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High Readmission Rates and Mental Distress after Infective Endocarditis - results from the national population-based CopenHeart IE survey

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High Readmission Rates and Mental Distress after Infective Endocarditis - results from the national population-based CopenHeart IE survey

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STRUCTURED ABSTRACT

Background: Infective endocarditis (IE) is a severe disease requiring lengthy hospitalization. Little is known about patients' recovery after IE. The aims of this study in IE patients were; (i) to describe mortality, readmission, self-reported health and rehabilitation up to 1 year post-discharge, (ii) to examine associations between self-reported health and readmission, and (iii) to investigate predictors of readmission and mortality.

Methods: All adults treated for IE in Denmark, January-June 2011 (N=347), were followed in registers. Eligible individuals (n=209) were invited to participate in a questionnaire survey (responders n=122). Responses were compared with those of a background reference population and a heart valve surgery population. Mortality and readmission data from registers 12 months post-discharge were investigated.

Results: Patients discharged after treatment for IE had a mortality of 18% (95% confidence interval (CI): 14%-23%) one year post-discharge and 65% (95% CI: 59%-71%) had been readmitted, the majority (82%) acutely. Patients had lower self-reported health compared to the background population (physical component scale (PCS); mean (standard deviation (SD)): 42.2 (11.1) vs. 47.1 (12.1), (p=0.0004), mental component scale (MCS); 50.1 (11.7) vs. 53.8 (9.2), (p=0.006), and more were sedentary (29 vs. 15%), (p=0.002). Large proportions had clinical signs of anxiety and depression, 25% and 22% respectively, exceeding a hospital anxiety and depression scale (HADS) cut-off score of 8. Almost half (47%) had not been offered cardiac rehabilitation (CR).

Conclusions: After IE, mortality and readmission rates were high and self-reported physical and mental health poor. These findings call for changes in in-hospital and post-discharge management.

1. INTRODUCTION

Infective endocarditis (IE) is an infection of the endocardial surface, most often involving the heart valves. It is one of the most serious infectious diseases in the Western world and is associated with high mortality and severe complications, such as acute heart failure and stroke [1].

Symptoms of IE often resemble symptoms in more commonly seen infections like influenza. As a consequence, there is often a delay in receiving an accurate diagnosis and treatment, which may cause frustration and anxiety to the patient [2] and, at worst, an increased risk of debilitating or fatal complications [3]. Treatment entails 4-6 weeks of hospitalisation, high-dosage antibiotic therapy and in about 50% of cases also valve surgery [4]. Patients often suffer considerable loss of weight and muscle mass as a result of reduced appetite and/or physical inactivity and can struggle with concerns about survival, recovery, family and work [2].

Patient-reported outcomes (PROs) during recovery following IE are sparsely reported. Studies indicate that patients treated for IE have persisting physical symptoms and decreased self-rated health for an extended time post-discharge [5,6]. Similarly, qualitative findings describe patient experiences of physical weakness and extreme fatigue, but also identify emotional instability, including anxiety and depression as major themes [7].

The incidence of IE has been rising, presumably due to an increase in predisposing factors [8,9]. The incidence is reported between 3 and 15 per 100 000 person-years in 21st century European and North American cohorts [4,9], and in Denmark 8-10 cases per 100 000 person-years [10]. In spite of advances in diagnostics and treatment, mortality remains at 15 - 20% in hospital [11] and 25 - 40% at 1 year post-discharge [12]. Current studies exploring long-term mortality in unselected populations are sparse.

Considering the severity of IE, its' complex and lengthy treatment, poor clinical outcomes and patient accounts of insufficient recovery, surprisingly few studies have explored the burden of disease post-discharge. So far, epidemiological descriptions have predominantly been based on single centre, referral hospital based cohorts and, thus, concerns about selection bias have been raised [13]. Furthermore, to our knowledge no prior studies have included data on all-cause readmissions, patient-reported anxiety and depression, physical activity levels and rehabilitation participation. As the understanding of patients' physical and mental health recovery is limited, and the causes and extent of readmissions and rehabilitation remain unexplored, clinicians and health care policy makers may fail to provide follow-up strategies to facilitate optimal recovery and reduce risks of adverse outcomes.

The aim of this nationwide unselected population based study was, (i) to describe mortality, readmissions, self-reported physical and mental health and rehabilitation participation up to 1 year after hospitalisation for IE, (ii) to examine the association between self-reported health and readmission, and (iii) to investigate predictors of readmission and mortality.

2. MATERIALS AND METHODS

2.1 Design, setting and participants

A national population-based survey, supplemented by data from Danish nationwide registers was conducted. Adults (≥ 18 years) hospitalised for IE (n=347), between January 1st and June 30th 2011, were identified through The Danish National Patient Register (DNPR) using the Danish ICD-10 codes for IE: I33, I38, I39, I09.1 and A39.5. Due to diagnostic delay, the initial date of admission for IE was difficult to ascertain, and so baseline data 6 months prior to discharge were described.

