Efficacy of primary preventive ICD therapy in an unselected population of patients with reduced left ventricular ejection fraction.

Sjöblom, J; Kalm, T; Gadler, F; Ljung, L; Frykman, V; Rosenqvist, M; Platonov, Pyotr; Borgquist, Rasmus

Published in: Europace

DOI: 10.1093/europace/euu219

2015

Link to publication

Citation for published version (APA):

General rights
Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

• Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying the publication in the public portal

Take down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.
Efficacy of primary preventive ICD therapy in an unselected population of patients with reduced left ventricular ejection fraction

Sjöblom J (1), Kalm T (2), Gadler F (2), Ljung L (3), Frykman V (1), Rosenqvist M (1), Platonov PG (4), Borgquist R (4).

1. Karolinska Institutet, Department of Clinical Sciences, Division of Cardiovascular Medicine, Danderyd University Hospital.
2. Karolinska Institutet, Department of Cardiology, Karolinska University Hospital.
3. Karolinska Institutet, Department of Cardiology, Södersjukhuset, Stockholm.
4. Lund University, Arrhythmia Clinic, Skåne University Hospital, Sweden.

Address for correspondence: Johanna Sjöblom, MD, Department of Cardiology, Danderyds Hospital, 18288 Stockholm, Sweden. Tel +46 8 12358818, Fax nr + 46 8 7534009, e-mail; johanna.sjoblom@ds.se
Abstract

Aims: International guidelines advocate an implantable cardioverter and defibrillator (ICD) in patients with reduced left ventricular ejection fraction (LVEF) to prevent sudden death (SCD). Previous data suggest that the benefit of ICD therapy in real life may be lower than expected from the results of controlled studies and side-effects are not negligible. It is also unclear if women benefit from treatment to the same extent as men. The aim of this study was to study the balance between benefits and complications of ICD therapy in a real-life population of patients with heart failure.

Methods: We studied 865 consecutive patients with reduced LVEF treated with ICDs for primary prevention of SCD in 2006–2011 in four tertiary care hospitals in Sweden (age 64 ± 11 years, 82% men, 62% ischaemic). The patients’ medical records were scrutinized as regards appropriate therapies, complications related to the defibrillator, all-cause mortality and gender differences. Mean follow-up was 35 ± 18 months.

Results: During follow-up 155 patients (18%) received appropriate ICD therapy, 61 patients (7.1%) had inappropriate shocks, 110 patients (13%) had at least one complication that required reoperation and 213 patients (25%) died. Men were twice as likely to receive ICD treatment compared with women (20% vs. 9%, p=0.02), but neither total mortality nor complication rates differed.

Conclusions: Ventricular arrhythmias necessitating ICD therapy are common (6% annually). Women are less likely to have correct ICD treatment, but have the same degree of treatment complications, thus reducing the net benefit of their treatment.
**Keywords:** Primary preventive defibrillator, appropriate therapy, complications, gender differences
**Introduction:**

Sudden cardiac death (SCD) primary prevention guidelines advocate ICD therapy in patients with reduced left ventricular ejection fraction (LVEF) (1). In a pooled analysis of ten different studies on primary preventive defibrillators in patients with heart failure, all-cause mortality with ICD therapy was on average reduced by 7.9% compared with optimal medical treatment only (2).

However, controversy still exists concerning the cost-efficacy of ICDs for primary prevention in patients with heart failure, partly because of the relatively high rates of post-implantation hospitalization and complications (3). The reported complication rates vary in different studies, but in a recent review of eleven well-known randomized ICD studies, the overall lead dislodgement rate was 1.8% (4). A much higher complication rate was reported in a real-life survey of 440 ICD patients in Germany, where 31% of the patients experienced some type of complication (5).

Another question is whether or not women experience the same benefit as men from ICD treatment. A meta-analysis of five trials with a total of 934 female patients failed to show a reduction in all-cause mortality (6), raising the question of whether indications for ICD treatment should be different for women than for men.

