Increased IGF1 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 IGF1 with cardiovascular (CV) morbidity and mortality. We assessed the relationship between IGF1 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 (ACE) inhibitors.

Design and methods: A total of 851 persons aged 66–81 years, in a rural Swedish municipality, were subjected to 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 higher IGF1 levels compared with those without ACE inhibitors. In patients on ACE inhibitors, higher IGF1 values were found in patients with an ejection fraction (EF) <40% compared with EF ≥40%, in patients with higher proBNP levels in quartile 4 vs 1, and in patients with IHD when compared to those without ACE inhibitors (P<0.001). In patients without ACE inhibitors, no relationship was found between IGF1 levels and HF or IHD. In multivariate regression, only ACE inhibitors, ECG changes characteristic for IHD, and gender had a significant impact on IGF1. Patients with higher IGF1 levels in quintiles 4 and 5 compared to quintiles 1 and 2 had a 50% higher risk for CV death (P=0.03). This was significant after adjustment for well-known CV risk factors and ACE inhibitors (P=0.03).

Conclusions: Our results show that treatment with ACE inhibitors in an elderly population is associated with increased IGF1 levels, especially in patients with impaired cardiac function or IHD. High IGF1 levels tend to be associated with an increased risk for CV mortality.

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Introduction

Cardiovascular (CV) disease is a major cause of morbidity and mortality in the western world. A number of studies have shown that insulin-like growth factor 1 (IGF1) is related to CV disease, but the mechanisms involved are still not clear (1–3). Both low and high levels of circulating IGF1 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 IGF1 on the CV system have been reported. In adults, IGF1 has anabolic effects on connective tissues, muscles, and heart (11, 12). It has been reported that infusion of IGF1 in healthy individuals has a positive inotropic effect (13) and improves left ventricular performance in those with heart failure (HF) (14).

It is conceivable that IGF1 plays a dual role in the vascular wall; stimulating nitric oxide (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 IGF1 expression, and it has therefore been suggested that angiotensin converting enzyme (ACE) inhibitors may enhance local IGF1 secretion (17). Indeed, treatment with ACE inhibitors, commonly used in patients with cardiac disorders, has been shown to moderately increase plasma IGF1 (18, 19).

By influencing IGF1 levels, ACE inhibitors could be a confounding factor in studies on IGF1 and CV disease and mortality. In this observational study on an elderly population, we tested the hypothesis that there is an association between IGF1 and cardiac function as well...
as between IGF1 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 southeast Sweden was chosen. All individuals aged 66–81 years residing in the municipality were invited to participate in the study. Of the 11,622 subjects, 8,511 (73.3%) agreed to participate.

All participants (8,511 persons) were examined by experienced cardiologists. A medical history was taken, and a clinical examination, including weight and height, was performed. Functional class was assessed by the New York Heart Association (NYHA Class), and an electrocardiogram (ECG) and Doppler echocardiography were done. Blood pressure was measured to the nearest 5 mmHg, 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 min. The samples were collected in pre-chilled plastic tubes containing EDTA (Terumo EDTA K-3), placed on ice, and centrifuged at 3,000 g for 10 min at 4 °C. The samples were then immediately stored at −70 °C pending analysis. Total plasma IGF1 was measured by a one-step ELISA after acid–ethanol extraction from its binding protein using a commercial kit (R&D Systems, Minneapolis, MN, USA). The assay was performed according to the manufacturer’s protocol. Interassay coefficients of variation were 10.9, 5.9, and 18.2% for high, medium, and low controls respectively. N-terminal proBNP (NT-proBNP) was measured using an electrochemiluminescence immunoassay (Elecys 2010, Roche Diagnostics), first described by Karl et al. (21). The assay was performed according to the manufacturer’s protocol. Interassay coefficients of variation were 10.9, 5.9, and 18.2% for high, medium, and low controls respectively. NT-proBNP was determined by a competitive immunoassay method using a commercial kit (Elecys 2010, Roche Diagnostics), as detailed previously (20). Briefly, a rural municipality with 10,300 inhabitants situated in southeast Sweden was chosen. All individuals aged 66–81 years residing in the municipality were invited to participate in the study. Of the 11,622 subjects, 8,511 (73.3%) agreed to participate.

Follow-up of included patients

All patients were followed for 8 years (7.9 ± 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 analyzed 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.