Of the identified cohort (n=347), 62 (15%) died in-hospital. No one emigrated, or were non-Danish citizens, leaving a total study population of patients discharged alive of 285. Of these, 33 had a research-protected address and 43 died before December 2011. The remaining 209 patients were invited to participate in a nationwide postal survey in December 2011. The length of time from discharge to survey enrolment in December 2011, varied from between 0 (not yet discharged) and 11 months. The total study population was followed in national registers regarding readmission and mortality 12 months after discharge (Fig. 1).

The Danish National Health Survey 2005 was used as a background reference population [14]. This is a comprehensive health survey with self-reported data, describing the prevalence and distribution of self-reported health and morbidity in the Danish population. Reference persons were randomly selected, including individuals with long-standing disease, and were matched on sex and age. For each respondent (n=122) four reference persons were selected (n=488).

A sample of patients recovering heart valve surgery (HVS) was also used as a reference. Data was collected in a parallel survey study conducted by the same research team as the present study [15]. We included data from 519 HVS responders, excluding those with concomitant IE.

2.2 Variables and outcomes

Register data were used for baseline assessment, and register data and generic and disease-specific questionnaires were used for outcome assessment.

2.2.1 Baseline variables

Baseline information was collected from the DNPR [16] and the Danish Civil Registration System [17]. Stays in Intensive Care Unit (ICU) were identified using the national Danish intensive care database. As adequate codes were missing in 33% of ICU admissions, these were not included in

analyses. Retrospective data, covering a period of 10 years, were collected for the calculation of Charlson comorbidity index score.

2.2.2 Patient-reported measures

Short Form 36 (SF-36) is a generic measure of self-rated health, consisting of 36 items measuring 8 health variables [18]. Scores range from 0 to 100 with higher scores indicating better perceived health, and are summarised into a physical component scale (PCS) and a mental component scale (MCS). Reliability is high, with an internal consistency coefficient (Cronbach's alpha) often exceeding 0.80 for the composite score, and usually 0.90 for both the MCS and PCS [19].

EQ-5D is a standardised measure of current health state [20]. Scores can be summarised into a crosswalk mean reflecting the five dimensions, and a visual analogue scale (VAS) score mean. Higher scores indicate better perceived health. An overall Cronbach's alpha of 0.73 has been found in patients with coronary heart disease [21].

HeartQoL is a heart disease-specific questionnaire, measuring health-related quality of life (HRQoL). Scores range from 0–3, with 3 indicating highest HRQoL. Scores are summarised in a global, a physical and an emotional score. Cronbach's alpha for the subscales has been shown to be between 0.80-0.91 [22].

Hospital anxiety and depression scale (*HADS*) assesses levels of anxiety and depression [23], and offers two scores, HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D), with higher levels indicating more symptoms. Scores 8 and above indicate the possible presence of a mood disorder and scores 11 and above indicate probable presence. HADS has been shown to be valid and reliable, with a Cronbach's alpha of 0.83 and 0.82 for HADS-A and HADS-D, respectively [23].

The Multidimensional Fatigue Inventory 20 (*MFI-20*) measures fatigue severity, yielding five dimensions; general fatigue, physical fatigue, reduced activity, reduced motivation and mental fatigue [24]. Higher scores indicate a higher level of fatigue, with 4 being no fatigue and 20 the worst imaginable fatigue. The instrument has been tested in different populations with Cronbach's α of 0.84 [24].

Physical Activity was assessed using the physical fitness question; *Looking at the <u>past 6-12 months</u>, what would you say best describes your leisure time physical activity, <u>after</u> your hospital admission?* used in The Danish National Health Survey [14] described in section 2.1. Yielding four possible answers, results were collapsed into the following two categories of physical activity level; moderate/high and low/sedentary.

Rehabilitation was investigated using a questionnaire developed by the Danish Heart Foundation about the extent and quality of rehabilitation for heart disease patients [25]. The instrument has not been formally validated.

2.2.3 Readmission and mortality

Hospital readmissions and mortality were ascertained from the DNPR [16] and the Civil Registration System [17, respectively. These are registers with national coverage with no loss to follow-up. All participants discharged alive were followed one year post-discharge.

A hospital readmission was considered to be any registration in the DNPR, according to the administrative coding, of an in-hospital stay where the date of discharge was different from the date of admission. The readmission was categorised according to primary discharge diagnosis (ICD-10 coding), or surgical procedure codes (NOMESCO coding) with following predefined codes: IE (I33, I38, I39, I09.1, A39.5), ischemic stroke (I63, I64), atrial fibrillation/flutter (I48), pacemaker (PM) or implantable cardioverter defibrillator (ICD) implantation (BFC), pericardial effusion and

pericardiocentesis (I30, KFE, KTFE00), congestive heart failure (I50), sternal infection (M96, T81), pneumonia (T81, J12-J18), surgery in the thoracic region (KFW), mediastinal infection (J98.5, KFWC00), and other cardiovascular diagnoses not included in the above (I00-I10, I12-I29, I31-I37, I39-I47, I49, I51-I99). All-cause mortality data was also ascertained.

2.3 Statistical methods

Baseline characteristics, self-reported outcomes and rehabilitation participation were explored using descriptive statistics. SF-36 scores and self-reported physical activity were compared with an age- and sex-matched background reference population and an unselected HVS population using independent Students t-test for continuous variables and chi2 tests for categorical variables.

