European Heart Journal (2001) **22,** 990–996
doi:10.1053/euhj.2000.2371, available online at http://www.idealibrary.com on IDEAL®

Clinical Perspective

Cost-effectiveness of implantable cardioverter-defibrillators

G. Boriani, M. Biffi, C. Martignani, M. Gallina and A. Branzi

Institute of Cardiology, University of Bologna, Bologna, Italy

Introduction

Arrhythmic death is the most frequent cause of sudden cardiac death in the adult population, even today; in the United States its incidence is 300–400 000 cases per year. The pathophysiological substrate of sudden cardiac death is coronary artery disease in more than 90% of cases, and in more than 75% a previous myocardial infarction is present at clinical history[1–3]. In spite of a reduction in coronary artery disease-related mortality in recent years, today the number of sudden cardiac deaths is nearly the same as in the past and accounts for about 50% of deaths[3].

The implantable cardioverter-defibrillator is the most effective tool to treat malignant ventricular tachyarrhythmias and a series of controlled studies are evaluating the capability of the implantable cardioverter-defibrillator to reduce total mortality in selected patients at high risk of sudden cardiac death[3].

In recent years, a striking technological evolution has led to important consequences on the modality of the implantable cardioverter-defibrillator implant, on the implantable cardioverter-defibrillator-related hospital stay and, in general, on implantable cardioverter-defibrillator costs (Table 1). The possibility of implanting an implantable cardioverter-defibrillator in the electrophysiological laboratory, with minimal risks for patients, has meant that the implantable cardioverter-defibrillator is considered the best therapeutic strategy in the prevention of arrhythmic death in selected patients at high risk of sudden cardiac death.

Key Words: Antiarrhythmic drugs, cardioverter defibrillator, cost-effectiveness, sudden death, ventricular fibrillation, ventricular tachycardia.

Revision submitted 10 July 2000, and accepted 12 July 2000.

Correspondence: Giuseppe Boriani, MD, FESC, Institute of Cardiology, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy.

The role of the implantable cardioverter-defibrillator in the primary and secondary prevention of sudden cardiac death

The implantable cardioverter-defibrillator is the most effective tool in the prevention of sudden cardiac death in patients with a previous cardiac arrest (secondary prevention), as proved by AVID, CASH and CIDS studies[1,3].

In recent years there has been strong interest in the possibility of preventive treatment in selected patients at high risk of sudden cardiac death caused by malignant ventricular arrhythmias, and the implantable cardioverter-defibrillator was considered the best choice in appropriately selected patients with a previous myocardial infarction[4,5].

The identification of high-risk patients is the main aspect of this strategy; in general, the risk of death caused by ventricular arrhythmias is low among non-selected patients or among all patients with a previous myocardial infarction. For these reasons, the use of a sophisticated and expensive strategy, such as an implantable cardioverter-defibrillator, must be based on careful selection of patients with a previous myocardial infarction and a high risk of arrhythmic death in order to obtain the best cost-effectiveness and risk-effectiveness ratios.

Numerous tests and prognostic indicators have been proposed to evaluate the risk of sudden death in patients with a previous myocardial infarction (Table 2). Even today, left ventricular ejection fraction is the most powerful indicator of survival: total mortality increases exponentially when left ventricular ejection fraction decreases from 0·40 to 0·30. About the 20% of the population with a previous myocardial infarction has a left ventricular ejection fraction $\leq 0{\cdot}40$ in spite of the use of all the therapeutic tools available today. Among these patients, 50–60% of all deaths are registered soon after a myocardial infarction[3,6,7].

In recent years, other prognostic factors have been evaluated to identify patients at high risk of malignant ventricular arrhythmias among those who had a previous myocardial infarction[8,10]. Indeed, the possibility of supplying primary prevention strategies efficiently

0195-668X/01/120990+07 $35.00/0

Table 1 Implantable cardioverter-defibrillator technological evolution and consequences in clinical practice

	First ICDs	Actual ICDs
Volume and weight	>200 cc, >280 g	<60 cc, <100 g
Kind of implant	Thoracotomy	Transvenous
Implant position	Abdominal	Pectoral
Implant place	Operating room	Electrophysiological laboratory
Implant duration	2–6 h	1–1·5 h
Hospital stay	14–24 days	2–5 days
Perioperative mortality	Up to 9%	<1%
Battery longevity	2–3 years	6–9 years