**Statistical analysis**

Data are presented as mean ± S.D. For normally distributed variables, analysis was performed 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%, body mass index (BMI), creatinine, and NT proBNP on IGF1 levels. Survival analysis was performed 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 < 0.05 was considered statistically significant. Data analysis was performed using commercially available statistical analysis software packages PASW Statistics version 18 (SPSS, Inc., Headquarters, Chicago, IL, USA).

**Results**

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

Table 1 shows the baseline characteristics of the study population. Among the 8,511 participants, there were an almost equal number of women and men (n = 4,36 vs
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 population ($P=0.03$).

**IGF1 levels and characteristics of the study population**

Significantly higher levels of circulating IGF1 were found in males compared with females, $84.1 \pm 29.2$ vs $74.3 \pm 25.8$ μg/l ($P<0.001$; Table 1). In the whole population, there was a significant correlation between IGF1 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 IGF1 regarding age ($P=0.006$, $r=-0.1$), weight ($P<0.001$, $r=0.2$), height ($P<0.001$, $r=0.2$), and BMI ($P=0.04$, $r=-0.1$).

**IGF1 levels and treatment with ACE inhibitors**

Of all the 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 IGF1 compared with those without ACE inhibitors, $86.8 \pm 31.4$ vs $77.2 \pm 26.7$ μg/l ($P<0.001$). The difference in IGF1 values between the sexes was independent of treatment with ACE inhibitors.

IGF1 values were compared between the four 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 (EF <30%) systolic function. In patients on ACE inhibitors, the highest values were found in class 3 (92.9 ± 9.1 μg/l) compared with 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, patients with an EF <40% had significantly higher IGF1 values compared with those with an EF ≥40% (103.4 ± 39.7 vs 84.4 ± 30.0 μg/l; $P=0.02$; Table 2). There were also significantly higher IGF1 levels in those patients on ACE inhibitors who had higher proBNP levels in quartile 4 vs 1 (93.2 ± 35.3 vs 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 IGF1 levels than those without CAD history and ECG changes characteristic for IHD (100.1 ± 34.7 vs 80.5 ± 28.1 μg/l; $P<0.001$; Table 2). For patients on ACE inhibitors, the highest IGF1 levels were found in patients with ECG changes characteristic for IHD compared with those without ECG changes.

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**Table 1** Population baseline characteristics.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Whole population</th>
<th>Female</th>
<th>Male</th>
<th>$P$ values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total ($n$)</td>
<td>851</td>
<td>436</td>
<td>415</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± s.d.; years)</td>
<td>73.0 ± 3.5</td>
<td>73.3 ± 3.4</td>
<td>72.6 ± 3.5</td>
<td>0.002</td>
</tr>
<tr>
<td>History ($n$ (%))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>123 (14.4)</td>
<td>64 (52.0)</td>
<td>59 (48.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>IHD</td>
<td>157 (18.4)</td>
<td>68 (53.3)</td>
<td>89 (56.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>ECG</td>
<td>47 (5.5)</td>
<td>14 (29.8)</td>
<td>33 (70.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>CAD</td>
<td>127 (14.9)</td>
<td>60 (47.3)</td>
<td>67 (52.7)</td>
<td>0.3</td>
</tr>
<tr>
<td>NYHA I</td>
<td>519 (61.0)</td>
<td>255 (49.1)</td>
<td>264 (50.9)</td>
<td>0.1</td>
</tr>
<tr>
<td>NYHA II</td>
<td>266 (31.2)</td>
<td>146 (54.8)</td>
<td>120 (45.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>NYHA III</td>
<td>66 (7.7)</td>
<td>35 (53.0)</td>
<td>31 (47.0)</td>
<td>0.8</td>
</tr>
<tr>
<td>Clinical variables</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (mean ± s.d.; kg)</td>
<td>75.4 ± 13.1</td>
<td>71.4 ± 1.4</td>
<td>79.7 ± 11.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Height (mean ± s.d.; cm)</td>
<td>168.1 ± 10.5</td>
<td>151.7 ± 9.7</td>
<td>174.8 ± 6.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (mean ± s.d.; kg/m²)</td>
<td>26.6 ± 4.2</td>
<td>27.2 ± 4.8</td>
<td>26.1 ± 4.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EF ≥40% ($n$ (%))</td>
<td>795 (93.4)</td>
<td>413 (51.9)</td>
<td>382 (44.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>EF &lt;40% ($n$ (%))</td>
<td>42 (5.0)</td>
<td>12 (28.6)</td>
<td>30 (71.4)</td>
<td>0.003</td>
</tr>
<tr>
<td>Treatment ($n$ (%))</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>173 (20.3)</td>
<td>91 (52.6)</td>
<td>82 (47.4)</td>
<td>0.7</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>200 (23.5)</td>
<td>102 (23.4)</td>
<td>98 (23.6)</td>
<td>0.9</td>
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<tr>
<td>Diuretic</td>
<td>240 (28.2)</td>
<td>145 (33.3)</td>
<td>96 (22.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Laboratory analyses (mean ± s.d.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IGF1 (μg/l)</td>
<td>79.1 ± 27.9</td>
<td>74.3 ± 25.8</td>
<td>84.1 ± 29.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>92.0 ± 18.5</td>
<td>86.1 ± 16.9</td>
<td>98.2 ± 18.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NT-proBNP (ng/l)</td>
<td>276.7 ± 558.1</td>
<td>284.6 ± 642.6</td>
<td>272.6 ± 453.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Hb (g/l)</td>
<td>140.2 ± 12.6</td>
<td>136.1 ± 11.2</td>
<td>146.5 ± 12.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACE, angiotensin converting enzyme; BMI, body mass index; BP, blood pressure; IGF1, insulin-like growth 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.
(115.7 ± 27.1 vs 82.9 ± 30.1 µg/l; P < 0.001). IGF1 levels tended to be higher in patients on ACE inhibitors with a CAD history than in those without CAD history (98.4 ± 35.0 vs 83.6 ± 29.8 µg/l; P = 0.07). No relationship was found between IGF1 levels and the presence of IHD in patients without ACE inhibitors.

