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## **Increased IGF-1 levels in relation to heart failure and cardiovascular mortality in an elderly population: impact of ACE-inhibitors.**

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**Abstract**

**Objective.** There are conflicting results regarding the association of circulating insulin-like growth factor-1 (IGF-1) with cardiovascular (CV) morbidity and mortality. We assessed the relationship between IGF-1 levels and heart failure (HF), ischemic heart disease (IHD) and CV mortality in an elderly population taking into account the possible impact of angiotensin-converting enzyme inhibitors (ACE-inhibitors).

**Design and methods.** 851 persons aged 66-81 years, in a rural Swedish municipality were evaluated by medical history, clinical examination, electrocardiography, echocardiography and fasting plasma samples. They were then followed for 8 years.

**Results and conclusion.** Patients on ACE-inhibitors had elevated IGF-1 levels compared to those without.

In patients on ACE-inhibitors higher IGF-1 values were found in those with an EF<40% compared to EF≥40%, in those with higher pro-BNP levels in quartile 4 versus 1, and in patients with IHD when compared to those without (p<0.001). In patients without ACE-inhibitors, no relationship was found between IGF-1 levels and HF or IHD. In multivariate regression only ACE-inhibitors, EKG-changes characteristic for IHD and gender had a significant impact on IGF-1.

Persons with higher IGF-1 levels in quintiles 4 and 5 compared to quintiles 1 and 2 had a 50% higher risk for cardiovascular death (p=0.03). This was significant after adjustment for well-known CV risk factors and ACE-inhibitors (p=0.03).

Our results show that treatment with ACE-inhibitors in an elderly population is associated with increased IGF-1 levels especially in patients with impaired cardiac function or IHD. High IGF-1 levels tend to be associated with an increased risk for CV mortality.

**Keywords.** Insulin-like growth factor-1, heart failure, ischemic heart disease, elderly population.

**Introduction**

Cardiovascular disease is a major cause of morbidity and mortality in the western world. A number of studies have shown that IGF-1 is related to CV disease, but the mechanisms involved are still not clear (1-3). Both low and high levels of circulating IGF-1 have been reported to be associated with increased mortality (4-6) as well as with cardiac failure (7). Protective (1, 8, 9) as well as harmful (5, 10) effects of IGF-1 on the CV system have been reported. In adults IGF-1 has anabolic effects on connective tissues, muscle and heart (11, 12). It has been reported that infusion of IGF-1 in healthy individuals has a positive inotropic effect (13) and improves left ventricular performance in those with HF (14).

It is conceivable that IGF-1 has a dual role in the vascular wall; stimulating NO-production in the intact endothelium thereby inhibiting smooth muscle cell proliferation, but may directly stimulate smooth muscle cell proliferation if the endothelium is damaged (10, 15, 16). Angiotensin II is a potent inhibitor of local IGF-1 expression and it has therefore been suggested that ACE-inhibitors may enhance local IGF-1 secretion (17). Indeed, treatment with ACE-inhibitors, commonly used in patients with cardiac disorders, have been shown to moderately increase plasma IGF-1 (18, 19)

By influencing IGF-1 levels ACE-inhibitors could be a confounding factor in studies on IGF-1 and CVD-disease and mortality. In this observational study on an elderly population we tested the hypothesis that there is an association between IGF-1 and cardiac function as well as between IGF-1 and CV mortality considering the impact of ACE-inhibitors.

**Research design and methods**

The study population has previously been described in detail (20). Briefly, a rural municipality with 10,300 inhabitants situated in south-east Sweden was chosen. All individuals aged 66 to 81 years residing in the municipality were invited to participate in the study. Of 1162 subjects, 851 (73.3%) agreed to participate.

All participants (851 persons) were examined by experienced cardiologists. A medical history was taken, and a clinical examination, including weight and height, was performed. The New York Heart Association functional class (NYHA Class) was assessed, and an electrocardiogram and Doppler echocardiography were taken. Blood pressure was measured to the nearest 5 mm Hg, with the patient resting in the supine position. The study protocol was approved by the Ethics Review Board in Linköping.

