## Karolinska Institutet, Department of Medicine, Cardiology Unit, Karolinska University Hospital, Stockholm, Sweden

# Diabetes Mellitus and Heart Failure – Registry Based Studies on Risk Factors, Prognosis and Impact of Treatment

## AKADEMISK AVHANDLING

Som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Ekens föreläsningssal plan 2, Norrbacka, S2:02, Karolinska Universitetssjukhuset, fredagen den 19 maj 2017 klockan 09.00

av

## Isabelle Johansson



## Huvudhandledare

Docent Anna Norhammar Karolinska Institutet Institutionen för medicin, Solna Enheten för kardiologi

#### Bihandledare

Senior Professor Lars Rydén Karolinska Institutet Institutionen för medicin, Solna Enheten för kardiologi

Docent Magnus Edner Karolinska Institutet Institutionen för medicin, Solna Enheten för kardiologi

Lektor Per Näsman KTH Kungliga Tekniska Högskolan Centrum för säkerhetsforskning

## **Fakultetsopponent**

Professor Tomas Jernberg Karolinska Institutet Institutionen för kliniska vetenskaper Danderyds sjukhus

## Betygsnämnd

Docent Erik Moberg Karolinska Institutet Institutionen för medicin Huddinge

Professor Isabel Gonçalves Lunds Universitet Institutionen för kliniska vetenskaper Malmö

Docent Mats Frick Karolinska Institutet, Institutionen för klinisk forskning och utbildning Södersjukhuset (KI SÖS)

## **ABSTRACT**

Heart failure and diabetes is a common combination. In the presence of diabetes heart failure prognosis becomes very serious, but the exact reasons are not understood. A limitation while interpreting existing data is that they usually derive from heart failure populations in whom patients with diabetes are selected, in small proportions and their characteristics are less well explored. This explains why it still is uncertain which factors are prognostically most important. Moreover, whether diabetes impacts prognosis differently in heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced (HFrEF) ejection fraction has not been fully investigated. In these respects analyses of nationwide registry based heart failure populations may provide valuable information.

#### Aims

To study the combination of diabetes and heart failure in a contemporary, unselected heart failure population by analysing

- 1. Demographic characteristics and long-term prognosis
- 2. Whether there are differences between women and men in this respect
- 3. The impact of diabetes in ischaemic versus non-ischaemic heart failure and the role of revascularization
- 4. The influence of diabetes in different types of heart failure

#### Diabetes and heart failure

Of 36 274 patients with clinician judged heart failure registered in the Swedish Heart Failure Registry (SwedeHF) from specialist care between 2003-2011, 24% had reported diabetes. The patients were followed for mortality until September 2011. Diabetes was an independent predictor of mortality particularly in the age group ≤65 years (OR 1.61; 95%CI 1.36-1.92) compared to patients >80 years (OR 1.46; 95%CI 1.31-1.62). This pattern was apparent despite a more extensive pharmacological treatment in patients with diabetes and although a similar left ventricular and renal function in patients with and without diabetes.

#### Influence of diabetes in women and men with heart failure

Women represented 39% of the SwedeHF population irrespective of diabetes state. In the presence of diabetes the mortality risk increased by 70% in women (OR 1.72; 95% CI 1.53-1.94) and by 40% in men (OR 1.47; 95% CI 1.34-1.61), but age-adjusted survival did not differ between women and men with diabetes (log-rank p=0.18). In contrast women without diabetes had a better prognosis than their male counterparts (log-rank p<0.0001). Women with diabetes and heart failure, in particular those  $\leq$ 65 years, had a risk factor profile resembling that of men with a high prevalence of ischaemic heart disease and hypertension.

#### Ischaemic versus non-ischaemic heart failure and the role of previous revascularization in diabetes

The impact of diabetes in ischaemic versus non-ischaemic heart failure was studied in 35 163 patients in SwedeHF. A particularly high proportion of diabetes was reported in patients with ischaemic compared with non-ischaemic heart failure (31% versus 18%). As many as 90% of patients with diabetes had at least one preventable comorbidity of which ischaemic heart disease and hypertension were most frequent. Diabetes had a negative impact on survival irrespective of whether the aetiology was ischaemic or non-ischaemic. The highest mortality was, however, seen in those with ischaemic aetiology (adjusted HR 1.41; 95% CI 1.33-1.50 versus 1.30; 1.20-1.41). A history of coronary revascularization was associated with better survival after propensity score adjustment. Still revascularisation had only been performed in half the diabetes patients.

#### Impact of diabetes in heart failure with different left ventricular function

Among 30 696 patients in SwedeHF followed until December 2014, 22% had HFpEF, 21% HFmrEF and 57% HFrEF. The prevalence of diabetes was similar across the groups (24-25%). In the presence of diabetes the clinical characteristics of patients with HFmrEF resembled those in the HFrEF group. Diabetes had a negative impact on mortality with the highest risk increase in patients with HFmrEF (HR 1.51; 95% CI 1.39-1.65) and HFrEF (HR 1.46; 95%CI 1.39-1.54). A similar impact although slightly less apparent was seen in patients with HFpEF (HR 1.32; 95%CI 1.22-1.43).

#### Conclusion

From these analyses in a nationwide, contemporary heart failure population it can be concluded that diabetes is present in 24% to 31% of the patients. The combination of heart failure and diabetes compromises survival irrespective of sex, heart failure aetiology or heart failure entity. The increased mortality risk varies between 30-70% depending on age, sex and aetiology. Systolic dysfunction and ischaemic heart disease are associated with the worst prognosis. Although associated with an improved longevity coronary revascularization seems to be underused. The worse prognosis associated with diabetes may partly be explained by a heavier comorbidity burden but the existence of a diabetes cardiomyopathy cannot be ruled out. In the future improved attention of these patients are needed and studies searching for a better understanding of underlying mechanisms opening for novel treatment modalities.

ISBN: 978-91-7676-633-0