ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA
VOL. LXI, N 2, 118 SECTIO D 2006

Interfaculty Chair and Department of Public Health, Cardiology Department
Medical University of Lublin

MARCIN DZIDUSZKO, TERESA WIDOMSKA-CZEKAJSKA

Implantable cardioverter/defibrillator treatment – method development, results of multi-centre trials and current indications

Sudden cardiac death (SCD) is understood as a natural death for cardiac reasons preceded by the loss of consciousness accompanied by the previous symptoms occurring no sooner than within an hour accounts for the cause of 750,000 to 900,000 deaths in the USA and Europe. According to Lubiński in 1999 SCD was the cause of 63.4% of a total of cardiac deaths in The United States. On the basis of the population research results (Framingham Heart Study, Maastricht study) it is estimated that an average incidence of sudden cardiac death in the population reaches 1/1000/year. The ischemic heart disease is considered to be the most frequent cause of SCD. The other diseases that increase the risk of sudden cardiac death include: hypertrophic cardiomyopathy, dilated cardiomyopathy, arrhythmogenic right ventricular dysplasia, long QT syndrome and Brugada syndrome. Ventricular fibrillation is the most frequent mechanism of sudden cardiac death accounting for 75–80% of a total. It is followed by considerably less frequent primary mechanisms of cardiac arrest: electromechanical dissociation and asystole.

The research and tests that aim at finding methods to control the phenomenon of sudden cardiac death have been done since the 1940s. The most important stages of fight against this phenomenon include the first ever successful attempt of defibrillation performed by C. Beck in 1947 due to cardiac arrest during an elective chest surgery as well as the first successful external defibrillation accomplished by Zoll in 1956.

The creation of the implantable cardioverter-defibrillator (ICD) by the Pole Mieczysław Mirowski became a major breakthrough in the fight against SCD. The first ICD was implanted on February 4, 1980. However, the method was approved by the Food and Drug Administration only in 1985, specifying that patients had to have survived 2 cardiac arrests to qualify for ICD implantation. Initially, ICDs were large (160 ml, 250 g) devices capable of terminating arrhythmia only by means of high-energy defibrillation. Due to its considerable size, the implantation of the device was a serious operation. Two defibrillation electrodes as well as a sensing electrode were implanted into the epicardium, while the device itself was being placed in the abdominal integument. The first defibrillators were capable of delivering approximately 100 shocks of single-phase current, while the period of their efficiency reached a maximum of 1.5 year. In 1989 transvenous implantation of the electrodes was initiated, and since 1993 the constant miniaturization of ICDs has enabled to implant them into the subclavian region similarly to pacemakers. Another improvement in the system was the replacement of a single-phase defibrillation shock with a biphasic shock, which significantly increased the antiarrhytmic efficiency and prolonged the battery longevity. In 1988 the method of sequential therapy was introduced (ICD obtained the opportunity of programming antitachycardia

pacing and cardioversion). In 1996 the steroid eluting electrodes were introduced, which limited the problem of increased defibrillation thresholds and increased the longevity of ICD by 48%. In 1997 the dual-chamber ICD systems were introduced, which improved the algorithms of arrhythmic detection and differentiation owing to the presence of the precordial electrode.

The fourth generation implantable cardioverter-defibrillator (ICD) systems currently available have an option of antitachycardia pacing (overdrive), low-energy cardioversion (0.1–5J), bradycardia pacing, resynchronising ventricular pacing in case of the asynchronic ventricular contraction in patients with the advanced heart failure. The latest systems also include the option of fighting against the atrial arrhythmias.