**Blood samples and biochemical analysis**

Blood samples were obtained from fasting subjects after a resting period of 30 minutes. The samples were collected in pre-chilled plastic tubes containing EDTA (Terumo EDTA K-3), placed on ice and centrifuged at 3000g for 10 minutes at 4°C. The samples were then immediately stored at -70°C pending analysis. Total plasma IGF-1 was measured by a one-step enzyme-linked immunosorbent assay (ELISA) after acid-ethanol-extraction from its binding protein with a commercial kit (R&D Systems, Minneapolis, MN, USA). The assay was performed according to the manufacturer's protocol. Interassay coefficients of variation (CV) was for high, medium and low controls 10.9%, 5.9% and 18.2%, respectively. N-terminal proBNP (NT-proBNP) was measured using an electrochemiluminescence immunoassay (Elecsys 2010, Roche Diagnostics, Mannheim, Germany), first described by Karl (21). The analytical range was

5 to 35,000 ng/L (0.6 to 4130 pmol/L). Total coefficient of variation was 4.8% at the level of 217 ng/L (26 pmol/L) (n = 70) and 2.1% at the level of 4261 ng/L (503 pmol/L) at our laboratory.

### **Doppler echocardiography**

Doppler echocardiography (Accuson XP-128c) was performed on all patients in the left supine position. Both M-mode and 2-dimensional methodologies were used. Left ventricular systolic function was determined semi-quantitatively, with the global systolic function classified as follows: normal (ejection fraction [EF]  $\geq 50\%$ ); mild impairment (EF 40% to 49%); moderately impaired function (EF 30% to 40%); and severely impaired function (EF  $< 30\%$ ). The method has been validated against the modified Simpson algorithm (22, 23).

### **Concomitant disease**

Diabetes mellitus was defined as a fasting plasma blood glucose concentration  $\geq 7.0$  mmol/L, or current treatment for diabetes (diet, oral therapy or insulin). Ischemic heart disease (IHD) was defined as a history of coronary artery disease (CAD), angina pectoris, treatment for angina pectoris, a verified myocardial infarction, coronary artery bypass surgery, percutaneous coronary intervention, and/or ECG changes characteristic for IHD (evaluated by 3 experienced cardiologists).

### **Follow-up of included patients**

All patients were followed-up for 8 years ( $7.9 \pm 2.6$ ) and no patient was lost during this period.

During the follow-up period all patients received standard treatment according to clinical routines.

In all cases reported as dead, death certificates were obtained from the Swedish Central Population Register and information about cause of death and autopsy reports were analysed by the authors. All autopsies had been performed at the University Hospital in Linköping. All-cause

mortality and CV mortality were chosen as end points. CV mortality was defined as death caused by HF, fatal arrhythmia, sudden death, IHD, or cerebrovascular death as deduced from the autopsy report or death certificate issued by the physician in charge of the patient.

### **Statistics**

Data are presented as mean  $\pm$  SD. For normally distributed variables analysis was done using Student's *t*-test. A multivariate regression analysis was used to assess the impact of gender, ACE-inhibitors, ECG changes for IHD, CAD-history, IHD, EF<40%, BMI, creatinine and NT pro-BNP on IGF-1 levels. Survival analysis was made using Kaplan–Meier survival curve analysis. A Cox proportional hazard regression analysis was performed to identify the weight of the individual risk variables for CV mortality. A p-value less than 0.05 were considered statistically significant. Data analysis was performed using commercially available statistical analysis software packages PASW Statistics version 18 (SPSS Inc. Headquarters, Chicago, Illinois, USA).

## **Results**

### **Basic characteristics of patients in the study population**

Table 1 shows the baseline characteristics of the study population. Among the 851 participants there was an almost equal number of women and men (n=436 versus 415). With regard to age there was a small but significant difference between females and males (p=0.002), females being older than males. With regard to the medical history, the male population had a higher prevalence of IHD than the female (p=0.03).

### **IGF-1 levels and characteristics of the study population**

Significantly higher levels of circulating IGF-1 was found in males versus females,  $84.1 \pm 29.2$   $\mu\text{g/L}$  versus  $74.3 \pm 25.8$   $\mu\text{g/L}$ , (p<0.001) (Table 1). In the whole population there was a significant correlation between IGF-1 and weight (p<0.001, r=0.1), height (p<0.001, r=0.21) and serum creatinine (p<0.001, r=0.1). In males, but not in females, we found a significant correlation between IGF-1 regarding age (p=0.006, r= - 0.1), weight (p<0.001, r=0.2), height (p=0.001, r=0.2), and BMI (p=0.04, r= - 0.1).

