Cardioverter defibrillator therapy in the primary and secondary prevention of sudden cardiac death

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Abstract
Implantable cardioverter defibrillators (ICDs) are the mainstay of modern device-based therapy for ventricular arrhythmias. Originally developed for patients resuscitated from cardiac arrest, the vast majority of today’s ICDs are implanted prophylactically in patients with heart failure at increased risk for ventricular arrhythmias. The objective of this review is to provide a concise overview of current ICD indications and device selection criteria. Furthermore, remaining limitations of ICD therapy are discussed and current trends are outlined.

Key words: implantable cardioverter defibrillator, primary prevention, secondary prevention, sudden cardiac death, heart failure, cardiac resynchronization therapy

Introduction
Since the first cardioverter defibrillator was implanted in 1980 in a cardiac arrest survivor, overwhelming technological progress has enabled a continuous expansion in indications and clinical use of ICD systems. Starting with thoracotomy systems with epicardial electrodes exclusively used in survivors of cardiac arrest, the vast majority of modern transvenous ICDs are implanted in patients with heart failure at risk for future cardiac arrest (1, 2). Reflecting this development, implantation rates have grown steadily: An estimated number of 70,000 ICDs have been implanted in Europe in the year 2009 (3).

This review aims to provide a brief overview of our current understanding of ICD use in the primary and secondary prevention of sudden cardiac death. Following the chronological development of ICD therapy, secondary prevention indications are reviewed first, succeeded by current primary prevention indications. Then, determinants for the choice of device type are reviewed briefly with a focus on cardiac resynchronization therapy systems (CRT-D). Finally, major limitations of ICD therapy are discussed and current trends are outlined.

ICD therapy for secondary prevention of sudden cardiac death
Initially, the ICD was developed to prevent sudden cardiac death from recurrent arrhythmia in high-risk patients who had survived one or more resuscitations because of ventricular tachycardia or ventricular fibrillation (1, 2). This group of indications in patients having already experienced a life-threatening event of documented or presumed ventricular tachyarrhythmia was later classified as “secondary prevention” (fig. 1) (1, 2).

Current recommendations regarding ICD
indications in secondary prevention are mainly based on a group of prospective randomized trials that were conducted in the 1990s (overview in table 1) (1, 4-7). The largest and most important of those trials was AVID (4). It included approximately 1000 patients who had either survived resuscitation from ventricular fibrillation or who had experienced a symptomatic ventricular tachycardia. Notably, the index ventricular tachycardia had to be associated with either syncope or at least with hemodynamic instability and structural heart disease with a reduced left ventricular ejection fraction (LVEF ≤ 40%). Patients were prospectively randomized to receive either ICD implantation or amiodarone therapy. After a mean follow up of merely 1.5 years, the trial was stopped prematurely because of a significant mortality benefit in the ICD group. Two other large trials with similar design – CIDS and CASH – also found a reduction of overall mortality and arrhythmic mortality in association with ICD therapy (5, 7). However, in CIDS and CASH those effects did not reach statistical significance, possibly as a consequence of smaller sample sizes, use of early invasive thoracotomy ICD systems and less well-tailored inclusion criteria (5, 7). Eventually, a meta-analysis of pooled data from AVID, CIDS and CASH demonstrated an overall mortality benefit with a risk reduction of 28% in death from any cause and 50% in arrhythmic death (6).

The majority of patients included in those large secondary prevention trials had coronary heart disease with reduced ejection fraction (4-7). However, observational and registry data support the use of ICDs also in secondary prevention patients with other types of structural heart disease such as dilated non-ischemic cardiomyopathy and hypertrophic cardiomyopathy (1).

Figure 1: ICD Holter recording showing an episode of fast ventricular tachycardia (cycle length 230-240 ms) that was effectively terminated by an ICD shock. Abbreviations: AP – atrial pacing, F – signal detected in the ventricular fibrillation zone, HV – ICD shock (high voltage therapy), VP – ventricular pacing.
Hence, present guidelines recommend ICD implantation in patients who have survived a prior cardiac arrest or sustained ventricular tachycardia regardless of the type of underlying structural heart disease (1, 2). Notably, however, possible transient reversible causes for cardiac arrest such as acute myocardial infarction and acute myocarditis should be evaluated thoroughly (1, 2). Furthermore, idiopathic ventricular tachycardia in the absence of structural heart disease should primarily be treated with catheter ablation (2).

**ICD therapy for primary prevention of sudden cardiac death**

The term “primary prevention of sudden cardiac death” refers to ICD implantation in individuals who are at risk for, but have not yet experienced an episode of sustained ventricular tachycardia, ventricular fibrillation or resuscitated cardiac arrest (1, 2). A considerable number of large trials have evaluated the use of ICDs in those patients after risk stratification depending on the type and severity of structural heart disease (overview in table 2) (8-12).