The cardioverter-defibrillator system consists of an ICD device enclosed in a titanium can (currently approx. 30 ml, 50 g) containing electronic systems, efficient battery (capable of 300 shocks, 5–9 years) as well as a condenser. According to the applied type of ICD, the system contains one or two pacing electrodes in addition to a defibrillation electrode (placed in the tip of the right ventricle). Defribrillation electrodes contain one or two defibrillation coils and inner bipolar electrodes responsible for sensing and stimulation (5). The basic functions of ICD include tachyarrhythmia detection, its classification, administration of an appropriate therapy, heart monitoring after the applied therapy as well as Holter test that enables to determine the occurrence of ventricular tachycardia or ventricular fibrillation (VT/VF) as well as the efficiency of their termination. The detection of arrhythmia occurs the moment it meets the detection criteria e.g. heart rate and duration of arrhythmia, rhythm change speed and its stability. According to the detection of arrhythmia an appropriate therapy is administered. Antitachycardia Pacing (ATP) is a very efficient method of arrhytmic termination, which is based on generating a set of shocks of the frequency higher than the frequency of arrhythmia. In case of inefficiency of this therapy the device may perform low-energy cardioversion, while in case of its inefficacy or transition from ventricular tachycardia to VF it perfroms defibrillation. Another benefit of ATP, apart from its testified efficiency, is painlessness of the therapy. Defibrillation is caused by an electric shock of 25–42J sent between the coils of the bipolar defibrillation lead or between the ring of the lead and the device cover (Active Can, Hot Can mechanism).

The development of ICD technology triggered the extended therapeutic indications for implantable cardioverter defibrillator. The role of ICD in the prevention of sudden cardiac death is confirmed by a great number of randomised and multi-centre trials published in recent years. The most important of the ones that evaluated ICD therapy efficiency in primary prevention (in patients with an increased risk of sudden cardiac death) include: MADIT, MADIT II, CABG-Patch, MUSTT, SCD-HeFT, DINAMIT, DEFINITE, COMPANION, while AVID, CIDS and CASH in secondary prevention (in patients who have survived SCD). Each of the studies, except for CABG-Patch, proved a considerable advantage of the ICD therapy.

The Cardiac Arrest Study Hamburg (CASH) carried out in the years 1987–1998 involved 400 patients surviving sudden cardiac death due to ventricular tachycardia and/or ventricular fibrillation. 288 patients were included in the ICD implantation group or one of the three groups of antiarrhythmic drug therapy with: metoprolol, amiodarone and propafenone. The propafenone treatment group was deleted from the study as there had been a significant increase (61%) in total mortality in patients randomized to propafenone compared with those randomized to the ICD treatment group. After the observation period of 57 months a statistically insignificant difference (23%) was found in mortality between the patients randomized to ICD treatment group as compared with metoprolol and amiodarone limbs. The benefit of ICD treatment application was most apparent within the first five years after the implantation (10).

The Canadian Implantable Defibrillator Study (CIDS) was performed from 1990 to 1997 among a total of 659 patients. They were included in the study on the basis of the recorded ventricular fibrillation or unmonitored syncope requiring defibrillation or cardioversion, sustain ventricular tachycardia (sVT) , the reported sVT with a heart rate ≥ 150 /min resulting in presyncope or anginal disorders with a simultaneous decrease of EF ≤ 35%, loss of consciousness as well as the recorded monomorphic sVT ≥ 10s or ≥30s induced during EPS. The patients were assigned to two groups – a total of 328 patients were randomized to receive an ICD treatment, while 331 patients were randomized to apply amiodarone therapy. As a result of a 36-month observation a statistically insignificant reduction of 19.7% (8.3% vs 10.2%) of mortality incidence in the ICD group as well as 32.8% reduction of risk of arrhythmic death (3.0 % vs. 4.5 %) were found (4).

Another significant study concerning secondary prevention carried out in the years 1993–1997 among 1,016 patients was AVID (*Antiarrythmics Versus Implantable Defibrillators*). The patients were enrolled into the trial on condition they met one of the following criteria: history of ventricular fibrillation, symptomatic or hemodynamically significant sVT or reduced (≤ 40%) ejection fraction. The patients were divided into two groups: 507 people received ICD treatment, while 509 people were assigned to the other group and were applied antiarrhythmic therapy (metoprolol, sotalol). After an average of 18 months of the observation there was a significant (29%) relative death risk reduction among ICD patients as compared with the antiarrhythmic group (15.8% vs 24%) (9).

The first large randomized study to evaluate the efficiency of ICD therapy in primary prevention was MADIT (*Multicenter Automatic Defibrillator Trial*) carried out from 1990 to 1996 among 196 people. The study enrolled patients with heart failure (NYHA class I–III) who had suffered an acute myocardial infarction prior to the study, left ventricular ejection fraction ≤ 35%, with a history of non-sustained ventricular tachycardia, an episode of sVT or VF induced in an electrophysiology test. After an average 27-month observation period 54% mortality reduction was recognized in the ICD group as compared with the pharmalogically treated group. The results validate the efficacy of ICD therapy in patients with prior myocardial infarction, reduced ejection fraction and threatened with dangerous arrhythmia (11).

