# Risk Stratification and Benefit of ICD-Therapy in Congestive Heart Failure Patients

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## Summary

*The therapy of congestive heart failure has been improved significantly by new therapeutic measures such as cardiac resynchronization by biventricular pacing. In addition, optimized medication regimens are helping to preserve cardiac function, thus delaying terminal cardiac failure. Nevertheless, the mortality of heart failure patients remains high due to sudden cardiac death, emphasizing the need to evaluate the benefit of implantable cardioverter defibrillator therapy in these patients and establish a suitable method of risk stratification. The prospective multicenter implantable cardioverter defibrillator-congestive heart failure registry was initiated to assess the benefit of implantable cardioverter defibrillator therapy in patients with coronary artery disease or dilated cardiomyopathy who are in an advanced stage of heart failure. Patients with an ejection fraction of £ 30% who have previously been in a stage of decompensation, but are currently in stable heart failure with optimal medication, are further evaluated with respect to the sudden cardiac death risk by Holter electrocardiography and programmed stimulation. The study will evaluate the total cardiac mortality and the arrhythmic mortality, and will assess possible risk parameters for their use in a risk stratification of heart failure patients. The first case included in this study is reported.*

## Key Words

Heart failure, risk stratification, sudden cardiac death, implantable cardioverter-defibrillator (ICD)

## Introduction

Congestive heart failure (CHF) is a major health problem worldwide, currently afflicting more than six million people in Europe and two to four million in the United States. This already represents 1 % – 2 % of the total population, but incidence and prevalence are continuously increasing in the aging population. Congestive heart failure patients have an annual mortality rate of 12 to 32 % [1]. Patients not only succumb to terminal cardiac failure, but they are also at a high risk of sudden cardiac death (SCD), depending on the degree of heart failure. The SCD risk has been shown to constitute between 31 % and 64 % of all deaths, depending on the stage of heart failure, and is proportionally the highest in patients with better preserved cardiac function as assessed by the NYHA classification system for heart failure [1-3].

Malignant ventricular tachycardia (VT) and ventricular fibrillation (VF) are the major causes of SCD, although terminal bradycardia is also common. Antiarrhythmic therapy was shown to be ineffective in preventing SCD in CHF patients [4].

## Current Treatment Strategies of Congestive Heart Failure

The treatment of CHF has been improved in recent years due to individually tailored medication regimens combining several drugs. Several prospective studies have shown the benefit of β-blockers [3,5-8] and angiotensin converting enzyme (ACE) inhibitors [9,10] in preserving cardiac function and reducing total mortality by delaying terminal heart failure. Even in

the patient group with severe CHF, who were in NYHA stages III or IV and had an indication for elective heart transplantation, optimized therapy was able to delay deterioration of cardiac function and extend the time before transplantation becomes indispensable [11,12].

In addition to progress being made in optimizing standard therapies, recent technological advances in the field of electrotherapy have provided totally new concepts for the treatment of CHF. New lead technologies and corresponding devices have made new innovative stimulation therapies such as cardiac resynchronization by left ventricular and biventricular stimulation possible. The combination of optimized medication and the more widely applied use of the newly available stimulation therapies can significantly improve hemodynamics, cardiac function, and quality of life in specific patients. It still remains to be demonstrated whether cardiac resynchronization can also reduce mortality in patients who benefit from this treatment with respect to hemodynamics or cardiac function. The impact on total mortality of the collective CHF patient group is, however, expected to remain relatively insignificant, since only 15 % to 30 % of all CHF patients are expected to be eligible for cardiac resynchronization by stimulation therapy [13].

Treating known arrhythmias has become a well-established, though increasingly elaborate aspect in managing CHF patients, as summarized in Figure 1 [14]. In the past decade, implantation of an implantable cardioverter defibrillator (ICD) has become a widely accepted treatment for arrhythmia. The ICD has been shown to be very effective in preventing SCD, and was used initially for secondary prevention in patients resuscitated from cardiac arrest. More importantly perhaps, the ICD has also been shown in recent trials to be equally effective in the primary prevention of SCD in certain high risk patient groups [15,16]. Specifically, patients with coronary artery disease (CAD), prior myocardial infarction, left ventricular dysfunction, and documented, non-sustained VT (nsVT), have been shown to benefit from ICD implantation, which is reflected in current implantation guidelines [17,18].