Readmissions were investigated at patient and readmission level, using descriptive statistics. Time to first acute readmission and mortality were analysed using Kaplan-Meier survival methods. Analyses of self-reported measures scores, comparing readmitted with non-readmitted IE patients were performed using linear and logistic regression. Fatigue scores were not tested as residuals were not normally distributed. Predictors of readmission and mortality were analysed using a Cox proportional hazard model with time since discharge as underlying time scale. For all regression analyses an unadjusted and a model adjusted for age, sex and Charlson comorbidity index score were used. The pre-selected potential predictors tested in the cox models were chosen based on clinical relevance via discussions with clinicians and through literature review.

2.4 Ethics

The study complies with The Declaration of Helsinki and was approved by the Danish Data Protection Agency (Rec. no. 2011-41-6378/2013-41-1643) and by the institutional human research committee. Informed consent was obtained from participants and data were extracted and processed in accordance with the Act on Processing of Personal Data [25].

3. RESULTS

3.1 Participants

Of the patients discharged alive after IE (n=285), 69% were male, mean (SD) age was 64 (16) years, with 41% ≥ 70 years, and 49% married (Table 1). During the 6 months prior to discharge, 28% had had cardiac surgery, 6% had had cardiac device extraction, 51% had had other diagnosis of infection and 7% had had stroke. The mean number of days hospitalised (acute and scheduled), within the 6 months prior to discharge, were 49 (inter-quartile range (IQR), 30-63) days, 15% had had more than 5 days in an ICU and more than half had a Charlson comorbidity index score above 2 (Table 1).

The response rate to the survey, after two repeat reminders, was 58% (n=122). Responders were more often men, older and married than non-responders, and a larger proportion of responders had had cardiac- or device surgery and longer hospitalisation. There were no noticeable differences between responders and non-responders regarding time from hospital discharge to survey enrolment (Table 1).

3.2 Mortality and readmission within 12 months after surgery

Cumulative mortality one year post-discharge was 18% (95% CI: 14% - 23%) (n = 52), of which 87% were within 6 months (Fig 2A). Including in-hospital deaths, cumulative mortality was 33% (95% CI: 28% - 38%). Within 12 months post-discharge, 65% (95% CI: 59% - 71%) (n = 186) had had one or more readmissions, 59% (53% - 64%) (n = 167) acute (Table 2 and Fig. 2B). The total number of readmissions was 483, with an average readmission rate of 2.6 per person (Table 2). The most frequently reported primary diagnoses of readmissions were recurrence of IE (14%), congestive heart failure (5%) and atrial fibrillation and/or flutter (5%) (Table 2).

3.3 Patient-reported outcomes in IE population versus reference populations

Following IE, participants had significantly lower scores on the SF-36, compared with a matched background population in all the sub-domains (except for bodily pain (p = 0.28)), and in the two component scales (PCS; mean (SD): 42.2 (11.1) vs. 47.1 (12.1), (p = 0.0004), MCS: 50.1 (11.7) vs. 53.8 (9.2), (p = 0.006)) (Table 3). Compared with the HVS population, IE patients scored significantly lower in 5 of 8 sub-domains, but not significantly lower in the two component scales. Participants also reported significantly lower physical activity levels, compared with background reference persons (p = 0.002) and HVS patients (p = 0.003) with 29% of the IE population reporting sedentary behaviour versus 15% in both the background and the HVS population (Table 3).

3.4 Patient-reported outcomes in IE population and association to readmission

For 85% (n = 61) of the responders, readmission had taken place prior to the survey. Readmitted and non-readmitted patients were similar in terms of age; mean (SD): 67.7 (11.6) vs. 65.7 (14.1), (p = 0.42) and sex; proportion of women: (58% vs. 60%), (p = 0.50), but were significantly more co-morbid: Charlson comorbidity index score mean (SD): 2.7 (2.7) vs. 1.5 (1.8), (p = 0.003). Lower self-reported physical and mental health seemed to be associated with readmission (Table 4). Differences were more evident in the physical scores, and were statistically significant in the physical component scale (PCS) of the SF-36, and the physical and global scores of the HeartQoL, however in the adjusted model, only PCS remained significant (Table 4). For scores reflecting probable anxiety or depressive disorders (HADS-A and HADS-D), large proportions of patients had scores exceeding 11 and proportions were larger among readmitted patients compared to patients not readmitted; 14% vs. 2% for the HADS-A, and 22% vs. 4% for the HADS-D. Possible depression (HADS-D ≥ 8) was significantly higher among readmitted patients, however not in the adjusted model. A smaller proportion of patients readmitted compared with those not readmitted had participated in rehabilitation (41% vs. 46%), however the difference was not statistically

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significant. Of the survey participants, 53% (n=55) reported having been invited to participate in

CR following hospitalisation, 47% (n=50) reported not having been invited and 10% (n=10) were

invited but declined participation. A total of 41% participated in exercise-based rehabilitation at a

hospital, or municipality setting (Table 4). Levels of fatigue for all responders were; mean (SD),

general fatigue: 11.1 (4.4), physical fatigue 12.9 (4.7), reduced activity 12.1 (5.0), reduced

motivation 9.3 (4.4) and mental fatigue 9.1 (4.1).