The eligibility criteria for 900 patients for the CABG (*Coronary Artery Bypass Graft Patch Trial*) carried out in 1990–1997 were: ischemic heart disease requiring CABG treatment, an improper signal-averaged ECG (SAECG) as well as a reduced ejection fraction (EF≤ 35%). After a 32-month screening period no statistically significant difference was found in mortality incidence between patients who received epicardial ICDs along with CABG (446 people) and the control group treated with CABG alone (454 people) (1).

Multicenter Unsustained Tachycardia Trial (MUSTT) performed in 1990–1996 was another essential study. The inclusion criteria were: ischemic heart disease, reduced left ventricular ejection fraction ≤ 40%, symptom-free non-sustained VT, VT inducible with electrophysiological testing. A total of 704 patients were assigned to treatment groups: 351 patients were included in the group treated with antiarrhythmic drugs: 158 of them received pharmalogical treatment (amiodaron, sotalol), while 161 underwent ICD implantation. The treatment progress in this group was evaluated on the basis of the subsequent electrophysiology test. The remaining 353 people received no antiarrhythmic treatment. The 39-month screening indicated 76% sudden death incidence reduction for the ICD implantation treatment group (3).

MADIT II (1997–2001) was carried out among 1232 patients with myocardial infarction at least 30 days prior to enrollment, and a considerably reduced ejection fraction EF ≤30%. 742 people had ICDs implanted, while the remaining 490 were treated pharmalogically. After an average 20-month observation period 31% mortality reduction was recognized in the ICD group as compared with

the patients who underwent pharmalogical therapy (β-blocker, ACE inhibitors, statin). The results proved ICD efficacy in SCD reduction in the group of patients with prior MI and reduced ejection fraction (12).

The inclusion criterion for the SCD-HeFT (*Sudden Cardiac Death in Heart Failure Trial*, 1997–2001) was left ventricular heart failure (NYHA II or III) for at least 3 months prior to the test with a reduced left ventricular ejection fraction ≤ 35 %. A total of 2521 patients were assigned to the group treated with amiodarone (845 people), with no antiarrhythmic treatment (847 people) and a group of 829 patients who had a single-chamber ICD implanted. After an average of 45-month screening no influence of amiodarone on the mortality rate was determined as compared with placebo-controlled patients, while the ICD implantation group demonstrated 23% mortality rate reduction.

DYNAMIT (*Defibrillator in Acute Myocardial Infarction Trial*) – a multi-centre, randomized study carried out in 1998–2003 included 674 patients with the myocardial infarction 6–40 days prior to the inclusion into the study, reduced ejection fraction ≤ 35%, lowered cardiac rythm amplitude measured by Holter monitoring. 332 patients received a cardioverter defibrillator, while 342 people were included in the control group. 30-month observation did not show any statistically significant differences in the total mortality between ICD group as compared with patients receiving pharmacological treatment (7).

The DEFINITE (*Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation*) study carried out in 1998–2003 included 458 patients with dilated cardiomyopathy, reduced ejection fraction ≤ 35%, non-sustained VT diagnosed in Holter test or ≥ 10/h premature ventricular contractions. All the patients received an optimum pharmalogical treatment (ACE inhibitors, β-blocker), with a half undergoing ICD implantation in addition. After an average of 29-month screening 56% total mortality rate reduction was found in the ICD group (7.9% vs 14.1%). The study also showed the efficacy of ICD implantation in patients with dilated cardiomyopathy, reduced ejection fraction and ventricular contractions (8).

The COMPANION study (*Comparison of Medical Therapy, Pacing and Defibrillation in Patients with Left Ventricular Systolic Dysfunction Trial*) carried out in 2000–2002 included 1,520 patients with chronic heart failure (class NYHA III or IV), ejection fraction ≤ 35%, QRS duration > 120ms and PR duration > 150 ms. 308 people were assigned to pharmacological treatment, 617 people – to cardiac resynchronization therapy (CRT) and 595 people to cardiac resynchronization therapy combined with implantable cardioverter-defibrillator – (CRT-ICD). After an average of 16-month screening the reduction of the complex final point (death or hospitalization due to heart failure) by 34% was found in the GRT group and by 40% in the CRT-ICD group. There was also a significant reduction of total mortality in CRT patients (24%) and CRT-ICD patients (36%) as compared with patients who received pharmacological treatment only (2).