**Ischemic heart disease.** ICD therapy in chronic ischemic heart disease has particularly been influenced by MADIT II, DINAMIT and IRIS (9, 11, 12). The MADIT II trial enrolled more than 1200 patients with prior myocardial infarction and a LVEF ≤ 30% (11). Notably, the median time between myocardial infarction and study enrolment was 6 years, indicating that most patients were in the chronic post-infarction phase. Patients were prospectively randomized to receive optimal medical therapy either with or without ICD implantation. After less than 2 years

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**Table 1: Brief overview of major clinical trials that compared ICD therapy and medical therapy for the secondary prevention of sudden cardiac death. Patients with a reversible cause of VF/VT such as acute myocardial infarction or electrolyte imbalance were excluded in all trials.**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Follow Up</th>
<th>Main Inclusion Criteria</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVID</td>
<td>1016</td>
<td>1.5 years (early termination)</td>
<td>(i) resuscitation from VF (ii) VT with syncope (iii) VT with haemodynamic instability and LVEF ≤ 40%</td>
<td>ICD therapy reduced all-cause death in comparison to amiodarone therapy (relative risk reduction 33%).</td>
</tr>
<tr>
<td>CIDS</td>
<td>659</td>
<td>3 years</td>
<td>(i) resuscitation from VT/VF (ii) VT with syncope (iii) VT with haemodynamic instability and LVEF ≤ 35% (iv) unexplained syncope and VT inducible by PVS</td>
<td>ICD therapy was associated with a non-significant reduction of both all-cause death and arrhythmic death in comparison to amiodarone therapy (relative risk reduction 20% and 33%, respectively).</td>
</tr>
<tr>
<td>CASH</td>
<td>288</td>
<td>3 years</td>
<td>resuscitation from VT/VF</td>
<td>ICD therapy was associated with a non-significant reduction of all-cause death in comparison to therapy with either amiodarone or metoprolol (relative risk reduction 23%).</td>
</tr>
</tbody>
</table>

Abbreviations: LVEF – left ventricular ejection fraction, PVS – programmed ventricular stimulation, VF – ventricular fibrillation, VT – ventricular tachycardia
of follow up, the trial was stopped due to a significant reduction of overall mortality in the ICD group. By contrast, the DINAMIT trial focused on the direct post-infarction phase and enrolled patients 6-40 days after an acute myocardial infarction with a LVEF ≤ 35% who also had electocardiographic risk markers on Holter monitoring (9). Surprisingly, in this high-risk group of patients ICD therapy did not confer an overall survival benefit (9). Instead, ICD implantation was associated with a reduction of arrhythmic death that was offset by an increase of non-arrhythmic death (9, 13). This observation has been attributed to a conversion of the cause of death in high-risk individuals with patients dying from the progression of ischemic heart disease instead of dying from ventricular arrhythmia (9, 13). This notion was affirmed by the IRIS trial that had a similar objective and also focused on patients in the early phase (5-31 days) after an acute myocardial infarction with risk markers (12). As in DINAMIT, ICD therapy did not reduce

Table 2: Brief overview of landmark clinical trials that compared ICD therapy and optimal medical therapy (or amiodarone (SCD-HeFT)) for the primary prevention of sudden cardiac death.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Follow Up</th>
<th>Main Inclusion Criteria</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADIT II</td>
<td>1232</td>
<td>1.7 years (early termination)</td>
<td>Prior myocardial infarction and LVEF ≤ 30%</td>
<td>Prophylactic ICD implantation significantly reduced overall mortality in comparison to OMT (relative risk reduction 31%).</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>2521</td>
<td>3.8 years</td>
<td>Congestive heart failure NYHA II/III and LVEF ≤ 35%</td>
<td>Prophylactic ICD implantation significantly reduced overall mortality in comparison to amiodarone or placebo (relative risk reduction 23%).</td>
</tr>
<tr>
<td>DEFINITE</td>
<td>458</td>
<td>2.4 years</td>
<td>Non-ischemic DCM and LVEF ≤ 36% and PVB or NSVT</td>
<td>In comparison to OMT, prophylactic ICD implantation significantly reduced the risk of sudden death and was associated with an nonsignificant reduction of overall mortality (p=0.08, relative risk reduction 35%).</td>
</tr>
<tr>
<td>DINAMIT</td>
<td>674</td>
<td>2.5 years</td>
<td>Myocardial infarction within the preceding 6-40 days, LVEF ≤ 35% and impaired cardiac autonomic function on Holter</td>
<td>Prophylactic ICD therapy did not reduce overall mortality in those high-risk patients in comparison to OMT.</td>
</tr>
<tr>
<td>IRIS</td>
<td>898</td>
<td>3.1 years</td>
<td>Myocardial infarction within the preceding 5-31 days, LVEF ≤ 40% and initial HR&gt;90 bpm or NSVT on Holter</td>
<td>As in DINAMIT, prophylactic ICD therapy did not reduce overall mortality in those high-risk patients in comparison to OMT.</td>
</tr>
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overall mortality in those patients and a reduction in arrhythmic death was offset by an increase in non-arrhythmic death (12).