3.5 Predictors of mortality and readmission

Predictors of mortality were higher age (hazard ratio (95% CI): 5.2 (1.8-18.7)) and severe

comorbidity (2.0 (1.1-3.6)), and cardiac surgery was associated with reduced risk of mortality (0.4

(0.2-1.0)) (Table 5). Severe comorbidity (1.6 (1.2-2.2)) and length of hospital stay over 64 days (1.4

(1.0-2.0)) were found to predict readmission, however in the adjusted model only severe

comorbidity remained significant (Table 5).

4. DISCUSSION

4.1 General discussion

A third of all patients contracting IE died within a year, almost one in five while hospitalised.

Concurring with findings of previous research [11,12], these mortality rates were not unexpected.

Although the comorbidity burden in this population was substantial (52% Charlson comorbidity

score ≥ 2), the observed readmission rate of 65% (59% acute), within the first year post-discharge,

seems high. This reveals that the burden of IE for both the patient and healthcare system, does not

cease at the end of the primary admission, but potentially continues to be significant following

discharge. Fourteen percent was readmitted with a diagnosis of IE, which, compared with previous

clinical findings of around 5%, was a relatively high proportion [1,3,26]. These readmissions may

not actually be distinct episodes of relapse/recurrence of IE, but be symptoms of re-infection or

other complications related to the previous episode with IE, which transfers to the primary diagnosis code at readmission. Nonetheless, this evidence adds gravitas to the argument that the close monitoring of this high risk patient population post-discharge is crucial, as is the future development of patient education interventions, including symptom appraisal.

Findings of low self-perceived health and quality of life concur with previous studies [5-7], however were more evident in the present IE cohort, suggesting that the magnitude of the phenomena might be greater than previously thought. Physical health appeared to be more severely affected in IE patients, indicating that physical health problems are probably inadequately addressed after hospitalisation. Almost a quarter of the IE patients reported clinical signs of possible anxiety and depressive disorder (HADS scores ≥ 8). Furthermore, low perceived physical health and the prevalence of possible depression was significantly associated with readmission in this IE cohort. When adjusting for confounders there was a reduction in the effect of readmission on self-reported health, which in all likelihood is a reflection of the effect of comorbidity as a covariate, as a significant difference in comorbidity was observed between patients readmitted and not readmitted. Furthermore, we cannot conclude whether the differences identified are the effects of readmission on patient-reported outcomes or vice versa. Prior research has shown depression to be an independent predictor of mortality in other cardiac populations [27,28]. In light of the severity and prolonged disease trajectory of IE, patients are especially vulnerable to physical deconditioning and psychological distress, which is highlighted by the evidence presented here. There is a need to develop effective interventions to alleviate these adverse consequences in order to improve patients' mental well-being and possibly prevent other adverse outcomes, including readmission and mortality.

Fatigue scores in the present IE cohort were 2-5 points higher, on a 16 point scale, compared to a healthy sample [29]. Fatigue has been shown to be strongly associated to mortality in IE patients [30], and so persisting fatigue in patients recovering IE may be indicative of a high risk subgroup. Moreover, qualitative findings reveal fatigue to be distressing for patients, affecting physical and emotional capabilities and, consequently, hampering patients' daily living, family life and occupational capacity [7]. Therefore levels of fatigue may lead to negative human and socioeconomic consequences. Exercise has been shown to be effective in reducing fatigue in patients with advanced progressive illness, such as cancer and multiple sclerosis [31] and is, therefore, a relevant factor to investigate further in patients following IE.

Almost a third of IE patients, or twice as many as both the background and the HVS population, reported being sedentary. Indeed, the present findings suggest that patients up to one year following IE struggle to regain physical strength and would presumably benefit from exercise-based rehabilitation. In spite of this, almost half were not referred to CR. Although there are currently no disease-specific evidence or guidelines describing effective components of rehabilitation for patients treated for IE, CR is being provided and of the entire cohort, 41% participated in an exercise-based rehabilitation program at a hospital or municipality setting. Compared with the number of patients participating in CR programmes following MI, where average rates are reported to be between 20-50% [32], a participation rate of 43% seems relatively high. That being said, almost half of the cohort (47%) reported that they had not been offered exercise-based rehabilitation, and only 10%, who were offered a program, declined.

Looking at predictors for all-cause readmissions have to our knowledge not been previously explored, however finding comorbidity as the only predictor of the variables tested was not surprising. Contradictive to our anticipation, neither length of stay in ICU nor length hospital stay

were identified as predictors of mortality and/or readmission. These results may reflect that patients are at the same risk, when completing a lengthy stay at ICU or hospital, however, may also be due to a lack of power in the sample size.

The findings of this study contribute to a complex and multifaceted picture of the health status of patients surviving endocarditis, emphasising the continuing challenge in the 21st century for clinicians and researchers to investigate causes and possible interventions to improve serious adverse outcomes. We must be tentative in our conclusions though, as our sample is small, particularly for the responders, leaving us with imprecise estimates. Further research is required to explore patients' self-reported health and associations to poor outcomes and patient characteristics, and to expound causative mechanisms and identify patients at risk. To this end, further consideration should be given to incorporating PRO's in both international and national guidelines as important clinical outcome parameters at discharge. Interventions targeted at regaining physical health and capacity, as well as coping strategies dealing with the psychological challenges after IE may be relevant and should be tested for effectiveness.