Table 2 Stratification of the risk of sudden cardiac death: sensitivity, specificity and predictive positive value of some non-invasive markers and inducibility of monomorphic sustained ventricular tachycardia

	Percentage of patients with positive test (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
LVEF ≤40%	25–45	45–80	55–75	9–24
Late potentials	30–50	60–85	65–80	8–29
Complex ventricular arrhythmias	30–60	50–80	42–85	6–23
Heart rate variability	27–35	90	77–98	15–17
Baroreflex sensitivity		80	91	44
Inducibility of monomorphic sustained ventricular tachycardia at EPS	7–42	50–100	75–98	21–75

EPS=electrophysiological study; LVEF=left ventricular ejection fraction.
Modified from Zoni Berisso *et al.*[10].

(e.g. the implantable cardioverter-defibrillator) to patients at high risk of sudden cardiac death may reduce social costs, and their potential adverse effects in patients at low risk of sudden cardiac death. It is possible to identify patients at high-risk of sudden cardiac death with a series of invasive and non-invasive prognostic indicators whose sensitivity, specificity and preventive accuracy are summarized in Table 2.

It is well known that the best primary end-point with which to evaluate implantable cardioverter-defibrillator effectiveness is total mortality reduction[1–3,11–13]. Other end-points, such as sudden cardiac death, arrhythmic death or different arrhythmic events represent end-points strictly linked with the effectiveness of the treatment. However, since a correct classification of these events is difficult, evaluation of the effectiveness of an implantable cardioverter-defibrillator is similarly laborious. Besides the reduction of total mortality, other important secondary end-points are quality of life and cost-effectiveness. Thirty to sixty percent of all deaths after a myocardial infarction are directly caused by primary ventricular arrhythmias. From this, together with additional factors such as problems during implantation, bradyarrhythmias, device dysfunction, and other causes of death, such as ischaemia or heart failure, it can be estimated that the reduction of mortality achievable by means of an implantable cardioverter-defibrillator is about 20–50% (these data depend on the characteristics of the selected population with a previous myocardial infarction)[2].

In regards to the effectiveness of cardioverter defibrillators for the reduction of total mortality, the results of longitudinal controlled studies (AVID, CASH and CIDS for secondary prevention and MADIT and MUSTT for primary prevention) must be considered.

The reservations expressed by MADIT[4,14], regarding the problems in applying the results of that study to the general population and the necessity to compare the use of a defibrillator with complete post-myocardial infarction therapy (primarily beta-blockers, ACE inhibitors and antithrombotics), led to the planning of a series of prospective trials[12], listed in Table 3.

Cost-effectiveness of various treatments

Cost-effectiveness analysis aims to evaluate the cost of any therapeutic intervention in relation to possible benefits[15–18]. The cost of a therapy is the sum of direct costs (initial costs of therapy, costs to maintain therapy

Table 3 Prospective randomized controlled studies about sudden cardiac death: use of antiarrhythmic or conventional therapy vs implantable cardioverter-defibrillators[112]

Type of treatment studied	Patients survived to a cardiac arrest	Patients with previous myocardial infarction	Heart failure
Antiarrhythmic therapy	CASCADE ESVM	BASIS CAST CAMIAT EMIAT PAS SSSD SWORD DIAMOND ALIVE*	CHF-STAT GESICA EPAMSA
Cardioverter-defibrillators	AVID CASH CIDS	MADIT ICDIOS* MUSTT MADIT II* PRONORDICA* BEST-ICD* SAMI* SEDET* DINAMIT*	SCD-He FT* CAT*

*Ongoing trials.

and costs caused by unfavourable effects or by complications) and of indirect costs to the patient's family or the community. Efficacy of a treatment is defined by the mean number of years survived after an adverse event by means of a therapy. Usually incremental cost-effectiveness analysis is considered when two new therapeutic strategies are compared. The cost-effectiveness ratio is usually expressed in dollars per year of life saved ($/YLS). In the literature[15–18], a treatment is considered valid if the cost-effectiveness ratio ranges between 0 and 20 000 $/YLS, convenient if it ranges between 20 000 and 40 000 $/YLS, borderline if between 40 000 and 60 000 $/YLS, unfavourable if between 60 000 and 100 000 $/YLS and absolutely unfavourable above 100 000 $/YLS. Tables 4 and 5 list the cost-effectiveness ratios of the implantable cardioverter-defibrillator and of other different treatments, in the cardiovascular and non-cardiovascular fields.