The aim of this study was to investigate the net benefit of primary preventive defibrillators as regards the incidence of appropriate ICD therapies, inappropriate shocks, complications and possible gender differences in a real-life population.
Methods: Using ICD registry data, 865 consecutive patients receiving an ICD for primary prevention of SCD during 2006–2011 were identified at four tertiary care hospitals in Stockholm and Lund, Sweden. All patients who had a primary preventive ICD implanted because of heart failure, defined as LVEF \( \leq 35\% \), were originally included. We excluded patients with a history of previous sustained ventricular arrhythmias, cardiac arrest, Brugada and Long QT syndromes or familial cardiomyopathy, such as arrhythmogenic right ventricular dysplasia and hypertrophic cardiomyopathy.

All patients’ medical records were scrutinized in order to verify the data from the ICD registry regarding indications and to evaluate the patients’ morbidity before implantations. Atrial fibrillation was defined as any known episode of atrial fibrillation before implantation and kidney disease was defined as S-Creatinine >106 before implantation. All patients received antibiotic prophylaxis before ICD implantation. The ICDs were programmed according to the attendant physician’s preferences, and all patients had ATP programmed before shock therapy. The VT-zones were normally programmed from 180-190 beats per minutes, and the VF zone from 240-250 beats per minute. In the medical records we evaluated the presence of appropriate therapies such as ATP or shocks. If an arrhythmia episode required ICD discharge after unsuccessful ATP therapy, it was classified as shock treatment in the analyses. The therapy was classified as appropriate or not according to the attended physician’s medical notes. Appropriate therapy was defined as ventricular arrhythmias correctly sensed and treated by the devices. All complications related to defibrillator therapy were analysed. We investigated both procedure-related
complications and remote complications such as electrode problems, infections and inappropriate therapies. Electrode problems were defined as unacceptable high thresholds, low sensing amplitude or diaphragmatic stimulation that could not be resolved with re-programming. The data was cross-validated regarding survival status using the National Swedish Cause of Death Registry and the causes of death were taken from available data in the registry during 2006–2012.

Statistics: Continuous data is presented as mean ± standard deviation or median, as appropriate. Nominal data is presented as number (% of cases). Fisher's exact test was used for comparison of categorial variables and Student’s *t*-test was used for comparison of continuous variables. A two sided *p*-value < 0.05 was considered statistically significant. For survival analysis, Kaplan-Meier curves and multivariate Cox analysis were used. All statistical analyses were performed using IBM SPSS Statistics version 21.

Ethics: The study received approval from the Regional Ethics Committee (Dnr 2012/771).

**Results**

*Baseline Characteristics*

A total of 865 patients received primary prophylactic ICD implantation during the time period. Baseline clinical characteristics are presented in Table 1. In summary, the mean age at implantation was 64 ± 11 years, 82% were men, 62% had ischaemic aetiology and 51% received a CRT-D system. The mean follow-up time was 35 ± 18
months. No patients were lost to follow-up with regard to mortality, but 48 patients were lost to follow-up because they were treated outside the hospitals catchment areas and four patients were lost to follow-up because of heart and lung transplant. There were no significant differences between genders in respect of age, LVEF, NYHA class or morbidity, with the exception of prevalence of atrial fibrillation (42% of the males vs. 23% of the females, p<0.001). The male patients were also more likely to have had a previous CABG operation (34% vs. 11%, p<0.001) and ischaemic aetiology compared with the women (64% vs. 53%, p=0.01).

ICD treatment

The annual rate of patients that received their first appropriate ICD interventions was 6.2%. Men were more than twice as likely to have received ICD treatment than women (20% (141 men) vs. 9% (14 women), p=0.02; Figure 1). Eighty-three patients (9.6%) were treated by means of ATP only and 72 patients (8.3%) had shock treatment. Of the latter, 30 patients (3.5%) had both ATP and shock treatment. One patient had unsuccessful shocks, but the arrhythmia later self-terminated. The median time to first appropriate therapy was 20 (range 1–57) months for shocks and 16 (<1–52) months for ATP treatment. The baseline characteristics of the patients with appropriate therapy compared to those with no therapy are listed in Table 2. A stepwise multivariate Cox analysis was performed and the only significant factors that were correlated to appropriate therapy was gender, which had a Hazard ratio of 2.4 CI 1.2–4.5 and p-value 0.01.