### **IGF-1 levels and treatment with ACE-inhibitors**

Of all 851 persons studied 173 patients (20.3%), 91 women (52.6%) and 82 men (47.4%), were treated with ACE-inhibitors. Our results show that the patients on ACE-inhibitors had significantly higher levels of IGF-1 compared to those without ACE-inhibitors,  $86.8 \pm 31.4$   $\mu\text{g/L}$  versus  $77.2 \pm 26.7$   $\mu\text{g/L}$ , (p<0.001). The difference in IGF-1 values between the sexes was independent of treatment with ACE-inhibitors.

IGF-1 values were compared between the 4 systolic ventricular function classes according to EF defined as normal (EF>50%), mildly impaired (EF 40-49 %), moderately impaired (EF 30-40%) and severely impaired systolic function (EF<30%). In patients on ACE-inhibitors, the highest values were found in Class 3 (92.9±41.9 µg/L) compared to Class 1 (78.2±27.6 µg/L) (p= 0.04).

Of the 851 participants, 42 (5.0%) had an EF < 40% and 765 (93.4%) an EF ≥ 40. Among patients treated with ACE-inhibitors, those with an EF<40% had significantly higher IGF-1 values compared to those with an EF≥40% (103.4 ± 39.7 µg/L versus 84.4 ± 30.0 µg/L), (p=0.02) (Table 2). There were also significantly higher IGF-1 levels in those patients on ACE-inhibitors who had higher pro-BNP levels in quartile 4 versus 1 (93.2±35.3 µg/L versus 78.7±28.8 µg/L, respectively) (p=0.03) (Table 2).

Patients treated with ACE-inhibitors and diagnosed with IHD by CAD-history and ECG changes had higher IGF-1 levels than those without CAD-history and ECG- changes characteristic for IHD (100.1±34.7 µg/L versus 80.5±28.1 µg/L), (p< 0.001) (Table 2). For patients on ACE-inhibitors the highest IGF-1 levels were found in patients with ECG changes characteristic for IHD compared to those without ECG changes (115.7±27.1 µg/L versus 82.9±30.1 µg/L), (p<0.001). IGF-1 levels tended to be higher in patients on ACE-inhibitors with a CAD-history than in those without (98.4±35.0 versus 83.6±29.8 µg/L), (p=0.07). No relationship was found between IGF-1 levels and the presence of IHD in persons not taking ACE-inhibitors.

In multivariate regression analyses with IGF-1 as the dependent variable, gender, ACE-inhibitors and ECG indicative of IHD had an significant impact, whereas, IHD, EF<40%, creatinine, BMI and pro-BNP were not significant (Table 3).

**IGF-1 as a prognostic biomarker for CV mortality**

During the follow-up period of 8 years, the all-cause mortality was 27.0% (n=230) (Table 4). 134 (58.3%) patients died of CV disease and 40 (17.4%) died of malignant disease. IGF-1 values for CV non-survivors ( $83.7 \pm 30.0$   $\mu\text{g/L}$ ) was significantly higher than for those who survived the follow-up period ( $78.1 \pm 27.4$   $\mu\text{g/L}$ ), ( $p=0.034$ ). All- cause mortality tended to be associated with increased IGF-1 levels ( $p=0.09$ ).