It is evident that the cost-effectiveness ratio can change greatly depending on the type of population. The identification of high risk patients ('patient targeting')[18] seems to be the most important issue in order to reach a favourable cost-effectiveness ratio.

Implantable cardioverter defibrillator cost-effectiveness ratio

Implantable cardioverter-defibrillator cost-effectiveness has been the subject of analysis (Table 4) that compared the whole costs of an implantable cardioverter-defibrillator with alternative strategies based on therapy with amiodarone or on antiarrhythmic therapies guided by electrophysiological study[17–25]. At the outset, these studies evaluated the cost-effectiveness of the implantable cardioverter-defibrillator in the secondary prevention of sudden cardiac death, that is in patients with a previous cardiac arrest or previous ventricular tachyarrhythmias[16,19–23]; more recently, MADIT[4] and MUSTT[5] studies considered the implantable cardioverter-defibrillator as a strategy for primary prevention of sudden cardiac death in selected patients with coronary artery disease at high-risk of malignant ventricular arrhythmias.

In recent years implantable cardioverter-defibrillator costs have lowered, as a result of transvenous implantation, better performance of devices and leads and by an increase in battery duration, which implies a reduction in the number of replacements[18,21,23,26–30]. Moreover, it was estimated that by decreasing or eliminating antiarrhythmic therapy guided by electrophysiological studies, it was possible to decrease significantly the hospitalization time, and therefore costs[21,27].

Initially, cost-effectiveness studies for implantable cardioverter-defibrillators have been based on mathematical processing of non-randomized studies and have evaluated the cost-effectiveness ratio at $ 17 000[27], $ 18 100[21] and $ 21 800[20] per year of life saved. In patients with a low left ventricular ejection fraction, costs were high (44 000 $/YLS when the left ventricular ejection fraction was <0 25 vs 27 200 $/YLS when the left ventricular ejection fraction was ≥0·25)[21].

In a study by Kupersmith *et al.*[21] the transvenous implantable cardioverter-defibrillator implant in patients with a left ventricular ejection fraction ≥0·25, without a previous electrophysiological study, had an extremely favourable cost-effectiveness ratio, equal to 14 200 $/YLS.

Table 4 Cost-effectiveness of implantable cardioverter defibrillators

Author, year	Type of study	$/YLS per ICD
Kuppermann, 1990[19]	Secondary prevention (data from Medicare)	17 100
Larsen, 1992[20]	Secondary prevention (ICD vs amiodarone)	21 000
Kupersmith, 1995[17,21]	Secondary prevention (ICD vs therapy guided by EPS)	25 700
	Secondary prevention (without EPS and with LVEF $\geq$40%)	14 200
Kupersmith, 1995[17,21]	Secondary prevention	
	with LVEF <25%	44 000
	with LVEF $\geq$25%	27 200
Wever, 1996[22]	Secondary prevention (ICD vs class III antiarrhythmic drugs)	11 315
Owens, 1997[23]	Secondary prevention (ICD vs amiodarone)	
	with mortality reduction of 40%	27 300
	with mortality reduction of 20%	54 000
Larsen, 1997[24]	Secondary prevention (ICD vs amiodarone or sotalol in AVID study) [charges per year of life saved]	114 917
Mushlin, 1998[25]	Primary prevention (MADIT study)	27 000
	if transvenous ICD	22 800
	if life of ICD >4 years	12 500

ICD=implantable cardioverter-defibrillator; LVEF=left ventricular ejection fraction; EPS=electrophysiological study; $/YLS=dollars per year of life saved.

In a recent study, based on the analysis of randomized trials[23], the implantable cardioverter-defibrillator cost-effectiveness ratio was strictly dependant on the reduction of the risk of mortality. In fact, in comparison to amiodarone, the cost was 27 300 $/YLS for a relative reduction of the risk of mortality of 40% and 54 000 $/YLS for a relative reduction of 20%.