In multivariate regression analyses with IGF1 as the dependent variable, gender, ACE inhibitors, and ECG indicative of IHD had a significant impact, whereas IHD, EF < 40%, creatinine, BMI, and proBNP were not significant (Table 3).

**IGF1 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). In total, 134 (58.3%) patients died of CV disease and 40 (17.4%) died of malignant disease. IGF1 values for CV non-survivors (83.7 ± 30.0 µg/l) were significantly higher than for those who survived the follow-up period (78.1 ± 27.4 µg/l; P = 0.034). All-cause mortality tended to be associated with increased IGF1 levels (P = 0.09).

IGF1 values were then divided into quintiles in order to compare mortality and CV mortality in groups with low and high IGF1 levels (Table 5). The first and second quintiles were pooled, as well as the 4th and 5th and to quintile 3. In order to test the possibility to use IGF1 as a biomarker for HF and IHD and as a predictor of CV mortality. Furthermore, the role of ACE inhibitors was found. All inhabitants aged 66–81 years in the community were invited to participate and no participants were lost.

**Discussion**

In an elderly population with concomitant diseases representative for their age and followed for 8 years, we tested the possibility to use IGF1 as a biomarker for HF and IHD and as a predictor of CV mortality. Furthermore, the role of ACE inhibitors was found. All inhabitants aged 66–81 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 IGF1 levels, especially in patients with impaired cardiac function. High levels of IGF1 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 IGF1 compared with those without ACE inhibitors. In the ‘CHIANTI study’ (19), which encompassed 745 subjects ≥65 years of age, IGF1 levels were significantly higher in participants receiving ACE inhibitors compared with the rest of the study population. A 6-month treatment with fosinopril increased IGF1 levels in older adults with a high CV risk profile (18). Overall, there is strong evidence that ACE inhibitors lead to an increase in circulating IGF1 levels. We found significantly higher IGF1 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 are known to affect IGF1 (24, 25).

In our study, the most pronounced increase in IGF1 values was found between patients on ACE inhibitor treatment and an EF <40% and those with an EF ≥40%. High levels of NT-proBNP, another well-known marker for HF, were only associated with raised IGF1 levels in patients on ACE inhibitors. When stratified according to EF, the highest IGF1 values were found in patients with an EF 30–40%. Corbalan et al. (26), in a small, uncontrolled study on nine patients with HF NYHA Class III, reported that treatment with enalapril restored low IGF1 values and improved cardiac function. Andreassen et al. (27) reported increased IGF1 levels in patients treated with ACE inhibitors/angiotensin II receptor blockers. However, they did not find a significant difference in IGF1 levels between patients with HF and controls.

