiol 1990; 16: 521-30.

10. Al-Khatib SM, Granger CB, Huang Y, Lee KL, Califf RM, Simoons ML, Armstrong PW, Van de Werf F, White HD. Sustained ventricular arrhythmias among patients with acute coronary syndromes with no st-segment elevation incidence, predictors, and outcomes. Circulation 2002; 106: 309-312.

11. Al-Khatib SM, Stebbins AL, Califf RM, Lee KL, Granger CB, White HD, Armstrong PW, Topol EJ, Ohman EM; GUSTO-III trial. Sustained ventricular arrhythmias and mortality among patients with acute myocardial infarction: results from the GUSTO-III trial. Am Heart J 2003; 145: 515-21.

12. Al-Khatib SM, Granger CB, Huang Y, Lee KL, Califf RM, Simoons ML Armstrong PW, Van de Werf F, White HD, Simes RJ, Moliterno DJ. Sustained ventricular arrhythmias among patients with acute coronary syndromes with no st-segment elevation incidence, predictors, and outcomes. Circulation 2002; 106: 309-312.

13. Raitt MH, Renfroe EG, Epstein AE, McAnulty JH, Mounsey P, Steinberg JS, Lancaster SE, Jadonath RL. "Stable" ventricular tachycardia is not a benign rhythm: insights from the antiarrhythmics versus implantable defibrillators (AVID) registry. Circulation 2001; 103: 244-252.

14. Schläpfer J, Rapp F, Kappenberger L, Fromer M. Electrophysiologically-guided amiodarone therapy versus the implantable cardioverter-defibrillator for sustained ventricular tachyarrhythmias after myocardial infarction results of long-term follow-up. J Am Coll Cardiol 2002; 39: 1813–9.

15. Sarter BH, Finkle JK, Gerszten RE, Buxton AE. What is the risk of sudden cardiac death in patients presenting with hemodynamically-stable sustained ventricular tachycardia after myocardial infarction? J Am Coll Cardiol 1996; 28: 122-129.

16. Olson PJ, Woelfel A, Simpson RJ, Foster JR. Stratification of sudden death risk in patients receiving long-term amiodarone treatment for sustained ventricular tachycardia or ventricular fibrillation. Am J Cardiol 1993; 71: 823–826.

17. Stevenson WG, Friedman PL, Kocovic D, Sager PT, Saxon LA, Pavri B. Radiofrequency catheter ablation of ventricular tachycardia after myocardial infarction. Circulation 1998; 98: 308 –314.

18. Bocker D, Block M, Isbruch F, Fastemath C, Castrucci M, Hammel D, Scheld HH, Borggrefe M, Breithardt G. Benefits of treatment with implantable cardioverter-defibrillators in patients with stable ventricular tachycardia without cardiac arrest. Br Heart J 1995; 73: 158 –163.

19. Freedberg NA, Hill JA, Fogel RI, Prystowsky EN. Recurrence of symptomatic ventricular arrhythmias in patients with implantable cardioverter defibrillator after the first device therapy implications for antiarrhythmic therapy and driving restrictions. J Am Coll Cardiol 2001; 37: 1910 –5.

20. Raitt MH, Dolack GL, Kudenchuk PJ, Poole JE, Bardy GH. Ventricular arrhythmias detected after transvenous defibrillator implantation in patients with a clinical history of only ventricular fibrillation implications for use of implantable defibrillator. Circulation 1995; 91: 1996-2001.

21. Caruso AC, Marcus FI, Hahn EA, Hartz VL, Mason JW. Predictors of arrhythmic death and cardiac arrest in the ESVEM trial: Electrophysiologic Study Versus Electromagnetic Monitoring. Circulation 1997; 96: 1888-92.

22. CASCADE Investigators: Cardiac arrest in Seattle: conventional versus amiodarone drug evaluation. Am J Cardiol 1991; 67:578–584.

23. Weinberg BA, Miles WM, Klein LS, Bolander JE, Dusman RE, Stanton MS, Heger JJ, Langefeld C, Zipes DP. Five-year follow-up of 589 patients treated with amiodarone. Am Heart J 1993; 125: 109 –120.