Cost-effectiveness has been evaluated prospectively by the MADIT study, the first randomized study on the primary prevention of sudden death in patients with coronary artery disease, a low ejection fraction ($\leq$0·35), non-sustained ventricular tachycardia and a positive electrophysiological study for ventricular tachycardia, resistant to procainamide. The subsequent analysis[25] evaluated the cost-effectiveness at 27 000 $/YLS. However, the reservations expressed by the MADIT study[14] have suggested that this item should be re-evaluated, reflecting the many other prospective trials of primary prevention still in progress (Table 3).

Today, cost-effectiveness analyses show that the use of the implantable cardioverter-defibrillator in selected patients is favourable. In particular, the cost-effectiveness ratio is comparable to or lower than other accepted treatments, such as renal dialysis, that has a cost of about 50 and 60 000 $/YLS[16–18,31,32] (Table 5). An exception to this favourable cost-effectiveness evaluation is the AVID study[24]. In a substudy of AVID, charges per year of life saved were calculated at 3 years and resulted in a value of 114 917 $/YLS. The limitation of this analysis is related to the type of calculation (charges instead of costs) and the relatively short follow-up.

A series of prospective ongoing trials (Table 3) have the aim of evaluating not only the efficacy but also the cost-effectiveness ratio of the implantable cardioverter-defibrillator in specific subgroups of patients with a previous myocardial infarction. This is very important, in order to define the social costs of a strategy for primary prevention of sudden death based on the selective use of all the available pharmacological and interventional resources.

The problem of cost and cost-effectiveness of implantable cardioverter-defibrillators will be a socially relevant problem in the future. Indeed, in recent years implantable cardioverter-defibrillator implantation volumes have increased world-wide[36–38] and the cost is becoming an important issue. According to epidemiological surveys, important differences in implantation rates still exist between the United States and Europe[36,38] and within different European Countries[37–40]. The differences in implantable cardioverter-defibrillator use among different European Countries are probably related to inhomogeneity in regulatory and reimbursement support, lack of policy and historically lower implantable cardioverter-defibrillator implant rates[36–40].