Inappropriate shocks
In total, 61 patients (7.1%) had inappropriate shocks and the annual rate was 2.4%. The most common cause of inappropriate therapy was atrial arrhythmia (72%), followed by oversense problems (13%), often caused by T-wave oversense but in 4 cases the ICD-leads were replaced. The association between inappropriate therapy and atrial fibrillation was strong (p<0.001).

There was a tendency for men to have more inappropriate shocks than women (7.7% vs. 3.9%, p=0.10).

Complications

The total number of patients who had complications during follow up was 121 (14%). Of these 110 patients (13%) were re-operated (4.4% annually). There was no gender difference, 13% of both men and women (n=90 and n=20 respectively) had complications that required reoperation.

The types of complications, including inappropriate shocks, are listed in Table 3 and in summary the most common problem was dislocation or dysfunction of the ICD electrode or the LV electrode, which together accounted for 63% (n=76) of all the complications. Because of infections, 16 patients had to have the entire system removed. The median time from implantation to infection was 2 months (range 0–41 months). All infections except one was correlated to the primary implantation. Very few patients had perioperative complications (perforation or pneumothorax, for example).
The time between primary implant and reoperation varied widely, the median time being 10 months (range 0–67 months). An estimated 66% of the ICD lead problems appeared later than 2 months after primary implantation.

The total number of complications requiring reoperation was significantly lower among the patients with ICD-VR device (10%) compared to the patients with ICD-DR and CRT-D (13% and 16% respectively p=0.03). Among the 441 patients with CRT-D devices 37 (8.4%) had complications related to the LV lead requiring reoperation and in 2 cases the LV lead were just programmed off. Atrial lead complications affected 4 patients with CRT-devices and 8 patients with ICD-DR device.

*Mortality*

A quarter of the patients (213) died during follow-up, and among them only 45 (21%) had had a previous ventricular arrhythmia appropriately treated by means of ATP (n=23, 11%) or shocks (n=22, 10%). Of the patients receiving shock therapy, eight had also undergone appropriate ATP on other occasions. Neither previous shock nor ATP therapy were associated with death during follow-up (p=0.25 and p=0.48 respectively). The median time from first correctly treated arrhythmia to time of death was 16 months (range 0.2–47 months). Only 13 (6.1%) of those who died had previously received inappropriate shocks and the association between death and inappropriate therapy was not significant (p=0.64). Neither was reoperation associated with a higher risk of death during follow-up.
There were no gender differences as regards mortality. During follow-up 182 men (26%) and 31 women (20%) died (p=0.21).

_Cause of death_

The most common cause of death according to the Swedish Cause of Death Registry was heart failure (n=86 [40%]), while malignancy, acute myocardial infarction (AMI) and stroke were other frequent reasons. In only 8 patients (3.4%) was arrhythmia assumed to be the cause, but many deaths occurred during 2013 and unfortunately there are no data from the registry covering this time period (Figure 3).

There were no significant differences between genders as regards cause of death (p=0.64). No patients died before hospital discharge after ICD implant, but two patients died within 30 days after the implantation.

Among those who died, 36 patients (21%) had had their ICD inactivated before death according to the medical records and only 5 patients (4%) had their device interrogated after death.
Discussion

Our study in a real-life cohort of primary prophylactic ICD-treated patients demonstrates that overall, 6.2% of the patients annually receive presumably life-saving treatment for ventricular arrhythmias. However, the arrhythmia event rate was significantly lower in women, while the complication rate was similar, implying less total net benefit from ICD treatment for women compared with men.