Current guidelines recommend ICD implantation in patients with left ventricular dysfunction due to prior myocardial infarction and a LVEF ≤ 30-35% (1, 2). However, an ICD should not be implanted within the first 40 days after an acute myocardial infarction, resulting from the negative results of the DINAMIT and IRIS trials (1, 2, 9, 12). Furthermore, in individuals with an LVEF ≤ 40% and non-sustained VT, inducible sustained ventricular tachycardia on programmed ventricular stimulation may identify high-risk patients who benefit from an ICD (1, 2, 14, 15).

**Non-ischemic dilated cardiomyopathy.** For chronic heart failure of non-ischemic origin, existing clinical trial data are more heterogeneous. DEFINITE was the largest respective trial, enrolling nearly 500 individuals with non-ischemic dilated cardiomyopathy and LVEF ≤ 36% (10). In those patients, ICD therapy reduced both the risk of sudden cardiac death and of all-cause death. However, due to a low event rate the latter effect closely missed statistical significance (10). The SCD-HeFT trial had a principally different design: It included patients with symptomatic heart failure (NYHA classes II and III) and LVEF ≤ 35% irrespective of the type of underlying structural heart disease (8). 48% of patients had non-ischemic dilated cardiomyopathy and 52% had ischemic heart disease. In the SCD-HeFT cohort, ICD therapy was associated with a significant reduction of total mortality. Interestingly, although the event rate was lower in non-ischemic heart failure than in ischemic heart failure, the treatment effect did not vary according to the etiology of heart failure (8).

Hence, present guidelines recommend ICD implantation in patients with non-ischemic dilated cardiomyopathy with a LVEF ≤ 35% and symptomatic heart failure NYHA II or III (1, 2). In asymptomatic patients (i.e. NYHA I), the recommendation for ICD therapy is more restrictive because of a lack of data and lower event rates than in NYHA II-III (1, 2).

**Hypertrophic cardiomyopathy and primary electrical heart disease.** In less common cardiomyopathies such as hypertrophic cardiomyopathy and in primary electrical heart diseases such as Long QT or Brugada syndrome, much less data are available to support the use of ICDs, and the lack of randomized clinical trials limits the value of current recommendations for defibrillator implantation in this disease entities. There is general consent, however, that in cases of survived cardiac arrest in the setting of hypertrophic cardiomyopathy or ion channel disease, an ICD implantation is indicated as secondary prevention (1, 2). However, risk stratification for ICD implantation as primary prevention in those individuals can be very complex and relies on disease-specific schemes that are based mainly on observational studies and registries (brief summary shown in table 3) (1, 16, 17).

**Choice of device type in ICD therapy**

Standard single-chamber ICD systems are based on a single RV lead for sensing/pacing and cardioversion/defibrillation; they are capable of ventricular bradyheart defect, antitachycardia pacing, cardioversion and defibrillation. Dual-chamber ICDs have an additional RA lead, thus enabling AV sequential (physiological) pacing and holding the potential to improve the differentiation between supraventricular and ventricular tachyarhythmia based on dual-chamber detection algorithms. Triple-chamber systems (RA, RV and LV leads) are designed to provide cardiac resynchronization therapy in addition to the capabilities of dual-chamber systems (CRT-defibrillators). In clinical practice the choice of ICD type is influenced by many variables, and recent evidence suggests that the selection of device hardware affects important outcomes in ICD patients (1).
Table 3: Brief overview of major risk factors and principles of risk stratification with respect to ICD implantation in genetic cardiomyopathies and primary electrical heart diseases. For details, please refer to the listed references.