IGF-1 values were then divided into quintiles in order to compare mortality and CV mortality in groups with low and high IGF-1 levels (Table 5). The first and second quintiles were pooled, as well as the 4<sup>th</sup> and 5<sup>th</sup> and compared in between and to quintile 3. In order to assess the prognostic potential of IGF-1, a univariate Cox proportional hazard regression analysis was used. The results indicated that the risk for cardiovascular mortality increased by 50% for participants with higher plasma IGF-1 concentrations in the 4<sup>th</sup> +5<sup>th</sup> quintiles compared to those in the 1<sup>st</sup> +2<sup>nd</sup> quintiles ( $p=0.03$ ). A multivariate Cox proportional hazard regression analysis was then performed using a model including other well-known variables for cardiovascular mortality (Table 6). As shown in Table 6, high levels of IGF-1 in the 4<sup>th</sup> +5<sup>th</sup> quintiles compared to those in 1<sup>st</sup> + 2<sup>nd</sup> quintiles predicts a 1.6-fold increase in CV mortality ( $p=0.03$ ). Increased age had a 1.1-fold increase in risk for CV mortality ( $p<0.001$ ). For the patients with NYHA Class III HF, a 2.3-fold increase in risk for CV mortality was predicted ( $p=0.001$ ). For the patients with diabetes mellitus 2.0-fold increase in risk for CV mortality was predicted ( $p=0.001$ ). We analyzed the relationship between CV mortality and NT-proBNP, considering 100 ng/L as a relevant physiological change in NT-proBNP, and obtained a HR for CV mortality of 1.06 (CI 1.04-1.08,  $p<0.001$ ). For creatinine, considering 20  $\mu\text{mol/L}$  as a relevant physiological change, HR for CV mortality was 1.56 (1.35-1.79). We also examined the time-mortality relationship using Kaplan-Meier analysis, showing that the predictive value persists after 10 years (Figure 1).

**Discussion**

In an elderly population with concomitant diseases representative for their age and followed for 8 years we tested the possibility to use IGF-1 as a biomarker for HF and IHD and as a predictor of CV mortality. Furthermore the role of ACE-inhibitors was evaluated. All inhabitants aged 66 to 81 years in the community were invited to participate and no participants were lost during follow-up. Our results show that treatment with ACE-inhibitors is associated with increased IGF-1 levels especially in patients with impaired cardiac function. High levels of IGF-1 predict CV mortality independent of age and other known CV risk factors.

In this population 20.3% of the participants were treated with ACE-inhibitors and had significantly higher levels of IGF-1 compared to those without ACE-inhibitors. In the “CHIANTI study” (19) which encompassed 745 subjects  $\geq 65$  years of age, IGF-1 levels were significantly higher in participants receiving ACE-inhibitors compared to the rest of the study population. A six-month treatment with fasinopril increased IGF-1 levels in older adults with a high cardiovascular risk profile (18). All in all there is strong evidence that ACE-inhibitors lead to an increase in circulating IGF-1 levels. We found significantly higher IGF-1 values in men than in women in accordance with a recent publication (24). The reason for this difference is not known but testosterone and also physical activity is known to affect IGF-I (24, 25).

In our study the most pronounced increase in IGF-1 values was found between patients on ACE-inhibitor treatment and an EF  $<40\%$ , and those with an EF  $\geq 40\%$ . High levels of NT- pro BNP, another well-known marker for HF, were only associated with raised IGF-1 levels in patients on ACE-inhibitors. When stratified according to EF, the highest IGF-1 values were found in patients with an EF 30-40%. Corbalan *et al.*, in a small uncontrolled study on 9 patients with heart failure NYHA Class III, reported that treatment with enalapril restored low IGF-1 values and improved

cardiac function (26). Andreassen et al. (27) reported increased IGF-1 levels in patients treated with ACE-inhibitors/angiotensin II receptor blockers. However they did not find a significant difference in IGF-1 levels between patients with HF and controls.

When divided into those with and without ACE-inhibitors, the increase in IGF-1 levels in IHD was confined to those on ACE-inhibitors ( $p < 0.001$ ). Schneider and co-workers have shown that high IGF-1 levels are associated with coronary artery disease in women, but not in men. Patients with low IGF-1 levels also showed increased risk for coronary artery disease (3). Kaplan failed to show a relationship between IGF-1 and the risk for IHD in elderly subjects (28). The use of ACE-inhibitors was not commented on in the studies above.

We found that persons with higher IGF-1 levels in quintiles 4 + 5 compared to quintiles 1 + 2 had a 50% greater risk for dying of cardiovascular causes. This was still true after adjustment for age and other known CV risk factors: NYHA Class III, NT pro-BNP, diabetes mellitus, BMI, creatinine, age and gender (Table 6). A U-shaped association between CV mortality and low-normal and high-normal IGF-1 levels was recently reported by Bunderen et al (4). It should be noted that patients with prevalent CVD were excluded from cause-specific analysis of mortality in that study. In another study low IGF-1 levels, below the 90<sup>th</sup> percentile, were associated with increased risk for all-cause mortality, CV mortality and cancer mortality in men but not women (29). Low IGF-1 levels were associated with increased risk for fatal IHD among elderly subjects regardless of prevalent IHD and CVD risk factors (9). A recent population study in Australia, conducted on elderly men, failed to find a difference in CV mortality based on IGF-1 levels according to quintiles (30).