Real-life cohort

Our cohort was based on consecutive patients in four tertiary care hospitals in Sweden, representing almost 30% of the yearly ICD implants in the country, which supports the ability to generalize the study findings. Since all patients in the hospital catchment areas who received ICD treatment were included, the findings are more likely to represent the “true” net result of primary prophylactic ICD treatment in Sweden, compared with findings in selected patient cohorts in prospective randomized trial populations. Patients declining participation can always affect the results in prospective studies. Compared with patients in MADIT II, DEFINITE, COMPANION and SCD-Heft studies (7-10), our patients had a higher prevalence of atrial fibrillation and beta blocker therapy. The follow-up time in our study was also relatively long and complication rates increased over time. There are also several differences between our study and the newly published study from Denmark which investigated ICD complication rates (11). Unlike the Danish study, we investigated only patients with heart failure, only primary implantations and besides investigating complications we also examined both appropriate and inappropriate ICD therapies.
ATP and shock therapy

It is impossible to say if the arrhythmias treated in our study by means of ATP or shocks would have been fatal without therapy. Many arrhythmias are self-terminating and modern ICD programming tries to accommodate this and avoid unnecessary treatment by using delayed detection algorithms (12, 13). We chose to report both ATP and shocks because many clinicians select ATP even for very fast ventricular arrhythmias according to data from Pain Free and similar studies (12-14).

In our study 18% of the patients had appropriate therapy during 35 months of follow-up. This is almost the same proportion of patients as seen in the MADIT II, DEFINITE and SCD-heft studies (15).

Inappropriate shocks

Only 7.1% of the patients had inappropriate shocks, a figure slightly lower than in many studies, in which an occurrence of inappropriate shocks ranging from 9 to 24% has been reported (15-17). The main reason for inappropriate therapy in our study, as in many others, was atrial fibrillation. The tendency for men to have more inappropriate therapy compared with women could be a result of the higher incidence of atrial fibrillation among men. Better knowledge and more “conservative” programming (i.e. higher VT zones with longer detection intervals and more ATP therapy attempts before shock therapy) may have contributed to the reduced number of unnecessary shocks. Use of newer or improved discriminatory features such as continual update morphology templates may also have improved arrhythmia classification.
Complications

Many patients suffer from device-related complications and the complication rates in this real-life study group were much higher than in earlier randomized trials and almost as high as in a real-life survey in Germany (5). This is in spite of the fact that all of the participating centres are high volume sites. One important explanation for higher complication rates in real-life surveys may be that in randomized studies the patients are more selected. Another important factor is study duration. Complications increase with time. The longer you look, the more you find! The most frequent complications were lead-related, and our study showed that the more electrodes, the greater the risk for complications. The same results were also shown in the Danish study (11). We believe that this is an important issue to take under consideration when choosing type of ICD-system. Not surprisingly, many had problems with the left ventricular leads (4.3%), but ICD-lead complications were also common (4.5%) and the problems often appeared after several months. Other investigators have reported that some leads show an annual failure rate of 2.6% (18). Another issue, which will probably continue to increase over time, is device-related infections (19). Multiple studies confirm increasing infection rates and the National Hospital Discharge Survey in the USA revealed a 57% increase in infections but only a 12% increase in devices implanted between 2004 and 2006 (19). The reason for the increasing infection problem is unknown, but multiple leads, several surgical procedures, generator replacement, pocket haematoma and a high level of morbidity are factors that are correlated to higher infection rates (20). In our cohort there were no significant differences regarding morbidity or the proportion of LV-lead implants among the patients who suffered infections compared with the others. Perhaps greater
use of antibiotics and increased bacterial resistance in the community also contribute to the higher infection rates seen today.

Complications are resource-demanding and even in low absolute numbers they have an impact on the net health economic benefit of the treatment and the quality of life of the affected patients. However, no complications in our study were lethal and there was no association between complications and increased mortality.

Gender differences

In our study, as in many other studies regarding ICD therapy, there were significantly fewer women than men. One explanation could be that women have a lower incidence of coronary heart disease and are older when they become ill. Even so, the question remains – are women offered the treatment to the same extent as men? In the national Swedish registry for coronary heart disease, the incidence of AMI is consistently about 50% lower per age group in women compared with men, but this does not explain the fact that only 18% of primary prophylactic ICD recipients are women.