<table>
<thead>
<tr>
<th>Major Risk Factors for SCD</th>
<th>Principle Recommendations</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Prior cardiac arrest, spontaneous sustained VT, Family history of SCD, unexplained syncope, NSVT, abnormal blood pressure response to exercise, massive LV hypertrophy</td>
<td>ICD implantation is recommended in patients with prior VF or sustained VT. Prophylactic ICD implantation should be considered in high-risk patients. Patients with end-stage hypertrophic cardiomyopathy may have an ICD indication due to heart failure (LVEF≤35%, NYHA II/III).</td>
</tr>
<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>Prior cardiac arrest, spontaneous sustained VT, Extensive disease, one or more affected family members with SCD, unexplained syncope</td>
<td>ICD implantation is recommended in patients with prior VF or sustained VT. Prophylactic ICD implantation should be considered in high-risk patients.</td>
</tr>
<tr>
<td>Long QT syndrome</td>
<td>Prior cardiac arrest, spontaneous sustained VT, Unexplained syncope, QT duration, genotype, sex</td>
<td>ICD implantation is recommended in patients with prior VF or sustained VT despite adequate medical therapy. Prophylactic ICD implantation should be considered in high-risk patients.</td>
</tr>
<tr>
<td>Brugada syndrome</td>
<td>Prior cardiac arrest, spontaneous sustained VT, Unexplained syncope, Role of EP testing controversial</td>
<td>ICD implantation is recommended in patients with prior VF or sustained VT or unexplained syncope. Prophylactic ICD implantation should be considered in high-risk patients.</td>
</tr>
<tr>
<td>Catecholaminergic polymorphic ventricular tachycardia</td>
<td>Prior cardiac arrest, spontaneous sustained VT, Unexplained syncope</td>
<td>ICD implantation is recommended in patients with prior VF or sustained VT or unexplained syncope despite beta blocker therapy.</td>
</tr>
<tr>
<td>Short QT syndrome</td>
<td>Prior cardiac arrest, spontaneous sustained VT, Unexplained syncope</td>
<td>ICD implantation is recommended in patients with prior cardiac arrest. Due to the small number of patients, no evidence-based recommendation with respect to the treatment of asymptomatic patients can be made.</td>
</tr>
<tr>
<td>Idiopathic ventricular fibrillation</td>
<td>Prior cardiac arrest</td>
<td>ICD implantation is recommended in patients with prior cardiac arrest.</td>
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**Dual- versus single-chamber ICD.** Dual-chamber ICD systems may provide specific advantages in two patient groups: (i) patients with symptomatic sick-sinus-syndrome (incl. bradycardia-tachycardia-syndrome) and (ii) patients with known slow ventricular tachycardia or supraventricular tachycardia not amenable to catheter ablation.

In patients with dual-chamber ICDs, however, unnecessary RV pacing needs to be avoided. This is based on data demonstrating worse outcome with dual-chamber (70 bpm) vs. single chamber backup (40 bpm) pacing, if RV ventricular pacing rate in the dual-chamber mode is high (18, 19). Novel algorithms designed to minimize RV pacing in dual-chamber systems should be used to avoid adverse effects of RV pacing (20). These algorithms are appropriate for use in patients with sick-sinus-syndrome and patients with grade I AV block and well tolerated grade II AV block (e.g. asymptomatic mobitz I block).

The issue of dual-chamber versus single-chamber tachycardia discrimination has been addressed by a number of studies, but with conflicting results. Although theoretically dual-chamber discrimination should be superior in specificity for VT detection, clinical data do not unanimously demonstrate significant reductions in inappropriate ICD therapies (21-25). The performance of tachycardia discrimination algorithms does not only depend on the quality of algorithms per se, but also on the way how VT/VF detection is programmed in individual patients (e.g. choice of tachycardia detection rate/number of detection intervals, choice of specific combinations of detection criteria and VT therapies). This implies that optimization of clinical results with these algorithms largely correlates with the quality of patient-tailored programming, which clearly is operator-dependent to a certain degree. A few clinical studies with dual-chamber defibrillators have addressed the question whether dual-chamber ICDs improve detection and therapy of slow VTs. Basically, the detection of slow VTs can not necessarily be solved simply by using dual-chamber ICDs with sophisticated discrimination algorithms, but that VT ablation plays a major role in this subset of patients. Furthermore, one should remember that initiation of antiarrhythmic medication (e.g. with amiodarone) may prolong the cycle length of VT (i.e. reduce the rate in bpm), so that ensuring VT detection while avoiding inappropriate therapies may be very challenging, even in modern dual-chamber devices. Therefore, symptomatic sustained slow VT despite appropriate drug treatment (especially if unresponsive to antitachycardia pacing) remains an indication for catheter ablation.