4.2 Limitations

A nationwide, population based, unselected cohort is optimal in the pursuit of a representative sample of IE patients post-discharge. Considering that persons usually reporting worse PRO's, such as women and non-married, were less responsive to participate, and that the response rate was 58%, the risk of non-response bias and the degree of generalisability of results should be considered.

Study results based on register data are dependent on correct and complete registration and reporting by clinicians to the registers. The registration may be compromised by factors such as limited resources and misinterpretation of coding instructions, however, coding is done by treating

cardiologists and standards are generally high. According to national guidelines, the diagnosis of IE must be based on the Duke criteria and, thus, data on cases obtained from the DNPR should reflect true values. More clinical detail and further validation of diagnosis however, might have been obtained by patient record review. The self-reported information of the study is, by nature, subjective but data should be considered valid in being a reflection of the patient's perspective.

As so often is the case when doing research in a rare disease population, this study sample was small and results have inevitably suffered as a consequence.

5. CONCLUSIONS

After IE, mortality and readmission rates were high. Self-reported physical and mental health was significantly lower, compared to a matched background population and in part to an unselected heart valve surgery population. One in four had self-reported symptoms of possible anxiety and depression. Half were not referred to rehabilitation and a third was physically sedentary. Furthermore, associations between reduced self-reported health and readmission were identified. In order to improve patient outcomes, these findings strongly indicate the need for optimising the overall management of patients with IE, both during hospital stay as well as post-discharge.