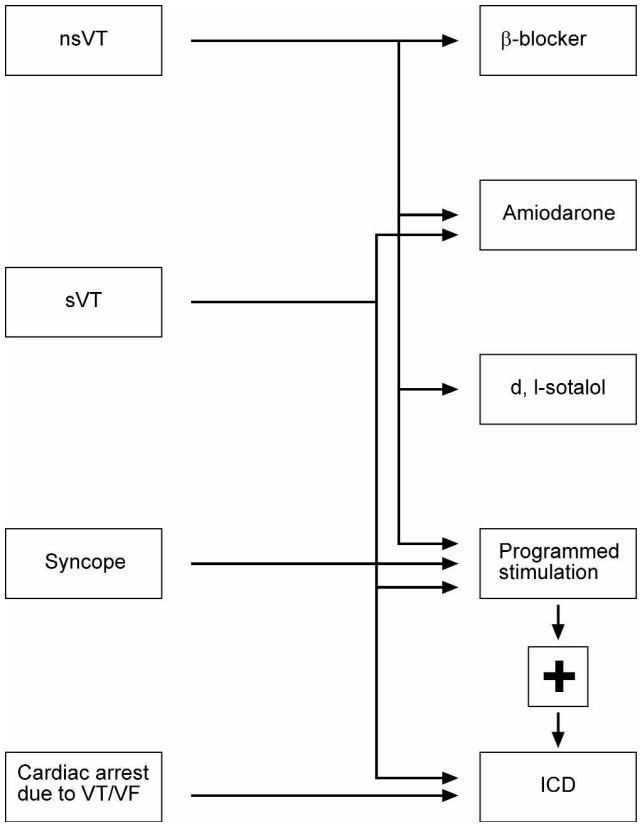


*Figure 1. Possible treatment of ventricular arrhythmias in congestive heart failure patients. nsVT = nonsustained ventricular tachycardia, sVT = sustained ventricular tachycardia, ✚ = inducible sVT or VF (schema adapted from reference [14]).*

### Rationale of the ICD-CHF Registry

Despite these obviously significant improvements in the treatment of CHF, which help in preserving cardiac functionality and delay terminal cardiac failure, the patient group presenting with advanced heart failure nevertheless remains at a high risk of arrhythmic death. As a consequence, total mortality remains unacceptably high.

The Merit HF trial showed that the incidence of SCD was proportionally greatest in patients with less severe heart failure. In that study, SCD as a mode of death varied from 64 % in patients in NYHA II to only 33 % in patients in NYHA IV. In a meta-analysis of 27 studies, similar mortality rates were determined [1]. Such clinical data seemed to lend support in the past to the view that mainly patients with preserved cardiac function would benefit from ICD therapy. However theses studies have shown that SCD rates are highest in those patients with more severe heart failure, indicating that these patients may also be candidates for an ICD. Indeed, recent subgroup reanalyses of clinical data from the AVID, MADIT, and CIDS trials have shown

that patients with a lower left ventricular ejection fraction (EF) reflecting seriously impaired cardiac function, actually tended to benefit more from ICD therapy with respect to mortality, compared to those with a higher EF and better preserved cardiac function [19-21].

In addition, there is still some controversy among clinicians whether SCD and heart failure are independent risks. One hypothesis is that SCD and heart failure may not be independent risks, and that SCD death and death due to heart failure might be directly linked. This would imply that preventing SCD would simply shift the mode of death from sudden death to subsequent heart failure, thus negating any benefit of ICD therapy in improving survival. An alternative viewpoint considers SCD and heart failure to be relatively independent risks. Based on this assumption, it may be postulated that as terminal heart failure is delayed and patients survive longer, the competing risk of sudden death is relatively increased. Retrospective data lend support to this thesis, with a shift in mode of death from terminal heart failure to sudden death being observed [11].

In the studies mentioned previously, only the subgroup of CHF patients implanted with an ICD or treated with antiarrhythmics was assessed, restricting possible generalizations derived from the study results. A further limitation for drawing definite conclusions from these data is that a larger proportion of ICD patients had received β-blockers compared to patients on drug therapy. In addition, the use of other drugs with antiarrhythmic properties or possible survival benefit such as sotalol, calcium antagonists, and digoxin differed in the study groups.

In summary, insufficient, prospective, clinical data on the collective patient group of heart failure patients are available to assess whether a reduction of the SCD rate can actually extend survival significantly. In particular, the available data could not take into account the recent improvements that have been made in conventional CHF therapy and the resulting shift in the mode of death. The current mortality rates and distribution of the modes of death are not precisely known. Therefore, it is still unclear which patient group will benefit from ICD therapy with respect to improved mortality. Also, there is currently no generally accepted risk stratification procedure that allows the identification of individual patients who will benefit from this elaborate and expensive therapy. A variety of non-invasive and invasive clinical parameters have been studied in the past. However, to date, no clinically feasible risk parameters have been universally established. The presence of nsVT has been prospectively shown to be an independent risk marker in patients with CHF, regardless of etiology [22]. Programmed stimulation during electrophysiological (EP)-study is a suitable method of stratifying risk in patients with CAD [15], and it has recently been the focus of more clinical research as a possible method of assessing individual risk in patients without CAD.