In our study there was a tendency towards an association of high IGF-1 levels with all-cause mortality ( $p=0.09$ ). When comparing IGF-1 levels according to quartiles, Andreassen et al. found high plasma IGF-1 levels to be independently associated with an increase in all-cause mortality (6). The association between circulating IGF-1 levels and all-cause mortality tended to be U-shaped, with increased mortality at both low and high IGF-1 levels (6). In the study by Bunderen et al. mentioned above, an increased risk for all-cause mortality was found for elderly subjects with lowest IGF-1 levels in the 1<sup>st</sup> quintile compared to the 3<sup>rd</sup> quintile (4). Other studies have failed to show an association between IGF-1 levels and all-cause mortality (9, 30-32). These conflicting results could be explained by differences in population age (>17 years in Saydah et al. (32), 51-89 years in Laughlin et al. (9) and >65 in Kaplan et al. (28), race and unrecognized differences in lifestyle factors that modulate IGF levels. The impact of ACE-inhibitors on CV and all-cause mortality was not taken into account in any of these studies.

To our knowledge this observational study is the first to specifically address the effect of ACE-inhibitors on IGF-I levels and HF, IHD and CV mortality. Previous large population studies have not focused on this question (19, 27) and the few reports from small studies are difficult to interpret (7, 18). As described above, there are only two studies which have shown high IGF-1 levels to be associated with all-cause mortality (4, 6) and CV mortality (4). Our results contradict the concept that high IGF-1 levels are protective against atherosclerosis-associated cardiac events (2). Most previous studies have shown that low IGF-1 levels correlate with increased CV and all-cause mortality (1, 2, 9, 33). We did not find any tendency towards increased mortality in subjects with low IGF-1 values. It should be pointed out that we did not see the very low IGF-1 values found in GH-deficient patients reported to have increased CV-mortality (33). However, also population studies have shown low IGF-1 levels to be associated with increased CVD.

What can be extracted from our findings? One may speculate that low IGF-1 levels have a protective role by increased resistance to oxidative stress associated with aging (34, 35).

Experimental animal models have also shown an association between a deficit of IGF-1 or non-functioning IGF-1 and longer life span (36-38). These together with our results support the idea that there is a complex relationship between IGF-1 levels and mortality, and that a high IGF-1 level could be a predictive biomarker for CV mortality.

The main strength of this population study is that the participants were recruited directly from the community without sampling, and every participant was followed over a long period of time up to 8 years ( $7.9 \pm 2.6$ ). No patient was lost during follow-up. Nevertheless, this study has some limitations. One important so is the size of the study population, which resulted in the subgroups of individuals with an EF < 40% being rather small. The results of comparisons between the subgroups should thus be interpreted with caution. Another limitation is the limited age span of study participants (66 to 81 years), which makes extrapolation of the results to other age groups unwise. Furthermore, we did not measure the interaction of IGF-1 with IGF-BPs which can modulate free IGF-1.

**Conclusion:** In this unique unselected population of elderly subjects from the community we found that treatment with ACE-inhibitors is associated with increased IGF-1 levels, especially in patients with impaired cardiac function. High levels of IGF-1 tend to be associated an increased risk for cardiovascular mortality.

### **Declaration of interest**

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research report

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**Legend to figure**

**Figure 1.** Kaplan-Meier analysis comparing IGF-1 levels quintiles 1+2, quintile 3 and quintiles 4+5, and cardiovascular mortality during a follow-up period of up to 8 years.