Another question is if women receive equal benefit. In our study, women had a significantly lower rate of correctly treated arrhythmia episodes (9% compared with 20% in men), but the mortality rate was the same (Figure 2). Earlier published meta-analyses of gender differences in relation to primary preventive ICD treatment have shown that women have a significantly lower rate of appropriate forms of therapy and fewer survival benefits (22). Multivariate Cox analysis showed that male gender was an independent predictor of appropriate ICD therapy and perhaps men have a greater propensity for ventricular arrhythmias, just as they have for sudden cardiac death.
There is a need for prospective observational studies including all patients with implants (“real-world” cohorts) in order to clarify this issue.

Death

In our study 25% of the patients died during follow-up, and in line with expectations only 3.8% died as a result of intractable ventricular arrhythmias, according to the Swedish Cause of Death Registry. This number could be falsely low because few patients (3%) had their devices interrogated after death according to the medical records. Relatively few of those who later died (21%) had suffered previous documented correctly treated arrhythmias before death. The mean time from first correctly treated arrhythmia to death was 16 months, implying that the ICD treatment had significantly prolonged their lives.

Even though the overall mortality rate in our study was significant, ICD treatment extends life for many patients, resulting in a higher rate of mortality from other causes – death from heart failure in particular. In this setting, ICD shocks in terminal stage illness can cause pain and anxiety, and it is of great importance to make a decision about deactivation in terminally ill patients to reduce the risk of harmful shocks,(24). In this study only 21% of the patients that died had their ICDs deactivated, although the majority of the patients died as a result of progressive disease.

Limitations:
This is not a randomized clinical trial but a retrospective study based on detailed analysis of medical records from patients with primary preventive ICD treatment. There is always a possibility that the clinicians did not classify the arrhythmias correctly and the numbers of both appropriately and inappropriately treated arrhythmias could be different. There is also a risk that problems with devices could have been undetected when the medical records were scrutinized. No patients were lost to follow up as regards mortality, but some arrhythmias may have been missed if the patients sought medical care elsewhere and the device memory was cleared at that time. Since there was no standardisation in programming the detection intervals and zones of therapy, this may have biased the results regarding therapies even though the majority of patients had very similar “standard primary prophylactic ICD programming” with only a fast VT zone (>188 bpm) and a VF zone (>250 bpm).

**Conclusion:**

Many patients (18%) with heart failure and primary preventive ICDs have correctly treated arrhythmias, but women have significantly less appropriate therapy than men, thus reducing the net benefit of their treatment. Furthermore, the treatment is associated with a 19.5% risk of serious complications, including inappropriate shocks (7%) during the first 3 years. These facts should be taken into account when informing patients preoperatively, and when calculating the net health-economic effects of the treatment.

**Conflict of interest:** none declared.


Table 1. Baseline characteristics before implantation.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>64 ± 11</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>713 (82)</td>
</tr>
<tr>
<td>Mean EF (%)</td>
<td>26 ± 11</td>
</tr>
<tr>
<td>Diabetes n (%)</td>
<td>254 (29)</td>
</tr>
<tr>
<td>Ischemic aetiology (%)</td>
<td>536 (62)</td>
</tr>
<tr>
<td>Previously AMI (n)</td>
<td>519 (60%)</td>
</tr>
<tr>
<td>Previous Coronary bypass surgery (%)</td>
<td>262 (30)</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>319 (37)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>407 (47)</td>
</tr>
<tr>
<td>Pulmonary disease (%)</td>
<td>94 (11)</td>
</tr>
<tr>
<td>Kidney disease (%)</td>
<td>307 (36)</td>
</tr>
<tr>
<td>NYHA I (%)</td>
<td>38 (4)</td>
</tr>
<tr>
<td>NYHA II (%)</td>
<td>221 (26)</td>
</tr>
<tr>
<td>NYHA III (%)</td>
<td>401 (46)</td>
</tr>
<tr>
<td>NYHA IV (%)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Beta blocker therapy (%)</td>
<td>822 (95)</td>
</tr>
<tr>
<td>QRS &gt;120 ms (%)</td>
<td>437 (51)</td>
</tr>
<tr>
<td>Left bundle-branch block (%)</td>
<td>348 (40)</td>
</tr>
<tr>
<td>Percent CRT-D / ICD-DR / ICD-VR</td>
<td>51 / 34 / 15</td>
</tr>
<tr>
<td>Manufacturer devices % Medtronic/ SJM/ Boston Scientific/ Biotronic/ Sorin Group</td>
<td>29 / 45 / 20 / 5 / 1</td>
</tr>
<tr>
<td>Manufacturer ICD-electrode % Medtronic sprint fidelis/ Medtronic other/ SJM Riata/ SJM other/ Boston Scientific/ Biotronic</td>
<td>13 / 13 / 15 / 33 / 14 / 13</td>
</tr>
</tbody>
</table>
Table 2. Differences in baseline characteristic between patient with appropriate ICD therapy and not.