6. ACKNOWLEDGEMENT

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Fig. 1. Patient flow chart


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┌─────────────────────────────────────────────────────┐
│  Patients > 18 years of age hospitalized for infective │
│  endocarditis in Denmark Jan 1st to Jun 30th 2011     │
│                    n = 347                             │
│  Total study population with register based follow-up  │
└─────────────────────────────────────────────────────┘
                        │
                        │──────────┐  ┌──────────────────┐
                        │          └─▶│  Died in-hospital │
                        │             │     n = 62        │
                        ▼             └──────────────────┘
┌─────────────────────────────────────────────────────┐
│  Total study population with register based follow-up  │
│                    n = 285                             │
└─────────────────────────────────────────────────────┘
              │                         │
              ▼                         ▼
┌─────────────────────────────────────────────────────┐
│  Eligible responders for survey (December 2011)        │
└─────────────────────────────────────────────────────┘
          │                         │
          ▼                         ▼
    ┌──────────┐              ┌──────────┐
    │    No    │              │   Yes    │
    │  n = 76  │              │ n = 209  │
    └──────────┘              └──────────┘
          │                    │        │
          ▼                    ▼        ▼
┌──────────────────┐  ┌──────────┐  ┌──────────────┐
│  Dead n = 43     │  │  Non-    │  │ Responders   │
│  Research        │  │responders│  │  n = 122     │
│  protection      │  │  n = 87  │  │              │
│  n = 33          │  │          │  │              │
└──────────────────┘  └──────────┘  └──────────────┘
```
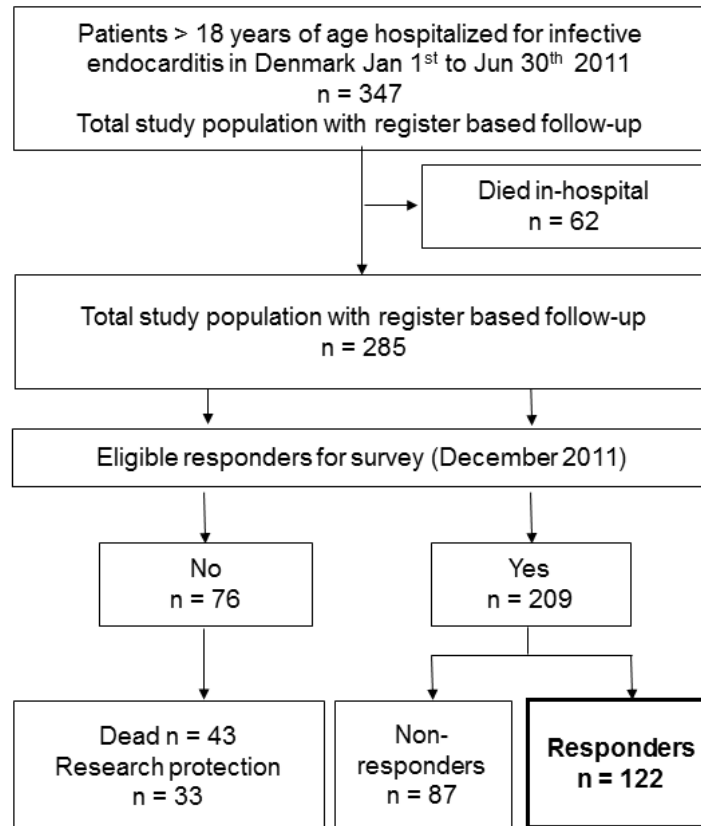
Figure 2. Cumulative mortality (panel A) and acute readmissions 1 year post-discharge (panel B)
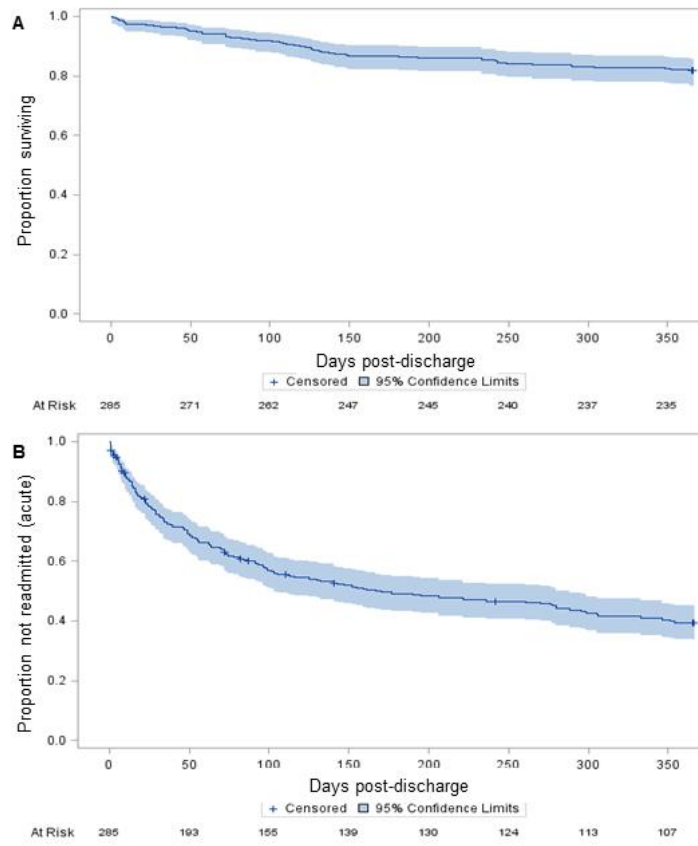
Table 1. Baseline characteristics

	Total population (n=285)	Survey population (n=209)	Responders (n=122)	Non responders (n=87)
Background				
Age	64 (22-99)	65 (22-93)	67 (25-90)	62 (22-93)
Gender, male	196 (69)	143 (68)	89 (73)	54 (62)
Age at discharge:				
22-49	57 (20)	37 (18)	11 (9)	26 (30)
50-69	111 (39)	86 (41)	60 (49)	26 (30)
≥70	117 (41)	86 (41)	51 (42)	35 (40)
Time from discharge to questionnaire:				
Not yet discharged at time of survey	1 (0)	1 (0)	0 (0)	1 (1)
0 – 4 months	16 (6)	15 (7)	7 (6)	8 (9)
5 – 8 months	149 (52)	100 (48)	63 (52)	37 (43)
9 – 11 months	119 (42)	93 (45)	52 (43)	41 (47)
Married at discharge	140 (49)	112 (54)	81 (66)	31 (36)
Mortality, post-discharge, prior to survey	43 (15)	0 (0)	0 (0)	0 (0)
Surgery within 6 months prior to IE discharge				
Cardiac surgery	79 (28)	60 (29)	51 (42)	9 (10)
PM[a]/ICD[b] electrode extraction	18 (6)	17 (8)	12 (10)	5 (6)
Cardiac surgery and electrode extraction	4 (1)	4 (2)	4 (3)	0 (0)
PM/ICD implantation	59 (21)	46 (22)	34 (28)	12 (14)
Hospitalization				
Days hospitalized (acute & scheduled) within 6 months prior to IE[c] discharge	49 (30-63)	49 (30-64)	53 (33-64)	44 (21-60)

Days in ICU[d] within 6 month prior to IE discharge (33% missing)				
0	233 (82)	170 (81)	94 (77)	76 (87)
1 - 4 days (< 75th percentile)	37 (13)	29 (14)	21 (17)	8 (9)
5 - 44 days (≥ 75th percentile)	15 (6)	10 (5)	7 (6)	3 (3)
New diagnosis within 6 months prior to IE discharge				
Other diagnosis of infection[e]	144 (51)	109 (52)	63 (52)	46 (53)
Heart failure	66 (23)	46 (22)	30 (25)	16 (18)
Stroke	21 (7)	18 (9)	14 (11)	4 (5)
Cancer	23 (8)	15 (7)	10 (8)	5 (6)
Hemodialysis	34 (12)	21 (10)	12 (10)	9 (10)
Comorbidities/cardiac history				
Previous heart valve disease[f]	70 (25)	46 (22)	31 (25)	15 (17)
Previous IE	32 (11)	22 (11)	13 (11)	9 (10)