When divided into those with and without ACE inhibitors, the increase in IGF1 levels in IHD was confined to those on ACE inhibitors (P<0.001). Schneider et al. (3) have shown that high IGF1 levels are associated with CAD in women, but not in men. Patients with low IGF1 levels also showed increased risk for CAD. Kaplan et al. (28) failed to show a relationship between IGF1 and the risk for IHD in elderly subjects. The use of ACE inhibitors was not discussed in the above studies.

We found that persons with higher IGF1 levels in quintiles 4 and 5 compared to quintiles 1 and 2 had a 50% greater risk for dying of CV causes. This was still true after adjustment for age and other known CV risk factors: NYHA Class III, NT-proBNP, diabetes mellitus, BMI, creatinine, age, and gender (Table 6). A U-shaped association between CV mortality and low–normal and high–normal IGF1 levels was recently reported by Bunderen et al. (4). In this study, it should be noted that patients with prevalent CVD were excluded from cause-specific analysis of mortality. In another study, low IGF1 levels, below the 90th percentile, were associated with increased risk for all-cause mortality, CV mortality, and cancer mortality in men but not in women (29). Low IGF1 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 IGF1 levels according to quintiles (30).

In our study, there was a tendency toward an association between high IGF1 levels and all-cause mortality (P=0.09). When comparing IGF1 levels according to quartiles, Andreassen et al. (6) found high plasma IGF1 levels to be independently associated with an increase in all-cause mortality. The association between circulating IGF1 levels and all-cause mortality tended to be U-shaped, with increased mortality at both low and high IGF1 levels (6). In the study by Bunderen et al. (4) mentioned above, an increased risk for all-cause mortality was found for elderly subjects with the lowest IGF1 levels in the 1st quintile compared with the 3rd quintile. Other studies have failed to show an association between IGF1 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 IGF1 levels and HF, IHD, and CV mortality. Previous

<table>
<thead>
<tr>
<th>Table 4</th>
<th>All-cause mortality, CV mortality, and malignancy mortality in the study population. Data are presented as n (%).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>Whole population</td>
</tr>
<tr>
<td>All cause</td>
<td>230 (27.0)</td>
</tr>
<tr>
<td>CV</td>
<td>134 (58.3)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>40 (17.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 5</th>
<th>IGF1 quintiles and all-cause, CV, and malignancy mortality.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile</td>
<td>n</td>
</tr>
<tr>
<td>1</td>
<td>169</td>
</tr>
<tr>
<td>2</td>
<td>171</td>
</tr>
<tr>
<td>3</td>
<td>171</td>
</tr>
<tr>
<td>4</td>
<td>170</td>
</tr>
<tr>
<td>5</td>
<td>170</td>
</tr>
<tr>
<td>Total</td>
<td>851</td>
</tr>
</tbody>
</table>

*Values are expressed as µg/l.
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 that have shown high IGF1 levels to be associated with all-cause mortality (4, 6) and CV mortality (4). Our results contradict the concept that high IGF1 levels are protective against atherosclerosis-associated cardiac events (2). Most previous studies have shown that low IGF1 levels correlate with increased CV and all-cause mortality (1, 2, 9, 33). We did not find any tendency toward increased mortality in subjects with low IGF1 values. It should be pointed out that we did not see the very low IGF1 values found in GH-deficient patients reported to have increased CV mortality (33). However, population studies have also shown low IGF1 levels to be associated with increased CVD.

What can be extracted from our findings? One may speculate that low IGF1 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 IGF1 or non-functioning IGF1 and longer life span (36–38). These together with our results support the idea that there is a complex relationship between IGF1 levels and mortality and that a high IGF1 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 ± 2.6). No patient was lost during the follow-up. Nevertheless, this study has some limitations. One important limitation 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 life span of study participants (66–81 years), which makes extrapolation of the results to other age groups unwise. Furthermore, we did not measure the interaction of IGF1 with IGFBPs, which can modulate free IGF1.

Conclusion
In this unique unselected population of elderly subjects from the community, we found that treatment with ACE inhibitors is associated with increased IGF1 levels, especially in patients with impaired cardiac function. High levels of IGF1 tend to be associated with an increased risk for CV 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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