24. Ceremuzynski L, Kleczar E, Krzeminska-Pakula M, Kuch J, Nartowicz E, Smielak-Korombel J, Dyduszynski A, Marciejewicz J, Zaleska T, Lazarczyk-Kedzia E. Effect of amiodarone on

mortality after myocardial infarction: a double-blind, placebo-controlled, pilot study. J Am Coll Cardiol 1992; 20: 1056-62.

25. Cairns JA, Connolly SJ, Gent M, Roberts R. Post-myocardial infarction mortality in patients with ventricular premature depolarizations. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Pilot Study. Circulation 1991; 84: 550-7.

26. Hockings BE, George T, Mahrous F, Taylor RR, Hajar HA. Effectiveness of amiodarone on ventricular arrhythmias during and after acute myocardial infarction. Am J Cardiol 1987; 60: 967-70.

27. Cairns JA, Connolly SJ, Roberts R, Gent M. Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Lancet 1997; 349: 675-82.

28. Julian DG, Camm AJ, Frangin G, Janse MJ, Munoz A, Schwartz PJ, Simon P. Randomised trial of effect of amiodarone on mortality in patients with left ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. Lancet 1997; 349: 667-74.

29. Sim I, McDonald KM, Lavori PW, Norbutas CM, Hlatky MA. Quantitative overview of randomized trials of amiodarone to prevent sudden cardiac death. Circulation 1997; 96: 2823-9.

30. Amiodarone Trials Meta-Analysis Investigators: Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomized trials. Lancet 1997; 350: 1417–1424.

31. Waller TJ, Kay HR, Spielman SR, Kutalek SP, Greenspan AM, Horowitz LN. Reduction in sudden death and total mortality by antiarrhythmic therapy evaluated by electrophysiologic drug testing: criteria of efficacy in patients with sustained ventricular tachyarrhythmia. J Am Coll Cardiol 1987; 10: 83–9.

32. Horowitz LN, Greenspan AM, Spielman SR, Webb CR, Morganroth J, Rotmensch H, Sokoloff NM, Rae AP, Segal BL, Kay HR. Usefulness of electrophysiologic testing in evaluation of amiodarone therapy for sustained ventricular tachyarrhythmias associated with coronary heart disease. Am J Cardiol 1985; 55: 367–71.

33. Naccarelli GV, Fineberg NS, Zipes DP, Heger JJ, Duncan G, Prystowsky EN. Amiodarone: risk factors for recurrence of symptomatic ventricular tachycardia identified at electrophysiologic study. J Am Coll Cardiol 1985; 6: 814–21.

34. Zhu J, Haines DE, Lerman BB, DiMarco JP. Predictors of efficacy of amiodarone and characteristics of recurrence of arrhythmia in patients with sustained ventricular tachycardia and coronary artery disease. Circulation 1987; 76: 802–9.

35. Kadish AH, Buxton AE, Waxman HL, Flores B, Josephson ME, Marchlinski FE. Usefulness of electrophysiologic study to determine the clinical tolerance of arrhythmia recurrences during amiodarone therapy. J Am Coll Cardiol 1987; 10: 90–6.

36. Yazaki Y, Haffajee CI, Gold RL, Bishop RL, Alpert JS. Electrophysiologic predictors of long-term clinical outcome with amiodarone for refractory ventricular tachycardia secondary to coronary artery disease. Am J Cardiol 1987; 60:293–7.

37. Greenspan AJ, Volosin KJ, Greenberg RM, Jefferies L, Rotmensch HH. Amiodarone therapy: role of early and late electrophysiologic studies. J Am Coll Cardiol 1988; 11: 117–23.

38. Mitchell LB. The role of pharmacological therapy for ventricular tachyarrhythmias: where to go from here? In: Singer I, Barold SS, Camm AJ, (eds.) Nonpharmacological Therapy of Arrhythmias for the 21st Century: The State of the Art. Armonk, NY: Futura Publishing Co., 1998: 565–87.