PM/ICD	52 (18)	44 (21)	27 (22)	17 (20)
Heart failure	50 (18)	34 (16)	20 (16)	14 (16)
Hemodialysis	20 (7)	12 (6)	5 (4)	7 (8)
Cancer	32 (11)	20 (10)	14 (11)	6 (7)
Diabetes	57 (20)	46 (22)	28 (23)	18 (21)
Stroke	19 (7)	15 (7)	8 (7)	7 (8)
Previous myocardial infarction	40 (14)	26 (12)	14 (12)	12 (14)
Charlson comorbidity score[g]				
No or mild comorbidity (score=0–1)	136 (48)	110 (53)	63 (52)	47 (54)
Severe comorbidity (score≥2)	149 (52)	99 (47)	59 (48)	40 (46)

* Continuous variables are presented as mean (range for age/interquartile range for days hospitalized), and

for categorical variables as number (percentage).

a Pacemaker, b Implantable Cardioverter Defibrillator, c Infective Endocarditis, d Intensive Care Unit,

e Including: Infection/inflammation of heart valve prosthesis and intracardiac or coronary implant, septicemia,

unspecified bacterial infection, unspecified fever, pneumonia, cystitis and spondylitis/discitis/spondylodiscitis.

f Including: Rheumatic and non-rheumatic heart valve disease and congenital heart valve disease.

g Charlson comorbidity score, an index score calculating the rate of co morbidity due to predefined

diagnoses.

Table 2. Readmissions specified by diagnosis on patient level and readmission level

	Number (%) of patients with readmissions (of total n = 285)	Total number of readmissions
Readmissions	186 (65)	483
Elective readmissions	61 (21)	88
Acute readmissions	167 (59)	395
Readmission diagnosis		
Endocarditis, relapse/recurrence	41 (14)	49
Congestive heart failure	14 (5)	18
Atrial fibrillation and/or atrial flutter	14 (5)	17
Cancer	12 (4)	20
Pacemaker implantation	11 (4)	13
Pneumonia	11 (4)	15
Pericardial effusion	2 (1)	2
Cardiac surgery	13 (5)	13
Ischemic stroke	2 (1)	2
Sternal infection	2 (1)	2
Mediastinitis	1 (0.4)	1
Other cardiac diagnoses	64 (22)	76

Table 3. Self-rated health and self-reported physical activity level of patients after IE compared with a sex- and age matched reference population including individuals with longstanding disease and compared with an unselected sample of patients 6-12 months after heart valve surgery (HVS).

	IE Population (n=122)	Reference population (n=488)	p	HVS Population (n=519)	p
Short Form 36, mean (SD)					
Physical functioning	64.1 (27.5)	79.8 (24.6)	**<0.0001***	69.8 (25.7)	**0.038***
Role physical	40.1 (42.3)	69.7 (41.1)	**<0.0001***	48.2 (43.5)	0.091
Bodily pain	73.4 (27.8)	76.4 (27)	0.2752	80.1 (23.8)	**0.017***
General health	54.9 (24.1)	71.1 (21.9)	**<0.0001***	65.9 (21.9)	**<0.0001***
Vitality	55.7 (27.2)	70.2 (23.1)	**<0.0001***	61.7 (24.3)	**0.032***
Social functioning	77.8 (27.1)	90.5 (17.9)	**<0.0001***	86.1 (22.2)	**0.002***
Role emotional	59.0 (42.3)	82.1 (33.2)	**<0.0001***	64.3 (40.7)	0.263
Mental health	75.8 (21.8)	84.5 (16.4)	**0.0001***	79.7 (19.3)	0.068
Physical component scale	42.2 (11.1)	47.1 (12.1)	**0.0004***	44.5 (10.6)	0.081
Mental component scale	50.1 (11.7)	53.8 (9.2)	**0.006***	52.1 (10.2)	0.107
Physical activity level, n (%)					
Vigorous or moderate exercise	16 (16)	84 (17)		74 (17)	
Low-level physical activity	56 (55)	327 (68)	**0.002***	296 (68)	**0.003***
Sedentary	30 (29)	72 (15)		66 (15)	

* p values between IE and reference population and between IE and HVS population are obtained by students t-test for continuous variables and X2 tests for categorical proportions. * p value less than 0.05.

Table 4. Readmission and associations with patient-reported outcomes

Self-reported outcomes	Total IE survey responders, n = 122	Readmitted, n = 72	Non-readmitted, n = 50	Unadjusted	P*	Adjusted	P*
Short Form 36				β (95% CI)		β (95% CI)	
PCS	42.2 (11.1)	38.9 (11.1)	46.5 (9.6)	-7.75 (-12.38;-3.11)	**0.001**	-6.52 (-11.27;-1.78)	**0.008**
MCS	50.1 (11.7)	49.1 (12.4)	51.3 (10.8)	-2.17 (-7.35;3.01)	0.41	-1.36 (-6.72;4.01)	0.62
EQ-5D							