In order to assess the benefit of ICD therapy in patients with advanced CHF in conjunction with a suitable risk stratification procedure, a prospective multicenter study, the ICD-CHF Registry, was recently initiated. The main objective of the registry is to evaluate the reduction of total cardiac mortality and the arrhythmic mortality with ICD therapy in the high risk sub-population of advanced CHF patients selected according to a defined risk stratification procedure. Assessing the efficacy of the risk stratification procedure, as well as identifying new possible non-invasive risk markers, are additional important goals of this clinical project.

**Risk Evaluation Procedure**

At the University of Leipzig Heart Center, all patients presenting with an EF ≤ 40 % and in NYHA stage II, III or IV heart failure are registered at the time of admission. From this larger population, consecutive patients who are eligible for inclusion in the multicenter ICD-CHF Registry are identified. Patients presenting with either CAD or dilated cardiomyopathy (DCM) with an EF ≤ 30 %, who are currently in NYHA stage II or III, and who have previously been in a stage of decompensation (NYHA class IV) may be included. Further inclusion criteria are treatment with optimal medication including diuretics, β-blocker and an ACE or angiotensin II inhibitor, as well as optimal therapy of concurrent diseases. Patients who are currently in decompensated heart failure or are listed for urgent heart transplantation will be excluded.

A 24-hour Holter electrocardiogram is recorded, and patients are evaluated for the presence of nsVT, which is defined in this study as the presence of between three and thirty consecutive beats at a frequency of 120 beats per minute or greater. Patients are subsequently assessed for inducible VT or VF during EP-study according to a defined stimulation protocol. Patients

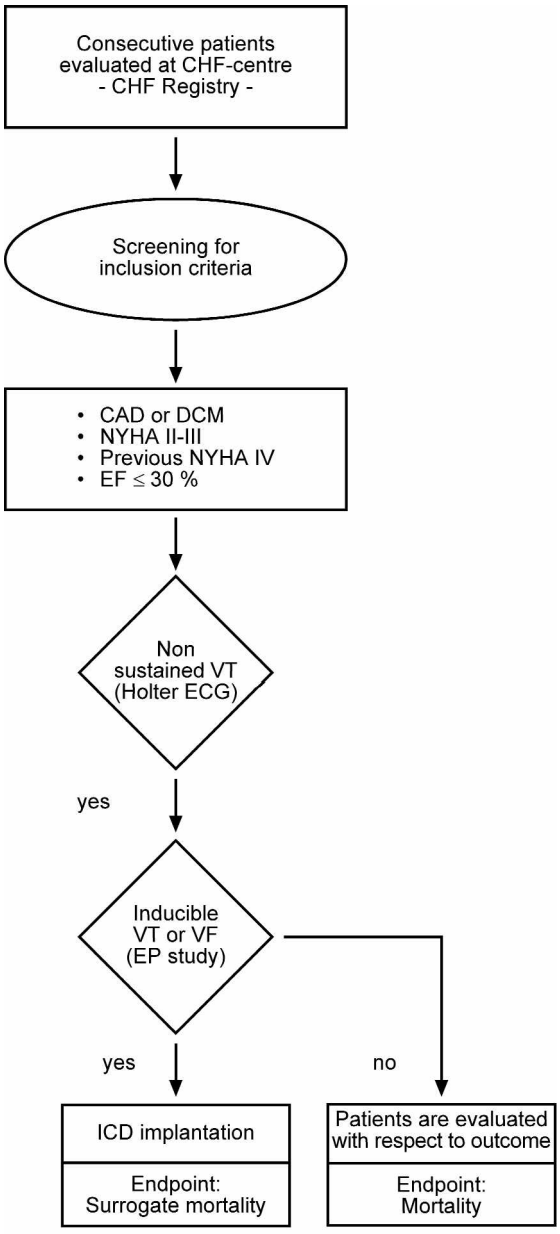


*Figure 2. Risk evaluation procedure for patients included in the ICD-CHF Registry. CAD = coronary artery disease; DCM = dilated cardiomyopathy; EF = left ventricular ejection fraction.*

with inducible sustained VT or VF will be implanted with a suitable ICD, whereas non-inducible patients will only be followed up (Figure 2).

Echocardiographic re-assessment will be performed at 6 and 12 months. To assess the cardiac mortality rates and the arrhythmic mortality rates, a surrogate endpoint is used. The endpoint surrogate arrhythmic mortality is initially defined as the first occurrence of a documented episode of VF or sustained VT with a cycle length < 300 ms or syncopal shock or severe bradycardia. Receiver operating characteristic (ROC) analysis will be performed to determine the optimal cut-off value for the cycle length of sustained VT in defining surrogate mortality for the studied patient group.