Table 5 Cost-effectiveness of different treatments

Treatment strategy	Substrate	Patient characteristics	$/YLS
Very favourable cost-effectiveness (<20 000 $/YLS)			
Pacemaker	Complete AV block		1400
Beta-blockers	Post-infarction	High risk	3600
Anticoagulant drugs	Mitral stenosis	AF, f, age 35	4200
Lovastatin	Hyperlipidaemia	Sec proph, chol $\geq$250 mg . day^{-1}, f, age 45–54	4700
Simvastatin	Hypercholesterolaemia in coronary artery disease	Age 70, cholesterol 309 mg . dl^{-1}	3800 (m) 6200 (f)
Simvastatin	Hypercholesterolaemia in coronary artery disease	Age 59, cholesterol 213 mg . dl^{-1}	2100 (m) 8600 (f)
Simvastatin	Hypercholesterolaemia in coronary artery disease	Age 59, cholesterol 309 mg . dl^{-1}	1200 (m) 3200 (f)
Simvastatin	Hypercholesterolaemia in coronary artery disease	Age 70, cholesterol 213 mg . dl^{-1}	6200 (m) 13 300 (f)
PTCA	Ischaemic heart disease	Severe angina, age 55, m, normal EF, 1-vessel disease	8700
CABG	Ischaemic heart disease	Severe angina, main left coronary stenosis	9200
PTCA	Ischaemic heart disease	Severe angina, age 55, m, low EF, 1-vessel disease	11 600
Captopril	Post-infarction	EF $\leq$0·40, age 60	10 200
Enalapril	Heart failure		10 300
Endocardial ICD without EPS	VT/VF	EF $\geq$0·25	14 200
CABG	Ischaemic heart disease	Non-severe angina, 3-vessel disease	18 500
Favourable cost-effectiveness (20–40 000 $/YLS)			
Beta-blockers	Post-infarction	Low risk	20 200
Antihypertensive therapy	Hypertension	Diast AP $\geq$105 mmHg	20 600
Lovastatin	Hyperlipidaemia	Sec proph, chol <250 mg . dl^{-1}, m, age 55–64	20 200
Endocardial ICD with EPS	VT/VF		25 700
Streptokinase	Acute myocardial infarction	Age $\geq$75	27 700
Screening with exercise testing after myocardial infarction*	Ischaemic heart disease	Previous uncomplicated myocardial infarction	21 700 36 166
Primary stent in PTCA	Ischaemic heart disease	Angina, age 55, m, 1-vessel disease	26 800
Endocardial ICD with EPS	Ischaemic heart disease	Low EF, nSVT, high risk	27 000
Borderline cost-effectiveness (40–60 000 $/YLS)			
Antihypertensive therapy	Hypertension	Diast. AP 95–104 mmHg	41 900
CABG	Ischaemic heart disease	Severe angina, 2-vessel disease	42 500
Cardiac transplant	Severe heart failure		44 300
Lovastatin	Hyperlipidaemia	Sec proph, chol <250 mg . dl^{-1}, f, age 55–64	48 600
Radiofrequency ablation	WPW	Without symptoms, age 40	57 100
Ambulatory peritoneal dialysis			57 300
Hospital emodialysis			59 500
Unfavourable cost-effectiveness (60–100 000 $/YLS)			
CABG	Ischaemic heart disease	No severe angina, 2-vessel disease	72 900
Lovastatin	Hyperlipidaemia	Prim proph, chol $\geq$300 mg . dl^{-1}, no RF, m, age 55–64	78 300
Coronary care unit admission	Suspected acute myocardial infarction	Patients with 20% probability of acute myocardial infarction	78 700
Very unfavourable cost-effectiveness (>100 000 $/YLS)			
PTCA	Ischaemic heart disease	Non severe angina, age 55, normal EF, 1-vessel disease (LADC)	109 000
Coronary care unit admission	Suspected acute myocardial infarction	Patients with 5% probability of acute myocardial infarction	328 500
CABG	Ischaemic heart disease	Non severe angina, 1-vessel disease	1 142 000
Lovastatin	Hyperlipidaemia	Prim proph, chol $\geq$300 mg . dl^{-1}, no RF, f, age 45–54	2 024 800

AF=atrial fibrillation; CABG=coronary artery bypass graft; Chol=cholesterolaemia; diast AP=diastolic arterial pressure; EF=left ventricular ejection fraction; EPS=electrophysiological study; f=female; ICD=implantable cardioverter-defibrillator; LADC=left anterior descending coronary artery; m=male; nSVT=non-sustained ventricular tachycardia; Prim=primary; Proph=prophylaxis; PTCA=percutaneous transluminal coronary angioplasty; RF=coronary risk factors; Sec=secondary; VF=ventricular fibrillation; VT=ventricular tachycardia; WPW=Wolff-Parkinson-White Syndrome; $/YLS=dollars per year of life saved. *assuming discounted life expectancy of 6–10 years with coronary revascularization.
Modified from: Kuppermann *et al.*[19], Kupersmith *et al.*[17,18], Anderson *et al.*[31], Johannesson *et al.*[33], Dittus *et al.*[34], Fineberg *et al.*[35].

Conclusions

The implantable cardioverter-defibrillator is an expensive treatment and in the first years of its use it was sometimes criticised because of its excessive cost for society. However, many studies and trials have suggested that implantable cardioverter-defibrillator implantation in selected patients has an acceptable cost-effectiveness ratio, at least comparable with the cost-effectiveness of other established treatments in cardiovascular and non-cardiovascular fields.

Moreover, the cost-effectiveness of implantable cardioverter-defibrillators is related to the characteristics of the treated population: it is more favourable in patients who are at high risk for arrhythmic death but at low risk of death from other causes (in particular from heart failure).

In the light of recent data, the use of the implantable cardioverter-defibrillator in patients with coronary artery disease at high risk of sudden death is deemable; many ongoing controlled trials are evaluating, in selected patients populations, the usefulness and costs of the implantable cardioverter-defibrillator when associated with standard treatments (beta-blockers, hypolipaemic therapy, ACE inhibitors, coronary revascularization, etc.) in order to offer a multifactorial and integrated approach to the problem of sudden death.

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