The initial indications for implantations allowed the application of ICD only in secondary prevention in patients who have survived at least 2 cardiac arrests. The technological development of ICD and the study results published gradually extended the indications for the use of cardioverter-defibrillators. The first recommendation worked out by the American College of Cardiology, American Heart Association and North American Society of Pacing and Electrophysiology were published in 1991. They were subsequently updated in 1998 and 2002. Currently there are three classes of qualification for automatic implantation of cardioverter defibrillators (6, 13).

Class I indication (administered treatment is efficient, useful and successful, which is proved by research results): sudden cardiac arrest in VT/VF mechanism not triggered by a reversible or transitory reasons, connected with the organic heart disease; inexplicable syncope in patients with hemodynamic instable ventricular tachycardia/ventricular fibrillation during EPS with inefficient or

badly tolerated pharmacological therapy; nsVT in patients after myocardial infarction with the EF ≤ 35%, with VT caused during EPS (MADIT); idiopathic sVT in patients with no structural heart disease resistant to different treatment methods.

Class IIa indication (study results and expert opinions indicate the usefulness and efficacy of the method): myocardial infarction at least one month or CABG at least three months prior to the application, accompanied by reduced ejection fraction (EF) ≤ 35%.

Class IIb indication (usefulness and efficacy supported more superficially): cardiac arrest possibly due to VF, with no possible EPS application due to medical reasons; severe symptoms (e.g. syncope) that accompany ventricular tachycardia in patients awaiting heart transplantation; family history indicating high risk of SCD or VT (LQTs, HCM): nsVT in patients with coronary heart disease, after myocardial infarction, with left ventricular failures and VT or VF released during EPS; repeated syncopes for unknown reasons with an accompanying left ventricular failure and ventricular arrhythmia inducible in EPS after the exclusion of other possible causes of syncopes; syncopes for unknown reasons or inexplicable sudden cardiac deaths in family history with a typical or atypical RBBB (Right Bundle Branch Block) and ST elevation (Brugada syndrome); syncopes in patients with the advanced organic heart disease whose reasons have not been explained on the basis of exact invasive and non-invasive tests.

Class III indication (conditions in which ICD implantation is useless, inefficient or, in some cases, harmful): syncopes for unknown reasons with no possible ventricular tachycardia and not diagnosed heart disease; persistent VT or VF, VT or VF resulting from diseases that can undergo surgeries (e.g. WPW, right ventricular outflow tachycardia); ventricular tachyarrhythmia caused by reversible or transitory disorders (e.g. recent myocardial infarction, elelectrolyte imbalance) where levelling of these disorders is possible as well as reducing the risk of arrythmia recurrence; serious mental diseases that can deteriorate as a result of implantation or disturb further constant screening; patients with life expectancy < 6 months; patients with coronary heart disease and left ventricular failure as well as prolonged QRS duration with no idiopathic or released stable or unstable VT, who undergo bypass surgeries): congestive heart failure resistant to pharmacotherapy NYHA IV in patients qualified for transplantation.

The extended indications for implantable cardioverter defibrillator treatment make an increasing number of people be able to take advantage of this therapy. While in the initial period of ICD development the number of implantations was 1,000 per year, in 2000 the number of implantations in the USA exceeded 50,000 and reached 100,000 in 2002. An annual increase in implantation number is estimated at approximately 25–50% there. According to 2002 data the number of ICD implantations/ mln residents/ year reached 200 in the USA, as compared with 50 in Europe and 16 in Poland (0–20 implantations depending on the voivodship). It needs to be stated that primary prevention in the USA concerns 50% of surgeries, 7% in Europe, while 3% in Poland. Despite the low implantation rate since the first ICD implanatation in Poland (1985 – epicardial defibrillator, 1995 transvenuous system) the number of surgeries has been rising by 50% annually (1995 – 13, 1996 – 33, 1997 – 62, 1998 – 99, 1999 – 144, 2000 – 250, 2001 – 327, 2002 – 505). By the end of 2004 a total of approximately 3,000 ICDs were implanted in our country. Thirty-two centers in Poland currently apply this treatment method.