**CRT- vs. single-/dual-chamber defibrillator.** Cardiac resynchronization therapy (CRT) requires the placement of a left ventricular lead, targeting a posterolateral or posterior cardiac vein through a transvenous access; rarely, epicardial lead implantation is required for anatomical reasons. Thus, AV-sequential biventricular pacing can be accomplished, intended to reduce electrical and mechanical dyssynchrony at multiple levels (atrioventricular, interventricular, intraventricular and intramural). Marked dyssynchrony is typically found in patients with wide QRS complex, particularly in those with left bundle branch block. Early CRT defibrillator trials have focused on patients with moderate to severe heart failure (NYHA III-IV), left ventricular EF ≤ 35% and QRS ≥ 120–130 ms (MIRACLE ICD, COMPANION) (26, 27). The MIRACLE ICD trial (n=369) demonstrated that CRT-D compared to single-chamber ICD programming improved QoL, NYHA functional class and peak oxygen consumption. The much larger COMPANION study (n=1520) showed that both CRT pacemakers and CRT defibrillators reduced the combined endpoint of death or hospitalisation by 20% compared with optimal pharmacologic therapy (27). Subsequently, CRT-D trials were extended to patients with mild to moderate heart failure (NYHA III, left ventricular EF ≤ 30-40% and QRS ≥ 120–130 ms (REVERSE, MADIT-CRT
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and RAFT) (28-31). REVERSE was the first trial in mildly symptomatic patients (NYHA I/II) with LVEF ≤ 40% and QRS ≥ 120 ms, demonstrating in the European cohort that CRT-pacing reduced the risk of clinical worsening measured with a composite index in patients with NYHA I/II heart failure. This was interpreted in a way that CRT prevents the progression of heart failure in patients with asymptomatic and mildly symptomatic heart failure. Two large randomized trials (MADIT-CRT and RAFT) have recently demonstrated in cohorts with mild to moderate heart failure (NYHA I-II/II-III), left ventricular EF ≤ 30% and QRS ≥ 130/≥ 120 ms that CRT defibrillators reduce the combined endpoint of death or hospitalization as compared to ICD therapy alone. In RAFT, the patients with a CRT-D system also benefitted with respect to all-cause mortality. The most relevant CRT defibrillator trials are summarized in table 4. Unfortunately, not all patients benefit from CRT defibrillators as far as alleviation of heart failure symptoms is concerned; the percentage of non-responders in major clinical trials was around 30%. Subgroup analyses from the largest CRT defibrillator studies (COMPANION, MADIT-CRT and RAFT) consistently revealed that patients with left bundle branch block and QRS width ≥ 150 ms benefit most from CRT defibrillators. Because we have learned that there are patients with wide QRS but minimal mechanical dyssynchrony and vice versa, the predictive value of various echocardiographic dyssynchrony parameters to identify responders to CRT is of major interest. However, two recent prospective studies on this issue (PROSPECT and RethinQ) were disappointing (32, 33). Currently the focus of research is on novel echocardiographic techniques (such as “speckle tracking”) as well as on CT- and MRI-based measurements of dyssynchrony, the latter modalities also providing data on scar localization and coronary venous anatomy (34).

Current ESC guidelines have defined a class I indication for CRT-pacemakers/CRT-defibrillators in patients with NYHA III/IV heart failure, LVEF ≤ 35%, QRS ≥ 120 ms and sinus rhythm (35). In less symptomatic patients (NYHA I/II), a class I indication was only assigned to candidates with QRS ≥ 150 ms (35).

Limitations and complications of ICD therapy

“Electrical storm”. The term electrical storm refers to repetitive appropriate ICD therapies delivered in a short period of time. In the absence of a formally approved definition, usually at least three appropriate VT/VF detections within 24 h, either associated with shocks or antitachycardia pacing (or untreated sustained VT documented in a device monitor zone), would be classified as “electrical storm” (36). Up to 25% of ICD patients have been demonstrated to experience such an event within 3 years (36). The reasons underlying the development of electrical storm are truly manifold: Progression of heart failure/underlying cardiac disease, acute coronary syndrome, electrolyte imbalance (e.g. hypocalcemia due to diarrhea), psychological stress, changes in antiarrhythmic medication/proarrhythmia, infective diseases and many other medical conditions have been shown to be associated with episodes of “electrical storm”. It is to be remembered that such events are associated with increased mortality (36), and every effort needs be made to minimize the risk for the patient. In the management of electrical storm, appropriate sedation (e.g. i.v. midazolam) and administration of antiarrhythmic drugs (i.v. amiodarone, i.v. betablocker if hemodynamically tolerated) are basic measures which usually need to be taken as early as possible. Correction of electrolyte imbalance (target serum potassium level 4.5-5.0 mmol/l; additional magnesium supplementation in individual cases, e.g. with torsade-de-pointes tachycardia) and modifications of ICD programming (e.g. optimization of antitachycardia pacing; overdrive pacing; etc.) usually represent the next steps. Once the situation
is stabilized, the components of further diagnostic workup are to be selected on an individual basis. If a reversible/correctable cause of electrical storm can be excluded, long-term amiodarone treatment is usually implemented (combined with betablocker therapy whenever possible). Sotalol may be tried in patients with contraindications against amiodarone, although a randomized trial demonstrated only a strong tendency towards shock reduction with sotalol versus betablocker treatment within one year (37). Ablation of ventricular tachycardia (usually guided by 3D mapping systems) is a valuable alternative, particularly for monomorphic VT in postinfarction patients. The long-term success rates of VT ablation in patients with electrical storm have been shown to largely depend on the primary result, the best outcome being achieved if no VT at all remains inducible af-