**Table 1.** Population baseline characteristics

Variable	Whole population	Female	Male	p-value
Total, n	851	436	415	
Age (mean $\pm$ SD), years	73.0 $\pm$ 3.5	73.3 $\pm$ 3.4	72.6 $\pm$ 3.5	0.002
<b>History</b>				
Diabetes mellitus, n (%)	123 (14.4%)	64 (52.0%)	59 (48.0%)	0.8
IHD, n (%)	157 (18.4%)	68 (43.3%)	89 (56.7%)	0.03
ECG, n (%)	47 (5.5%)	14 (29.8)	33 (70.2%)	0.003
CAD, (%)	127 (14.9%)	60 (47.3%)	67 (52.7%)	0.3
NYHA I, n (%)	519 (61.0%)	255 (49.1%)	264 (50.9%)	0.1
NYHA II, n (%)	266 (31.2%)	146 (54.8%)	120 (45.1%)	0.1
NYHA III, n (%)	66 (7.7%)	35 (53.0%)	31 (47.0%)	0.8
<b>Clinical variables</b>				
Weight (mean $\pm$ SD), kg	75.4 $\pm$ 13.1	71.4 $\pm$ 1.4	79.7 $\pm$ 11.3	<0.001
Height (mean $\pm$ SD),cm	168.1 $\pm$ 10.5	161.7 $\pm$ 9.7	174.8 $\pm$ 6.2	<0.001
BMI (mean $\pm$ SD), kg/m <sup>2</sup>	26.6 $\pm$ 4.2	27.2 $\pm$ 4.8	26.1 $\pm$ 3.4	<0.001
EF $\geq$ 40%, n (%)	795 (93.4%)	413 (51.9%)	382 (44.1%)	0.1
EF<40%, n (%)	42 (5.0%)	12 (28.6%)	30 (71.4%)	0.003
<b>Treatment</b>				
ACE-inhibitor, n (%),	173 (20.3%)	91 (52.6%)	82 (47.4%)	0.7
$\beta$ -blocker, n (%)	200 (23.5%)	102 (23.4%)	98 (23.6)	0.9
Diuretic n, (%)	240 (28.2%)	145 (33.3)	95 (22.9)	0.001
<b>Laboratory analyses</b>				
IGF-1 (mean $\pm$ SD), $\mu$ g/L	79.1 $\pm$ 27.9	74.3 $\pm$ 25.8	84.1 $\pm$ 29.2	<0.001
Creatinine (mean $\pm$ SD), $\mu$ mol/L	92.0 $\pm$ 18.5	86.1 $\pm$ 16.9	98.2 $\pm$ 18.1	<0.001
NT-proBNP (mean $\pm$ SD), ng/L	276.7 $\pm$ 558.1	284.6 $\pm$ 642.6	272.6 $\pm$ 453.3	0.7
Hb (mean $\pm$ SD), g/L	140.2 $\pm$ 12.6	136.1 $\pm$ 11.2	144.5 $\pm$ 12.6	<0.001

ACE = angiotensin-converting enzyme; BMI = body mass index; BP = blood pressure; IGF-1 = insulin-like factor-1; ECG = electrocardiogram indicative of IHD; IHD = ischemic heart disease; NYHA = New York Heart Association functional class; EF = ejection fraction; ASAT = serum aspartate aminotransferase; Hb = hemoglobin; NT-proBNP = N-terminal proBNP.

**Table 2.** IGF-1 levels in patients with HF or IHD with or without ACE-inhibitor treatment

Disease	Variables	without ACE-inhibitor	p-value	with ACE-inhibitor	p-value
HF	EF<40% / EF≥40%	n = 25 / 647		n=17 / 146	
	IGF-1 (mean±SD, µg/L)	82.0±25.4 / 77.0±26.7	0.4	103.4±39.7 / 84.4±30.0	0.02
	pro-BNP quartile 4/ pro-BNP quartile 1	n=173 / 149		n=39 / 62	
	IGF-1 (mean±SD, µg/L)	75.0±25.8 / 80.7±25.3	0.05	93.2±35.3 / 78.7±28.8	0.03
IHD	ECG and CAD (+/-)	n=106/572		n=51/120	
	IGF-1(mean±SD, µg/L)	74.9±27.8 / 77.6±27.2	0.3	100.1±34.7 / 80.5±28.1	<0.001
	ECG (+/-)	n=29/649		n=18/153	
	IGF-1(mean±SD, µg/L)	79.1±17.4 / 77.2±27.0	0.7	115.7±27.1 / 82.9±30.1	<0.001
	CAD (+/-)	n=85/593		n=42/131	
	IGF-1(mean±SD, µg/L)	73.3±24.7 / 77.7±26.8	0.2	98.4±35.0 / 83.6±29.8	0.07

ACE = angiotensin-converting enzyme; CAD = coronary artery disease; ECG =

electrocardiogram indicative of IHD; EF = ejection fraction; IGF-1 = insulin-like growth factor-

1; IHD = ischemic heart disease; NT-proBNP = N-terminal proBNP; n= number of patients.