EQ-5D crosswalk	0.78 (0.18)	0.77 (0.19)	0.81 (0.17)	-0.04 (-0.11;0.03)	0.24	-0.02 (-0.10;0.04)	0.46
EQ-5D VAS	65.0 (22.0)	61.8 (22.3)	69.4 (20.9)	-7.60 (-15.69;0.49)	0.07	-5.56 (-13.89;2.76)	0.19
HeartQoL							
HeartQoL global	1.94 (0.74)	1.79 (0.76)	2.14 (0.66)	-0.35 (-0.62;-0.80)	**0.01**	-0.26 (-0.53;0.01)	0.06

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HeartQoL physical	1.82 (0.84)	1.66 (0.84)	2.04 (0.81)	-0.38 (-0.69;-0.07)	**0.02**	-0.27 (-0.58;0.04)	0.09
HeartQoL emotional	2.22 (0.79)	2.11 (0.85)	2.39 (0.68)	-0.28 (-0.58;0.02)	0.07	-0.24 (-0.54;0.06)	0.12
HADS continuous							
HADS-A	4.4 (4.3)	4.58 (4.47)	4.24 (4.04)	0.34 (-1.31;1.99)	0.68	0.28 (-1.35;1.91)	0.73
HADS-D	4.68 (4.3)	5.28 (4.76)	3.85 (3.42)	1.43 (-0.20;3.06)	0.08	1.13 (-0.55;2.81)	0.19
HADS categorical				OR (95% CI) [§]		OR (95% CI) [§]	
HADS-A < 8 vs ≥ 8	25%	25%	24%	1.06 (0.44;2.56)	0.90	1.05 (0.39;2.79)	0.93
HADS-A <11 vs ≥ 11	9%	14%	2%	7.36 (0.90;60.32)	0.06	8.92 (0.98;81.49)	0.053
HADS-D < 8 vs ≥ 8	22%	29%	13%	2.75 (1.00;7.57)	**0.050**	2.49 (0.86;7.16)	0.09
HADS-D <11 vs ≥ 11	14%	22%	4%	6.04 (1.30;28.04)	**0.02**	6.31 (1.26;31.58)	**0.03**

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Physical activity							
Moderate/vigorous exercise	16%	15%	18%	1.25		0.62	
Sedentary /low-level physical activity	84%	75%	82%	(0.43;3.68)	0.69	(0.17;2.22)	0.46
Participation in cardiac **rehabilitation**							
Yes	43%	41%	46%	0.79		0.63	
No	57%	59%	54%	(0.36;1.75)	0.56	(0.27;1.46)	0.28

PCS: Physical component scale, MCS: Mental component scale, HADS: Hospital anxiety and depression scale. Continuous variables are presented as mean (standard deviation) and categorical variables as percentages. * p values are obtained by linear regression for continuous variables and by logistic regression for categorical proportions with readmitted vs. not readmitted (reference group) as the explanatory variable. [#] Adjusted for age, sex and comorbidity.

Table 5. Predictors of mortality and readmission following discharge

	Mortality*		Readmission*	
	Unadjusted HR (95% CI)	**Multifactorially adjusted**** HR (95% CI)	**Unadjusted** HR (95% CI)	**Multifactorially adjusted**** HR (95% CI)
Age				
22-49	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
50-69	3.2 (0.9-10.7)	2.8 (0.8-9.4)	0.9 (0.6-1.4)	0.8 (0.6-1.3)
≥70-99	**5.7 (1.8-18.7)**	**5.2 (1.6-17.1)**	1.2 (0.8-1.9)	1.1 (0.7-1.7)
Sex				
Men	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Women	1.5 (0.8-2.6)	1.6 (0.9-2.8)	1.0 (0.7-1.4)	1.0 (0.7-1.4)
Marital status post-discharge				
Unmarried	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Married	1.1 (0.6-1.9)	1.1 (0.6-1.9)	0.9 (0.7-1.3)	1.0 (0.7-1.3)

Charlson comorbidity score

No or mild (0-1)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
Severe (≥ 2)	**2.2 (1.2-4.0)**	**2.0 (1.1-3.6)**	**1.6 (1.2-2.2)**	**1.6 (1.2-2.2)**

Surgery

Cardiac versus no cardiac surgery	**0.4 (0.2-0.8)**	0.4 (0.2-1.0)	0.8 (0.5-1.1)	0.8 (0.5-1.1)
Device versus no device extraction	0.5 (0.1-2.2)	0.4 (0.1-1.6)	0.7 (0.4-1.4)	0.6 (0.3-1.2)

Days hospitalized

Below median (0-45 days)	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)
From median to 75th percentile (46-63 days)	0.7 (0.3-1.5)	0.6 (0.3-1.4)	1.2 (0.9-1.8)	1.3 (0.8-1.8)
Above 75th percentile (64-180 days)	1.5 (0.8-2.8)	1.4 (0.7-2.6)	**1.4 (1.0-2.0)**	1.3 (0.9-1.9)

Days in Intensive Care Unit

None	1.0 (ref)	1.0 (ref)	1.0 (ref)	1.0 (ref)

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Below 75th percentile among those admitted to ICU (1-4 days)	0.7 (0.3-1.6)	0.7 (0.3-1.7)	0.7 (0.4-1.2)	0.7 (0.4-1.2)
Above 75th percentile (5-44 days)	0.3 (0.0-2.3)	0.3 (0.0-2.4)	0.8 (0.4-1.6)	0.7 (0.3-1.4)

* Cox proportional hazard ratio with time since discharge as underlying time, presented as hazard ratio (HR) with 95% confidence interval (CI) **

Adjusted for age, sex and Charlson comorbidity score.