Table 4: Brief overview of major CRT defibrillator trials. In all trials shown here except for RAFT, patients with atrial fibrillation were excluded. Furthermore, it should be noted that in the European cohort of the REVERSE trial, several important patient baseline characteristics differed from the remainder of the REVERSE trial population.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Follow Up</th>
<th>Main Inclusion Criteria</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRACLE-ICD</td>
<td>369</td>
<td>6 months</td>
<td>NYHA III/IV, LVEF ≤ 35%, QRS ≥ 130 ms</td>
<td>CRT-D improved QoL and NY-HA class in comparison to ICD alone.</td>
</tr>
<tr>
<td>COMPANION</td>
<td>1520</td>
<td>1.3 years</td>
<td>NYHA III/IV, LVEF ≤ 35%, QRS ≥ 120 ms</td>
<td>CRT-P / CRT-D reduced the combined endpoint of all-cause death or hospitalisation.</td>
</tr>
<tr>
<td>REVERSE</td>
<td>610</td>
<td>1 year</td>
<td>NYHA I/II, LVEF ≤ 40%, QRS ≥ 120 ms</td>
<td>CRT-pacing “on” non-significantly reduced the risk of clinical worsening measured with a composite index (p=0.10) in comparison to CRT-pacing “off” (all study patients implanted with either CRT-D (83%) or CRT-P (17%)).</td>
</tr>
<tr>
<td>REVERSE European Cohort</td>
<td>262</td>
<td>2 years</td>
<td>NYHA I/II, LVEF ≤ 40%, QRS ≥ 120 ms</td>
<td>CRT-pacing “on” significantly reduced the risk of clinical worsening measured with a composite index (p=0.01) in comparison to CRT-pacing “off” (all study patients implanted with either CRT-D (68%) or CRT-P (32%)).</td>
</tr>
<tr>
<td>MADIT-CRT</td>
<td>1820</td>
<td>2.4 years</td>
<td>NYHA I/II, LVEF ≤ 30%, QRS ≥ 130 ms</td>
<td>CRT-D reduced the combined endpoint of all-cause death or hospitalisation in comparison to ICD alone.</td>
</tr>
<tr>
<td>RAFT</td>
<td>1798</td>
<td>3.3 years</td>
<td>NYHA I/II, LVEF ≤ 30%, QRS ≥ 120 ms or paced QRS ≥ 200 ms</td>
<td>CRT-D reduced the combined endpoint of all-cause death or hospitalisation in comparison to ICD alone.</td>
</tr>
</tbody>
</table>

Abbreviations: 6MWT – six minute walk test, LVEF – left ventricular ejection fraction, CRT-D – CRT with defibrillator function, CRT-P – CRT with pacemaker function, NYHA – New York Heart Association, OMT – optimal medical therapy, pVO2 – peak oxygen consumption, QoL – quality of life, QRS – QRS width
ter ablation (38). International guidelines recommend i.v. amiodarone (or procainamide) followed by VT ablation in patients with frequently recurring or incessant monomorphic VT (2).

**Inappropriate ICD shocks.** ICD shocks delivered for reasons other than ventricular tachycardia or ventricular fibrillation are defined as inappropriate shocks. In the MADIT II trial inappropriate shocks occurred in 11.5% of patients within two years of follow up, with about one third of total shock episodes (31.5%) being inappropriate (39). Probably explained by the longer follow up in SCD-HeFT (3.8 years), the percentage of patients with inappropriate shocks was even greater (17.4%) in this primary prevention trial (40). A similar percentage of inappropriate shocks (13% within a mean follow up of 3.4 years) was found in a Dutch single-centre observational study in 1,544 ICD recipients implanted between 1996 and 2006, suggesting that randomized studies and routine ICD use are comparable in this respect (41). Inappropriate shocks have a significant impact on prognosis, with doubled all-cause mortality rates compared to patients free of shock shown in both MADIT II and SCD-HeFT. The reason why inappropriate shocks have this negative impact on prognosis are not fully understood: It has been speculated that the development of atrial fibrillation in patients with heart failure plays a role, because this arrhythmia is associated with both adverse prognosis and inappropriate shocks. Furthermore, negative inotropic effects of the shock itself may increase mortality, particularly if patients receive multiple shocks due to oversensing or ongoing supraventricular tachycardia. Rarely, inappropriate shocks can provoke ventricular tachycardia of fibrillation, i.e. exert proarrhythmic effects.