**Table 3.** Multiple linear regression analyses with IGF-1 as the dependent variable and age, gender, BMI, ACE-inhibitors, ECG changes indicative of IHD, IHD, EF<40%, creatinine and NT-proBNP as independent variables.

Variables			p-value	95% CI for B	
	B	SE		Lower	Upper
Age, years	-0.38	0.3	0.2	-0.9	0.2
Gender	-8.4	2.04	<0.001	-12.4	-4.4
BMI, kg/m <sup>2</sup>	0.2	0.2	0.3	-0.2	0.7
ACE	-7.3	2.5	0.003	-12.1	-2.5
ECG	11.2	4.8	0.02	1.7	20.6
EF<40%	5.0	4.7	0.3	-4.3	14.2
IHD	-1.3	2.9	0.6	-6.9	4.2
Creatinine, µmol/L	0.06	0.06	0.3	-0.05	0.2
NT-proBNP, ng/L	0.001	0.002	0.6	-0.003	0.005

ACE = angiotensin-converting enzyme; B= Cox regression coefficient, BMI = body mass index, CI = confidence interval; ECG = electrocardiogram changes indicative of IHD; EF = ejection fraction; IGF-1 = insulin-like growth factor-1; IHD = ischemic heart disease; NT-proBNP = N-terminal proBNP, SE = standard error.

**Table 4.** All-cause mortality, CV mortality and malignancy mortality in the study population.

<b>Mortality</b>	<b>Whole population</b>	<b>Female</b>	<b>Male</b>	<b>p-value</b>
All-cause mortality, n (%)	230 (27.0%),	98 (42.6%)	132 (57.4%)	0.002
CV mortality, n (%)	134 (58.3%)	57 (42.5%)	77 (57.5%)	0.3
Malignancy mortality, n (%)	40 (17.4%)	22 (55.0%)	18 (45.0%)	0.6

**Table 5.** IGF-1 quintiles and all-cause, CV and malignancy mortality

<b>IGF-1</b>	<b>n</b>	<b>IGF-1</b> (mean±SD), µg/L	<b>All-cause mortality,</b> n (%)	<b>CV mortality,</b> n (%)	<b>Malignancy</b> <b>mortality,</b> n (%)
quintile 1	169	45.7±8.2	39 (16.9%)	21 (15.7%)	8 (20.0%)
quintile 2	171	62.2±3.6	42 (18.3%)	21 (15.7%)	9 (22.5 %)
quintile 3	171	74.8±3.6	48 (20.9%)	26 (19.4%)	8 (20.0%)
quintile 4	170	90.5±5.7	46 (20.0%)	34 (25.4%)	7 (17.5%)
quintile 5	170	122.0±19.7	55 (23.9%)	32 (23.9%)	8 (20.0%)
total	851		230 (100%)	134 (100%)	40 (100%)

**Table 6.** Multivariate Cox proportional hazard regression analysis of prognostic power concerning cardiovascular mortality over 8-year follow-up period.

Variables	p-value	HR	95% CI for HR	
			Lower	Upper
Age, years	<0.001	1.1	1.06	1.18
Gender	0.07	0.7	0.5	1.03
ACE	0.2	0.8	0.5	1.2
BMI, kg/m <sup>2</sup>	0.1	1.0	0.9	1.0
NYHA Class III	0.001	2.3	1.4	3.9
DM	0.001	2.0	1.4	3.1
IHD	0.7	0.9	0.6	1.4
Hb, g/L	0.2	1.0	1.0	1.0
Creatinine, µmol/L	0.02	1.01	1.001	1.019
NT-proBNP, ng/L	0.001	1.0	1.0	1.001
IGF-1, µg/L, quintiles 1+2 versus quintile 3	0.3	1.3	0.8	2.1
IGF-1, µg/L, quintiles 1+2 versus quintiles 4+5	0.03	1.6	1.03	2.3

ACE = angiotensin-converting enzyme; BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; Hb = haemoglobin; HR = hazard ratio; IGF-1 = insulin-like growth factor-1; IHD = ischemic heart disease; NT-proBNP = N-terminal proBNP; NYHA = New York Heart Association functional class.

**Figure 1.**