Additional risk parameters are to be prospectively recorded and assessed for their suitability in a risk stratification procedure. These include heart rate variability (HRV) parameters, heart rate turbulence (HRT) parameters [23], and parameters of nonlinear symbolic dynamics [24]. Additional rhythmologic parameters to be assessed are the presence of ventricular premature beats (VPB), the presence of left or right bundle branch blocks (BBB), and the mean heart rate.

## Results

Up to now 50 CHF patients were screened and two were included in the ICD-CHF Registry.

*Case 1*

The 65-year-old male with dilated cardiomyopathy and concurrent compensated renal insufficiency was admitted to our heart center because of increasing dyspnea and peripheral edema, corresponding to NYHA functional class III. He reported recurrent cardiac decompensation during the last half year. The last hospitalization due to cardiac decompensation was two months ago.

The ECG showed a sinus rhythm with first degree AV-block, a left axis deviation, no typical bundle branch block, but a QRS duration of 140 ms. During echocardiography, a dilated left ventricle with diffusely impaired left ventricular function, and moderate mitral and tricuspid regurgitation were revealed. The enddiastolic diameter was 8.9 cm and the endsystolic diameter was 7 cm. An angiography of the coronary system was performed. The venogram revealed no CAD, a dilated left ventricle with severely impaired function, and no regional wall motion abnormalities. The EF was 25 %. A 24-hour Holter ECG recording showed sinus rhythm and no supraventricular tachycardia. The mean heart rate was 92 beats per minute. Four runs of nsVT were recorded, with a maximum of nine consecutive beats and a cycle length (CL) of 380 ms.

The patient's medication was optimized to include a ß-blocker (metoprolol 100 mg), an ACE inhibitor

(ramipril 5 mg), a diuretic (furosemide 20 mg), and spironolactone (25 mg).
After receiving written consent we included the patient in the ICD-CHF Registry. EP-study was performed according to the protocol. A sustained monomorphic VT with a CL of 370 ms was induced. Therefore, the patient fulfilled all criteria for ICD implantation according to the study protocol. ICD Implantation is scheduled.

*Case 2*
The 71-year-old female with a history of myocardial infarction and concomitant diabetes mellitus presented with symptoms of advancing heart failure. Four weeks ago she had been in hospital because of pulmonary edema and supraventricular tachyarrhythmia. She was in a state of recompensated heart failure (NYHA class III) at the time of admission to the heart center.
The ECG revealed rate controlled atrial fibrillation, with a left axis deviation and negative T-waves in five leads. The Holter recording showed atrial fibrillation with normal ventricular response and a mean heart rate of 75 beats per minute. Two episodes of nsVT with a maximum of five beats and CL 450 ms were recorded. A dilated left ventricle with severely depressed left ventricular function, apical and posterolateral hypokinesis, and mild mitral regurgitation were seen during echocardiography. The EF was 25 %, the enddiastolic diameter was 6.9 cm, and the endsystolic diameter was 5.2 cm. Coronary angiography showed diffuse CAD with chronic occlusion of the marginal branch, as well as multiple peripheral stenosis of the left anterior descending branch, the circumflex branch, and the right coronary artery. The medication included a ß-blocker (carvedilol 100 mg), an A II inhibitor (candesartan 8 mg), a diuretic (hydrochlorothiacide 25 mg), and digitalis (digitoxin 0.07 mg).
The patient was included in the ICD-CHF Registry after giving her informed consent.
During EP-study no sVT or VF could be induced, therefore the patient was assigned to the non ICD study group.

## Conclusion

Treatment of CHF patients has seen impressive advances with the establishment of new treatment strategies such as biventricular pacing and optimized medication. Nevertheless, mortality remains high due to the occurrence of SCD. Obviously, not all patients with CHF should be implanted with an ICD since not all patients have an equally high risk. In addition, budgetary considerations would not allow for such an approach. It is important to improve risk stratification procedures in order to better identify sub-populations that are at an increased risk for arrhythmic death and will profit most from ICD therapy. This study aims to verify a combined risk evaluation procedure consisting of invasive and non-invasive parameters, by assessing the total cardiac mortality and the arrhythmic mortality in patients presenting with advanced CHF.
In addition, the design will provide systematic data that may identify additional high risk patient groups. This will permit a further risk stratification of CHF patients, and thus identify patients that may in the future benefit either from ICD therapy or new devices currently being developed specifically for the primary prevention of arrhythmias and risk monitoring.

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