Despite the proved efficacy both in primary and secondary prevention of sudden cardiac death, the high cost of the therapy still remains the largest obstacle against the widespread of implantable cardioverter defibrillators.

REFERENCES

1. Bigger J. T.: Prophylactic use of implanted cardiac defibrillator in patients in patients at high risk of ventricular arrythmias after coronary by-pass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N. Eng. J. Med., 337, 1569, 1997.
2. Bristow M. et al.: Comparison of medical therapy, pacing and defibrillation in heart failure investigators. Cardiac resynchronization therapy with ot without an implantable defibrillator in advanced chronic heart failure. N. Eng. J. Med., 350, 2140, 2004.
3. Buxton A. et al.: A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial investigators. N. Eng. J. Med., 341, 1882, 1999.
4. Conolly S. et al.: Canadian Implantable Defibrillator Study (CIDS). A randomized trial of the implantable cardioverter defibrillator against amiodaron. Circulation, 101, 1297, 2000.
5. DiMarco J.: Implantable Cardioverter-Defibrillator. N. Eng. J. Med., 349, 1836, 2003.
6. Gregoratos G. et al.: Guideline update for implantation of cardiac pacemakers and antiarrhythmia devices. Circulation, 106, 2145, 2002.
7. Hohnloser S. et al.: Prophylactic use of an implantable cardioverter defibrillator after acute myocardial infraction. N. Eng. J. Med., 351, 735, 2004.
8. Kadish A. et al.: Prophylactic defibrillator implantation in patients with non-ischemic dilated cardiomiopathy. N. Eng. J. Med., 350, 51, 2004.
9. Klein R. C. et al.: Analysis of implantable cardioverter defibrillator therapy in Antiarrythmics Versus Implantable Defibrillators (AVID). J. Cardiovasc. Electrophy, 14, 940, 2003.
10. Kuck K. et al.: Randomized comparison of antiarrythmic drug therapy with implantable defibrillator in patients resuscitated from cardiac arrest. Circulation, 102, 748, 2000.
11. Moss A. et al.: Improved survival with implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N. Eng. J. Med., 335, 1933, 1996.
12. Moss A. et al.: Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N. Eng. J. Med., 346, 877, 2002.
13. Priori S. G. et al.: Task force on sudden cardiac death, European Society of Cardiology. Eur. Heart J., 22, 1374, 2001.

SUMMARY

Sudden cardiac death (SCD) is responsible for 750,000 to 900,000 deaths in the USA and Europe. On the basis of the population research results (Framingham Heart Study, Maastricht Study) it is estimated that an average incidence of sudden cardiac death in the population reaches 1/1000/year. The creation of the implantable cardioverter-defibrillator (ICD) by the Pole Mieczysław Mirowski became a major breakthrough in the fight against SCD. The initial indications for implantations allowed the application of ICD only in secondary prevention in patients who have survived at least 2 cardiac arrests. The technological development of ICD and the study results published gradually extended the indications for the use of cardioverter-defibrillators. Nowadays 32 centers in Poland currently apply this treatment method, althought high cost of the therapy still remains the largest obstacle against the widespread application of implantable cardioverter defibrillators.

Leczenie przy pomocy wszczepialnych kardiowerterów/defibrylatorów – rozwój metody, wyniki wieloośrodkowych badań i aktualne wskazania

Nagła śmierć sercowa (*sudden cardiac death*, SCD) stanowi rocznie przyczynę 750–900 tys. zgonów w USA i Europie. Na podstawie wyników badań populacyjnych (Framingham Heart Study, badanie z Maastricht) stwierdzono, że średnia częstość występowania nagłej śmierci sercowej w populacji wynosi 1/1000/rok. Przełomem w walce z SCD stało się skonstruowanie przez Polaka Mieczysława Mirowskiego wszczepialnego, całkowicie automatycznego defibrylatora. Pierwsze wskazania do implantacji dopuszczały stosowanie ICD jedynie w prewencji wtórnej u chorych po co najmniej dwukrotnym zatrzymaniu krążenia. Postępujący rozwój technologii ICD i publikowane wyniki badań rozszerzały stopniowo wskazania do stosowania kardiowerterów–defibrylatorów. Obecnie w Polsce 32 ośrodki stosują tę metodę leczenia, jednak ciągle największym ograniczeniem w szerokim stosowaniu pozostaje wysoki koszt ICD.