39. Freedberg NA, Hill JN, Fogel RI, Prystowsky EN. Recurrence of symptomatic ventricular arrhythmias in patients with implantable cardioverter defibrillator after the first device therapy. J Am Coll Cardiol 2001; 37: 1910 –5.

40. Khairy P, Thibault B, Talajic M, et al. Prognostic significance of ventricular arrhythmia post-

myocardial infarction. Can J Cardiol 2003; 19: 1393-1404.

41. Connolly SJ, Hallstrom AP, Cappato R, Schron EB, Kuck KH, Zipes DP, Greene HL, Boczor S, Domanski M, Follmann D, Gent M, Roberts RS. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trial. Eur Heart J 2000; 21: 2071–2078.

42. Bokhari F, Newman D, Greene M, Korley V, Mangat I, Dorian P. Long-term comparison of the implantable cardioverter defibrillator versus amiodarone eleven-year follow-up of a subset of patients in the Canadian Implantable Defibrillator Study (CIDS). Circulation 2004; 110: 112-116.

43. Salukhe TV, Dimopoulos K, Sutton R, Coats AJ, Piepoli M, Francis DP. Life-years gained from defibrillator implantation markedly nonlinear increase during 3 years of follow-up and its implications. Circulation 2004; 109: 1848-1853.

44. Davis HT, DeCamilla J, Bayer LW, Moss AJ. Survivorship patterns in the post-hospital phase of myocardial infarction. Circulation 1979; 60: 1252–1258.

45. Bigger JT, Fleiss JL, Kleiger R, Miller JP, Rolnitzky LM, for the Multicenter Post-Infarction Research Group: The relationships among ventricular arrhythmias, left ventricular dysfunction, and mortality in the 2 years after myocardial infarction. Circulation 1984; 69: 250–258.

46. Mukharji J, Rude RE, Poole WK, Gustafson N, Thomas LJ Jr, Strauss HW, Jaffe AS, Muller JE, Roberts R, Raabe DS Jr. Risk factors for sudden death after acute myocardial infarction: two year follow-up. Am J Cardiol 1984; 54: 31–36.

47. Myerburg RJ, Kessler KM, Castellanos A. Sudden cardiac death: structure, function, and time-dependence of risk. Circulation 1992; 85 (suppl I): I-2–I-10.

48. Buxton AE. The clinical use of implantable cardioverter defibrillators: where are we now? Where should we go? Ann Intern Med 2003; 138: 512–514.

49. Wilber DJ, Zareba W, Hall J, Brown MW, Lin AC, Andrews ML, Burke M, Moss AJ. Time dependence of mortality risk and defibrillator benefit after myocardial infarction. Circulation 2004; 109: 1082-1084.

50. Credner SC, Klingenheben T, Mauss O, Sticherling C, Hohnloser SH. Electrical storm in patients with transvenous implantable cardioverter defibrillators: Incidence, management and prognostic implications. J Am Coll Cardiol 1998; 32: 1909-1915.

51. Greene M, Newman D, Geist M, Paquette M, Heng D, Dorian P: Is electrical storm in ICD patients the sign of a dying heart? Outcome of patients with clusters of ventricular arrhythmias. Europace 2000; 2: 263-269.

52. Dorian P, Mangat I. Role of amiodarone in the era of the implantable cardioverter defibrillator. J Cardiovasc Electrophysiol 2003; 14: S78-S81.

53. Arya A, Haghjoo M, Sadr-Ameli MA. Risk Stratification for arrhythmia death after myocardial infarction: Current perspective and future direction. Int J Cardiol (2006; 108: 155-164.

54. Arya A, Haghjoo M, Sadr-Ameli MA. ICD therapy: what we have learned from the clinical trials? Heart Lung Circ 2006; 15: 3-11.

55. Arya A, Haghjoo M, Dehghani MR. Prevalence and predictors of electrical storm in patients with implantable cardioverter defibrillator. Am J Cardiol 2006; 97: 389-392.

56. Arya A, Haghjoo M, Dehghani MR. Effect of cardiac resynchronizaion therapy on incidence of ventricular arrhythmias in patients with implantable cardioverter-defibrillator. Heart Rhythm. 2005; 2: 1094-1098.