The most common reason for inappropriate shocks is atrial fibrillation with rapid ventricular response, followed by (regular) supraventricular tachycardia and oversensing. The latter most commonly results from lead defects, but can also reflect (external) electromagnetic interference with the device or T wave oversensing (fig. 2). In a large ICD cohort, a history of atrial fibrillation, age below 70 years, no statin use and interim appropriate shocks were independent predictors of inappropriate shocks (41).

Minimizing the risk for inappropriate shocks remains a challenging goal, even with modern ICD systems. Basic considerations include tailoring of heart failure medication (with an appropriate dose of beta-blocker, etc.) and an appropriate choice of VT detection rate (no lower than necessary). Active VT zones (including shocks) below 170-180 bpm (particularly in single-chamber devices) should only be programmed if sustained “slow VT” is known (42). Standard tachycardia discrimination algorithms – such as stability, morphology and sudden onset criteria in single-chamber devices, and manufacturer-specific dual-chamber discrimination algorithms in dual-/triple-chamber devices – should routinely be programmed “on”, because the risk of inappropriate shocks usually is by far greater than the risk of VT underdetection. A concise overview published by Josephson and coworkers covers major aspects of shock reduction in ICD patients, addressing both appropriate and inappropriate therapies (43).

**Necessity of testing defibrillation effectiveness.** In order to ensure effective defibrillation, ICDs used to be tested routinely during implantation by repetitive induction of ventricular fibrillation and determination of an estimated minimal effective energy level for defibrillation commonly termed “defibrillation threshold” (DFT). Implanters aimed to reach a low DFT in order to acquire a safety margin between the DFT and the maximum output of the ICD. The value of this approach was self-evident in the early era of ICDs with significant rates of defibrillation failure and high rates of appropriate shocks (44). Later, this practice was modified in the way that successful termination of VF at an energy level 10 J below the maximal output of the device was considered appropriate to ensure
defibrillation effectiveness (e.g. termination of 2 induced VF episodes with 25 J each in a 35 J device). However, in modern high-output ICDs with left pectoral implantation the primary shock success rates have been estimated to be as high as 95% for submaximal and 99% for maximal shocks in the setting of induced ventricular fibrillation (44). Additionally, the incidence of shocks has declined, because most ICDs are implanted for primary prevention indications today and antitachycardia pacing is used as a first-line therapy for the termination of ventricular tachycardia. Hence, it has been questioned whether routine implant testing still is mandatory, and survey data indicate that many implanting centres have stopped this practice (44). This issue is still unresolved but novel data can be expected from current randomized trials (e.g. the SIMPLE trial) that prospectively test risk and benefit of routine DFT testing.

**ICD system infections.** Infections of ICD systems remain a significant problem in clinical practice. Infection rates may actually have risen in recent years with the use of increasingly complex ICD systems and the extension of ICD indications to older patients with more co-morbidities (45). As a matter of fact, ICD system infections are associated with considerable morbidity and mortality. Because antibiotic treatment alone is generally insufficient to manage this condition, complete ICD explantation (including all implanted leads) is mandatory to cure these patients.

**Defibrillation lead failure.** Defibrillation lead failure can occur as lead fracture, insulation defect, lead perforation, loss of capture and sensing defects. As may be expected, it has been shown that lead failure rates progressively increase with time after implantation (46). Reported rates of lead failure vary widely. For example, two large analyses have found cumulative rates of 2.5% after 5 years as opposed to 15% after 5 years and 40% after 8 years, respectively (46, 47). Long-term stability and safety of ICD leads remains an important goal of technological development.

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Figure 2: ICD Holter recording of an episode of T wave oversensing leading to an inappropriate ICD shock. In the near-field signal (“V”), large T wave amplitudes are detected and interpreted as ventricular fibrillation by the ICD.

Abbreviations: FF – far-field signal, V – near-field (bipolar) signal, Vs – signal detected, VF – signal detected in the ventricular fibrillation zone
Current trends in ICD technology

Remote patient monitoring. A growing number of ICD platforms is supplemented by tele-monitoring options, and a recent EHRA consensus paper has underlined the potential of this new technology (3). Remote monitoring of ICD patients may be realized through transmission of automatically measured data from the ICD to a service center with the use of a telephone station at the patient’s home. It has been shown that remote monitoring holds the potential to detect technical problems such as lead failure and T wave oversensing earlier if compared with the conventional practice of scheduled in-house visits at regular intervals; thus, the risk of inappropriate shocks can be reduced (3). Furthermore, several ICD systems can detect and record additional physiological parameters such as atrial fibrillation burden, intrathoracic volume status and patient activity status, which may allow for timely and individualized therapy adjustments. It is to be expected that remote monitoring of ICDs will become increasingly common in the near future, e.g. as part of telecardiology networks in ambulatory heart failure patients.