<table>
<thead>
<tr>
<th></th>
<th>Patients with appropriate therapy (n=121)</th>
<th>Patients without appropriate therapy (n=744)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>65 ± 10</td>
<td>63 ± 11</td>
<td>0.14</td>
</tr>
<tr>
<td>Gender male % (n)</td>
<td>16% (111)</td>
<td>84% (602)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mean EF (%)</td>
<td>25 ± 11</td>
<td>26 ± 11</td>
<td>0.29</td>
</tr>
<tr>
<td>Diabetes (n)</td>
<td>26% (32)</td>
<td>30% (222)</td>
<td>0.52</td>
</tr>
<tr>
<td>Ischemic ethiology (n)</td>
<td>69% (83)</td>
<td>61% (453)</td>
<td>0.06</td>
</tr>
<tr>
<td>Previously AMI (n)</td>
<td>66% (80)</td>
<td>59% (439)</td>
<td>0.08</td>
</tr>
<tr>
<td>Atrial fibrillation (n)</td>
<td>40% (48)</td>
<td>36% (271)</td>
<td>0.54</td>
</tr>
<tr>
<td>Kidney disease (n)</td>
<td>40% (49)</td>
<td>35% (258)</td>
<td>0.22</td>
</tr>
<tr>
<td>LBBB (n)</td>
<td>35% (54)</td>
<td>41% (294)</td>
<td>0.15</td>
</tr>
<tr>
<td>NYHA III or IV (n)</td>
<td>59% (70)</td>
<td>54% (386)</td>
<td>0.37</td>
</tr>
</tbody>
</table>
Table 3. Device related complications including inappropriate shocks. 13 patients had both complication requiring reoperation and inappropriate shocks and some patients were reoperated more than once.

<table>
<thead>
<tr>
<th>Type of complication</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perioperative complications</strong></td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>Perforation</td>
<td>2 (0.2%)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (0.5%)</td>
</tr>
<tr>
<td><strong>Postoperative complications</strong></td>
<td></td>
</tr>
<tr>
<td>ICD-electrode dysfunction</td>
<td>39 (4.5%)</td>
</tr>
<tr>
<td>LV-electrode dysfunction</td>
<td>37 (4.3%)</td>
</tr>
<tr>
<td>Atrial-electrode dysfunction</td>
<td>12 (1.4%)</td>
</tr>
<tr>
<td>Pocket-related problems</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td>Infection</td>
<td>16 (1.8%)</td>
</tr>
<tr>
<td>Multiple reoperations</td>
<td>7 (0.8%)</td>
</tr>
<tr>
<td>Inappropriate shocks total caused by atrial arrhythmia/ over-sense/other causes</td>
<td>44/ 8/ 9</td>
</tr>
<tr>
<td>Other complications</td>
<td>3 (0.3%)</td>
</tr>
<tr>
<td><strong>Total number of patients with ≥1 complication</strong></td>
<td>169 (19.5%)</td>
</tr>
</tbody>
</table>
Figure 1. Percentages of male and female patients receiving appropriate therapy, inappropriate shocks or complications requiring reoperation during follow-up.
Figure 2. Kaplan-Meier curves showing time to death or appropriate therapy (A) and time to appropriate therapy (B).
Figure 3. Causes of death

- Heart failure n=86
- Myocardial infarction n=19
- Arrhythmia n=8
- Malignancy n=28
- Stroke n=12
- Renal failure n=4
- Septicaemia n=6
- Miscellaneous n=14
- Unknown n=14/Not reported n=23