Shock reduction. It is well-documented that ICD shocks are a major cause of reduced quality of life in ICD recipients due to psychological stress and anxiety (48, 49). Hence, there is an ongoing effort to reduce the incidence of shocks. Major progress was made by establishing the effectiveness of antitachycardia pacing for fast ventricular tachycardia (188–250 bpm), which is associated with a marked reduction of shocked arrhythmias (48, 49). Further advances may be expected from optimization of detection algorithms to prevent inappropriate shocks (i.e. SVT discrimination, lead noise discrimination, etc.) and respective clinical evaluation (50). In patients with stable VT, prophylactic VT ablation before ICD implantation has been demonstrated to prolong survival free from VT or VF (51). Other aspects of shock reduction are discussed above (see “inappropriate ICD shocks” and “electrical storm”).

“Wearable cardioverter-defibrillator”. The “wearable cardioverter-defibrillator” (WCD) is an external device that is able to automatically detect and terminate ventricular tachycardia and ventricular fibrillation (52). It uses a set of monitoring and defibrillation electrodes and a defibrillation unit that is worn on a belt. Registry data show that the WCD is a feasible option for patients at temporary high risk for VT/VF, as bridge to decision for ICD implantation or as bridge to re-implantation after a device infection (53). Hence, use of the WCD is likely to further increase in the near future, e.g. in high-risk patients with myocarditis or in the early phase after the initial diagnosis of a cardiomyopathy (52).

Subcutaneous ICD systems. In 2010, Bardy et al. presented a comprehensive clinical evaluation of a new ICD system without transvenous leads, denoted “entirely subcutaneous ICD” (54). The system consists of a pulse generator that is implanted subcutaneously on the left lateral thorax and a subcutaneous electrode that is placed parasternally on the left side. It could be demonstrated that this system reliably detected and effectively defibrillated ventricular fibrillation (both induced and spontaneous episodes) with 65J shocks (54). However, defibrillation thresholds can be higher than 65J in individual cases. Basically, an “entirely subcutaneous ICD” is a valuable alternative for patients with limited central venous access. It may also offer some further advantages, mainly the absence of complications such as endocarditis, pericardial effusion, thrombosis and venous occlusion. However, clinical trials directly comparing subcutaneous with transvenous ICDs need to be performed, in order to clarify whether this concept may be developed towards a first line therapy.

MRI conditional systems. Magnetic resonance imaging (MRI) has rapidly become the
imaging modality of choice in many diagnostic areas. This includes a wide variety of diseases particularly in the fields of neurology, orthopedics and gastroenterology. But also in modern cardiology, MRI scans play a major role, both in the characterization of cardiomyopathies and the diagnosis of regional myocardial ischemia. To date, ICD recipients are excluded from MRI use except in cases of urgent need ("firm relative contraindication") due to potential electromagnetic interference with consequent device failure or damage to the myocardium. MRI conditional pacemaker systems, however, have already been developed and are in clinical use; the latest generation has been approved for both extrathoracic and thoracic MRI scans (55). It is to be expected that MRI conditional pacemakers will become the standard of care, and the development of MRI conditional ICD systems has now entered the phase of early clinical trials.

Conclusions

Originally developed for patients resuscitated from cardiac arrest, the vast majority of today’s ICDs are implanted in patients with heart failure at increased risk for ventricular arrhythmia ("primary prevention indication"). Based on a convincing body of evidence confirming a significant mortality benefit, postinfarction patients with severely depressed left ventricular function (LVEF ≤ 30%) have a class I indication for ICD implantation. The same is true for patients with symptomatic heart failure (NYHA II-III) of ischemic or non-ischemic origin and left ventricular ejection fraction ≤ 35%. Primary prevention ICD indications in less common cardiomyopathies (e.g. hypertrophic or arrhythmogenic right ventricular cardiomyopathy) or primary electrical heart disease (e.g. Brugada or Long-QT-syndrome), however, are based on individual risk stratification algorithms derived from observational studies and registry data.

Ongoing technological progress is likely to bring up further advances in the near future. Current ICD platforms will be optimized by systematic use of remote patient monitoring and novel algorithms designed to reduce shocks; the latter would be considerably supported by improving long-term stability of ICD leads. As far as novel device hardware is concerned, an entirely subcutaneous ICD as well as MRI-compatible ICD platforms are already under clinical investigation.

References


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